Measurement of FEF$_{25-75\%}$ and FEF$_{75\%}$ does not contribute to clinical decision making

Philip H. Quanjer Department of Pulmonary Diseases and Department of Paediatrics, Erasmus Medical Centre, Erasmus University, Rotterdam, the Netherlands
pquanjer@ziggo.nl

Daniel J. Weiner Children's Hospital of Pittsburgh, Pittsburgh, PA, USA
daniel.weiner@chp.edu

Jeffrey J. Pretto Department of Respiratory and Sleep Medicine, John Hunter Hospital, and School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia
jeff.pretto@hnehealth.nsw.gov.au

Danny J. Brazzale Department of Respiratory and Sleep Medicine, Austin Hospital, and Institute for Breathing and Sleep, Heidelberg, Victoria, Australia
Danny.Brazzale@austin.org.au

Piotr W. Boros Lung Function Lab, National TB & Lung Diseases Research Institute, Warsaw, Poland
piotr.boros@gmail.com

Correspondence and requests for reprints should be addressed to
Philip Quanjer, Kervel 19, 7443 GT Nijverdal, The Netherlands. E-mail: pquanjer@ziggo.nl

Corresponding author: Philip H. Quanjer, pquanjer@ziggo.nl

Running title: Diagnostic value of forced expiratory flows

Abstract: 199 words (200 allowed)
Manuscript: 2882 words (3000 allowed)
Tables: 2
Figures: 4
References: 29

Key words: airways obstruction, forced expiratory flow, spirometry, clinical decision making

AUTHOR CONTRIBUTIONS

FUNDING

COMPETING INTERESTS

Abstract

Objective: To determine the added value of measuring the forced mid-expiratory flow ($FEF_{25-75\%}$) and flow when 75% of the forced vital capacity (FVC) has been exhaled ($FEF_{75\%}$) over and above the measurement of the forced expiratory volume in one second (FEV_1), FVC and FEV_1/FVC ratio.

Material: Spirometric records with FEV_1, FVC and $FEF_{25-75\%}$ from 11,654 white males and 11,113 white females, aged 3-94 years, routinely tested in the pulmonary function laboratories of four tertiary hospitals. $FEF_{75\%}$ was available in 8,254 males and 7,407 females.

Methods: Predicted values and lower limits of normal, defined as the fifth percentile, were calculated for FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$ and $FEF_{75\%}$ using prediction equations from the Global Lung Function Initiative.

Results: There was very little discordance in classifying test results. In only 2.75% of cases the $FEF_{25-75\%}$, and in 1.29% of cases the $FEF_{75\%}$ was below the normal range whereas FEV_1, FVC and FEV_1/FVC were within normal limits. Airways obstruction went undetected by $FEF_{25-75\%}$ in 2.9%, by $FEF_{75\%}$ in 12.3% of cases.

Conclusions: Maximum mid-expiratory flow and flow towards the end of the forced expiratory manoeuvre do not contribute usefully to clinical decision making over and above information from FEV_1, FVC and FEV_1/FVC.

Introduction

The forced expiratory vital capacity (FVC) manoeuvre is the fundamental manoeuvre of the most frequently carried out test for assessing pulmonary function. Apart from the forced expiratory volume in 1 second (FEV_1) and the FEV_1/FVC ratio, a host of other indices have been derived from the FVC manoeuvre. These include peak expiratory flow, flows at 25%, 50% and 75% of the exhaled FVC and the average flow over the mid-half of the FVC ($FEF_{25-75\%}$, also called maximum mid-expiratory flow: MMEF). The latter sets of flows, as well as the assessment of closing volume, were described as being more reproducible and more sensitive than the FEV_1 to the presence of "small airways disease"[1-3]. It was generally accepted that obstruction in small airways led to reduced flows at low lung volumes, leaving flows at high lung volumes much less affected, resulting in the characteristic concave flow-volume curve [4-6]. The prospect of detecting lung disease at an early stage has led to widespread measurement of $FEF_{25-75\%}$ and $FEF_{75\%}$. However, the greater reproducibility of flows and better sensitivity of $FEF_{25-75\%}$ were also challenged [7-8]. In addition, flows at a percentage of the FVC are sensitive to measurement errors in the FVC. Furthermore, as the FVC and TLC may be affected by disease, forced expiratory flows in patients will be measured at a different lung volume than in healthy subjects, rendering the use of predicted values derived from healthy subjects problematic. For the same reason serial measurements in a subject in whom the FVC has changed due to disease progression and/or therapeutic intervention should only be compared if they have been made at the same lung volume [9]. Finally, the hypothesis that reduced mid-expiratory flows were specific for small airways disease has been shown to be incorrect [10].

These limitations of instantaneous and mid-expiratory flows in clinical practice have led to recommendations to disregard any suspected abnormality in flows if the FEV_1 and FEV_1/FVC ratio are within normal limits [11-13]. However, it is suggested that in the presence of a borderline value of FEV_1/VC, these tests may suggest the presence of airway obstruction [13]. Reporting of flow is also recommended for quality-control purposes in preschool children [14]. A search on PubMed using the keywords $FEF_{25-75\%}$, MMEF and $FEF_{75\%}$ revealed that these indices were used in 1,143 publications between 1975 and 2012, of which 385 have been published since 2000.

The purpose of this study is to investigate the extent to which the use of expiratory flows, namely the $FEF_{25-75\%}$ and $FEF_{75\%,}$ adds information to spirometry over and above that from FEV_1, FVC and FEV_1/FVC.

Material

The study is based on 22,767 consecutive patients routinely tested in the pulmonary function laboratories of the Children's Hospital of Pittsburgh, Pittsburgh, PA, USA, the Austin Hospital in Victoria, Australia (Australia 1), the John Hunter Hospital in New South Wales, Australia (Australia 2), and the National Research Institute of TB & Lung Diseases in Warsaw, Poland. The studies were carried out between January 2010 and December 2011 (USA), August 2008-June 2012 (Australia 1), January 2001-May 2012 (Australia 2) and April 2009-June 2012 (Poland). Spirometry was performed by trained respiratory therapists and scientists in accordance with internationally agreed standards applied at the time of data collection [15-16], and only baseline or pre-bronchodilator data was included in the analysis.

The data comprised consecutively collected test results from patients referred for lung function assessment for clinical purposes. The bulk of the subjects in the USA data set were referred for asthma control and suspected asthma, followed by cystic fibrosis, cough, dyspnoea, or miscellaneous conditions, in that order. The study is limited to people of European ancestry because other ethnic groups were poorly represented.

     The de-identified datasets were comprised of data on age, height, sex, ethnic group, FEV_1, FVC, FEV_1/FVC, and $FEF_{25-75\%}$ values. Data on $FEF_{75\%}$ were only available in data sets from Poland and the USA. $FEF_{25-75\%}$ and $FEF_{75\%}$ were taken from the FVC manoeuvre with the highest sum of FEV_1 and FVC [15]. If serial measurements had been performed on the same individual, the first test result only was included for analysis.

     This study is a retrospective analysis of de-identified data, obviating the need for approval from local Ethics Committees. Nonetheless, separate approval was obtained from the Institutional Review Board of the Children's Hospital of Pittsburgh (PRO12100285) and from the local ethics committees for the Australian laboratories.

Methods

Predicted values and z-scores for the various indices were derived using prediction equations from the Global Lung Function Initiative (GLI-2012) [17] using specialised software [18]. Plots were made of the z-scores for FEV_1/FVC, $FEF_{75\%}$ and $FEF_{25-75\%}$.

In males and females a best fit was obtained for height as a function of age using statistical modelling software (GAMLSS version 4.2-4). Heights outside ±3 z-scores from the mean were regarded as outliers. Z-scores for FEV_1/FVC, $FEF_{25-75\%}$ and $FEF_{75\%}$ <-1.645 were considered abnormal. Data analysis was performed using the statistical software R [Version 3.0.1; R Foundation, http://www.r-project.org].

Results

The numbers of males and females and age ranges in the four datasets are shown in table 1. Sixty-eight males and 67 females (0.59% of the total study population) were very short or very tall for age, leading to extreme z-scores for spirometric indices; these data were considered outliers and excluded, leaving 22,767 spirometry results for analysis. The overall prevalence of airways obstruction, defined as FEV_1/FVC <LLN, was 26.4%; on the basis of FEV_1 %predicted, using the ATS/ERS grading system [13], 8.85% were classified as mild airways obstruction, 4.34% as moderate, 4.19% as moderately severe, 5.45% as severe, and 3.56% as very severe . A "spirometric restrictive pattern" (where FEV_1/FVC >LLN and FVC <LLN) was found in 15.3% of the total group.

The mean z-scores for males and females for the various spirometric variables in the four datasets are shown in table 2. The LLN for $FEF_{25-75\%}$ and $FEF_{75\%}$ varied between 35%-67% and 31-56%, respectively, declining steeply with age. The relationship between the z-scores for the FEV_1/FVC ratio and $FEF_{25-75\%}$ is shown in figure 1A; no differences in this relationship could be discerned between males and females. Of the 22,767 subjects, there were 1,862 (8.18%) that showed an $FEF_{25-75\%}$ below the LLN but an FEV_1/FVC ratio in the normal range (quadrant Q3 in figure 1A). In 66% of these individuals (n=1,235) this was associated with an FVC below the LLN (figure 1C, figure 2). There was 2.87% of test results that revealed an $FEF_{25-75\%}$ in the normal range, but FEV_1/FVC < LLN (suggesting airways obstruction) as indicated in quadrant Q1 in figure 1A. The percentage of subjects in whom $FEF_{25-75\%}$ was <LLN but FEV_1, FVC, and FEV_1/FVC were in the normal range, is displayed as a function of age in figure 2. After adjusting for the z-score for the FEV_1/FVC ratio, the z-score for $FEF_{25-75\%}$ was somewhat but significantly lower (-0.12) in the Polish than in the other datasets.

Data on $FEF_{75\%}$ were available in 15,661 subjects and there was a similar relationship with FEV_1/FVC ratio as with $FEF_{25-75\%}$ (figure 1B). There were 477 cases (3.05% of the total) where $FEF_{75\%}$ was reduced (<LLN) but there was a normal FEV_1/FVC ratio (Q3 in figure 1B), and the majority of these cases (58%) showed a reduced FVC (figure 1D). Compared with $FEF_{25-75\%}$ there were significantly more results where FEV_1/FVC was reduced but $FEF_{75\%}$ was not (12.25% of the total). After adjusting for the z-score for FEV_1/FVC ratio, the z-score for $FEF_{75\%}$ was significantly lower (-0.17) in the USA than in the Polish dataset.

Thus only 2.75% of the total number of test results showed a reduced $FEF_{25-75\%}$ with both FEV_1/FVC and FVC within the normal range. The corresponding value for $FEF_{75\%}$ was lower at only 1.29% of the total. Of these cases, about half showed an FEV_1/FVC ratio close to the lower limit of normal (within 0.25 z-values). When we reviewed the discordances in a random sample of 100 cases, 67% of them were found to have artefact or submaximal exhalation which could affect results (71% in the 3-10 year age range, 29% in the 10-20 year age range).

A normal $FEF_{25-75\%}$ associated with an abnormal FEV_1/FVC ratio was rare (2.87%, Quadrant 1 in figure 1A). These cases were characterised by a low FEV_1 (mean z-score -0.79), an above average FVC (mean z-score 0.55) and mostly mild airways obstruction (87.2% using ATS/ERS grading system [13]). In 12.25% of cases a normal $FEF_{75\%}$ was associated with an abnormally low FEV_1/FVC ratio; characteristically there was more severe airways obstruction (mean z-score for FEV_1 -1.87, for FVC -0.52, and 49.7% cases of mild airways obstruction).

As the flow-volume curve clearly demonstrates, expiratory flows are highly dependent upon the lung volume at which they are determined. Similarly to the FEV_1, they were also expressed as a fraction of the FVC to take this dependency into consideration. The relationship between $FEF_{25-75\%}/FVC$ and $FEF_{75\%}/FVC$ with FEV_1/FVC was curvilinear; however, log transforming the data linearised the relationship and stabilised the variance, as shown in figure 3.

Forced expiratory flows are commonly presented as a percentage of the mean predicted value. Figure 4 depicts the lower limits of normal (5th percentile, at z-score of -1.645) for $FEF_{25-75\%}$ and $FEF_{75\%}$ as percent predicted, using the GLI-2012 equations and median height for age in males and females.

Discussion

To our knowledge this is the first study which has systematically investigated whether the use
of maximum mid-expiratory flow and instantaneous flows provides additional information
beyond that provided by traditional spirometric indices (FEV_1, FVC and FEV_1/FVC) in detecting
lung function impairment. Our findings in a large clinical dataset show that airways obstruction,
defined by an abnormally low FEV_1/FVC ratio, goes undetected by the $FEF_{25-75\%}$ and $FEF_{75\%}$ in
2.9% and 12.3% of cases, respectively. We have found that $FEF_{25-75\%}$ is reduced in the presence
of a normal FEV_1/FVC ratio in 8.2% of cases. Only 3.0% of cases revealed an abnormally low
$FEF_{75\%}$ with a normal FEV_1/FVC ratio. However, a large majority of these discrepant findings
occurred when the FVC was abnormally low. As such, in only a very small minority of cases was
a low $FEF_{25-75\%}$ or $FEF_{75\%}$ associated with normal FEV_1/FVC ratio and a normal FVC (2.8% and
1.3%, respectively). Of these discordant cases, we identified possible artefact or unsatisfactory
FVC efforts in approximately 63% of cases.

It is commonly perceived that the $FEF_{25-75\%}$ is diagnostically more helpful in a paediatric
population than in adults. Indeed we did find a trend of a higher prevalence rate of an
abnormally low $FEF_{25-75\%}$ when FEV_1, FVC, and FEV_1/FVC are in the normal range in youngsters
than in adults (fig. 2), but even then the rate is very low at only 3%. It is difficult to always
obtain high quality measurements in children, Indeed, in a random sample of 100 children with
discordant findings in the 3-10 year and 10-20 year age range, 71% and 29% respectively were
found to be associated with flow-volume curves with artefact or submaximal exhalation or
inhalation which could affect results. The very low incidence of discordant findings argues
against the notion that forced expiratory flows are more sensitive to small airways obstruction
than other spirometric indices. We suggest that these infrequent occurrences where flow
indices result in discordant findings from conventional spirometric indices probably represent
statistical noise and biological variability associated with spirometry, and in particular with the
high reliance of expiratory flow indices on the valid measurement of FVC. We would also
suggest that such findings should prompt a critical review of the quality of the FVC manoeuvre.
The practical implication is that the flow indices contribute little or no additional information
over and above that provided by the FEV_1 and FVC, and therefore do not add to the diagnostic
arsenal in detecting airways obstruction.

The frequent use of these flow indices is based on the notion that airways obstruction affects
flows towards the end of a forced expiratory manoeuvre much more than at the start of the FVC
manoeuvre, because at low lung volumes lung elastic recoil is low and airway dimensions are
small. Hence, such flows are thought to be more sensitive to small airways obstruction than the
FEV_1. This misconception arose at least in part because McFadden and Linden [1] based their

conclusions on the erroneous, yet still popular, idea that 80% of predicted denotes the lower limit of normal for any marker of lung function. This ignores the considerable age-related difference in variability of lung function with age [17] and has led to considerable over diagnosis of abnormality. The LLN for $FEF_{25-75\%}$ is 67% of mean predicted in childhood and 35% in those $\geq$80 years; corresponding values for $FEF_{75\%}$ are 56% and 31%. Indeed, as early as 1988 Flenley [10] contested the view that mid-expiratory flows were specific for small airways disease. By inference, partitioning into large and small airways obstruction in chronic lung diseases on the basis of spirometric test results is not warranted.

The dependency of forced expiratory flow on lung volume is immediately clear from flow-volume curves, unlike the mechanisms responsible for determining such flows. During a forced expiration the high pleural pressure leads to dynamic compression of intrathoracic airways. Flow through compressed airways is then determined by wave speed limitation, *i.e.* when local gas velocity is equal to the speed of propagation of pressure waves in the airways; the location of the flow-limiting segment (choke point) is determined by the interplay between lung elastic recoil and airway compliance [19-20]. As more volume is expelled, lung elastic recoil and pleural pressure diminish which allows the choke point to settle upstream in airway segments with pressure-area characteristics that allow lower flow [21-22]. It follows that forced expiratory flows are highly dependent on lung volume so that, like the FEV_1 (the average flow over the first second of the forced expiration), they should be standardised for true lung volume, which is the total lung capacity. This is usually not feasible, and hence the vital capacity is used as a proxy for lung size. The FEV_1/FVC ratio is dimensionally 1/s and represents the lung emptying rate. As our analysis has shown, standardising the $FEF_{25-75\%}$ and $FEF_{75\%}$ in a similar fashion by expressing them as a ratio of the FVC, reveals high correlations with the FEV_1/FVC (figure 3), signifying that the information content of these indices is very similar.

Obstructive respiratory disease with increasing residual volume causes flow at a fixed percentage of the FVC to be measured closer to the total lung capacity (which may be increased due to disease) than in a reference population; this partly masks a fall in forced expiratory flows due to airways obstruction and will diminish the sensitivity in diagnosing obstructive lung disease. In addition normal reference ranges for forced expiratory flows reflect between-subject variability in both flows and in the FVC. This leads to much higher coefficients of variation than for FEV_1, FVC or their ratio, and therefore to larger reference intervals around predicted values (figure 4). Variability might have been somewhat smaller if flows had been taken from the envelope of flow-volume curves [12,23], but in this study it was taken from the FVC manoeuvre with the highest sum of FEV and FVC in accordance with recommended

guidelines[15]. Such wide intervals render these indices essentially worthless for diagnostic purposes [12,17,24]. This also highlights that using 80% of predicted as the lower limit of normal for lung function indices lacks any scientific basis and leads to highly biased and erroneous clinical decisions. The use of a lower limit defined as the lower 5th or other percentile of the distribution in a healthy population of non-smokers is therefore the recommended procedure [12,14,17,25-28]. Z-scores indicate the number of age-specific standard deviations that a measured value differs from the predicted value and, unlike using a fixed percent of predicted as the basis for interpretation of lung function, they are free of bias due to age, height, sex and ethnic group [12,14,17,25-28] and were therefore used in this study.

This study is based on a large number of data from patients referred to tertiary hospitals for suspected or known lung disease. The relationship between the z-score for FEV_1 and that for flows differed only slightly albeit significantly between centres, indicating that our findings are robust and applicable to children and adults with a wide range of normal and abnormal lung function test results. However, the very large number of data precluded rigorous *post hoc* quality control of all original spirograms. In routinely collected data there will be a proportion where data are clinically useful and therefore accepted, but where the FVC manoeuvres do not meet stringent quality criteria. As shown by this study a low $FEF_{25-75\%}$ or $FEF_{75\%}$ when the FVC, FEV_1 and FEV_1/FVC ratio are within normal limits is rare and should lead to reviewing whether the FVC manoeuvre was performed correctly.

Conclusions

Measurements of $FEF_{25-75\%}$ and $FEF_{75\%}$ are highly correlated with conventional spirometric indices, leading to minimal discordance in classifying test results. Most reductions in $FEF_{25-75\%}$ and $FEF_{75\%}$ measurements in the absence of classically defined airways obstruction using FEV_1/FVC result from reduced lung volume rather than from airways disease. The low incidence of abnormal expiratory flows with normal FEV_1 and FVC values may reflect measurement "noise". These data suggest that maximum mid-expiratory flow and flow towards the end of the forced expiratory manoeuvre do not contribute usefully to clinical decision making.

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Table 1 – Numbers of males and females and age ranges in the four datasets.

	Males		Females	
Centre	N	Age (yr)	N	Age (yr)
Australia 1	1,418	6.3-93.6	1,401	6.5-94.6
Australia 2	1,980	8.2-92.4	2,304	9.1-94.6
Poland	5,662	18.0-91.0	5,183	18.0-92.0
USA	2,594	3.8-65.0	2,225	3.7-77.1

Table 2 – Mean z-scores (standard deviations in brackets) for males and females for the various spirometric variables in the four datasets.

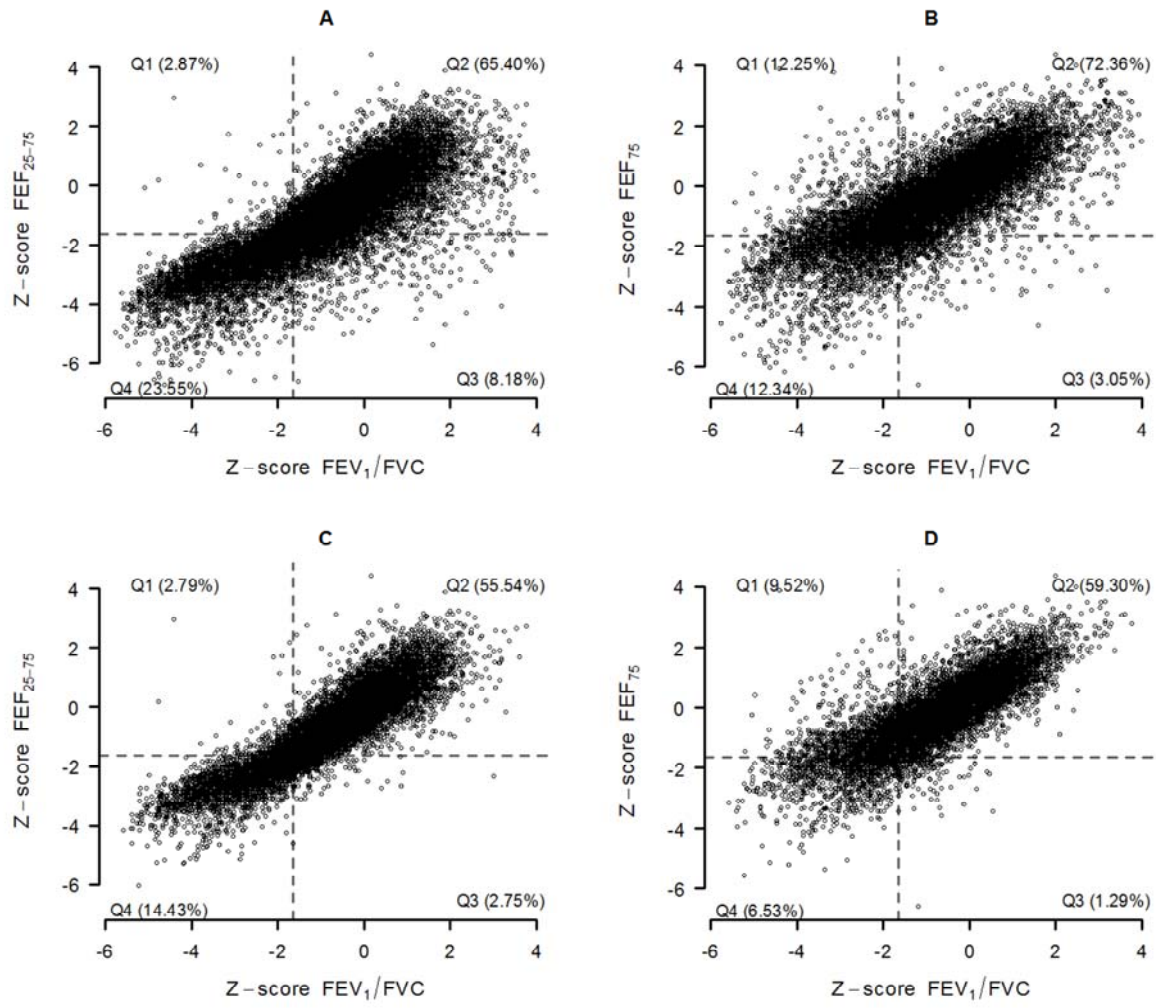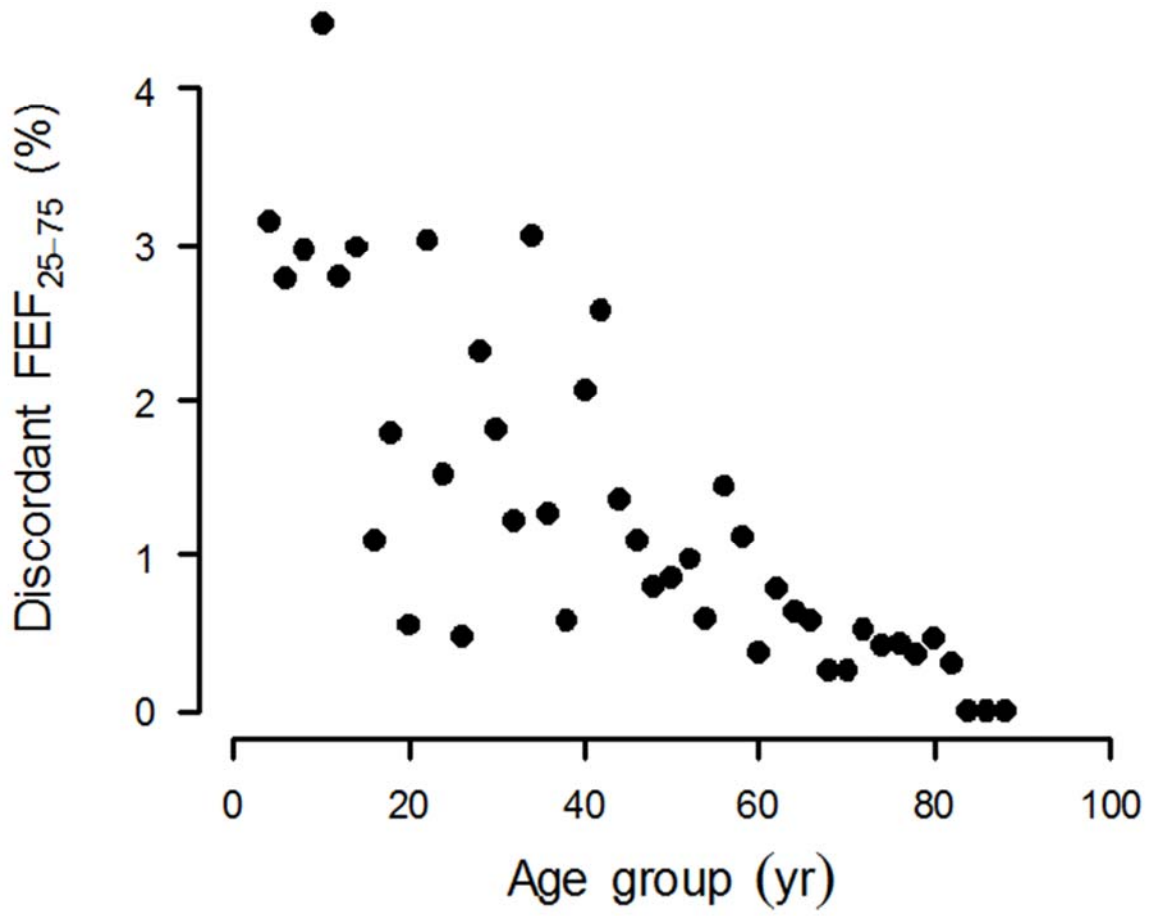|	Australia 1		Australia 2		Poland		USA	
	Male	Female	Male	Female	Male	Female	Male	Female
FEV_1	-1.73	-1.54	-1.31	-1.05	-1.49	-1.36	-0.25	-0.14
	(1.46)	(1.55)	(1.32)	(1.37)	(1.55)	(1.54)	(1.60)	(1.53)
FVC	-1.00	-0.91	-1.00	-0.84	-0.96	-1.02	0.07	0.11
	(1.41)	(1.40)	(1.30)	(1.35)	(1.49)	(1.46)	(1.52)	(1.43)
FEV_1/FVC	-1.48	-1.24	-0.77	-0.51	-1.07	-0.71	-0.52	-0.49
	(1.59)	(1.47)	(1.36)	(1.14)	(1.63)	(1.47)	(1.22)	(1.17)
$FEF_{25-75\%}$	-1.43	-1.33	-0.89	-0.73	-1.17	-1.06	-0.68	-0.57
	(1.33)	(1.44)	(1.25)	(1.21)	(1.33)	(1.35)	(1.48)	(1.39)
$FEF_{75\%}$	N.A.	N.A.	N.A.	N.A.	-0.57	-0.27	-0.31	-0.25
					(1.24)	(1.19)	(1.36)	(1.35)

N.A.: not available.

Figure 1

Figure 2

Figure 3

Figure 4