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Original article

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Predicted Values for the Forced Expiratory Flow Adjusted for Forced Vital Capacity, a descriptive study

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Take home massage

FEFs may be more sensitive in detecting peripheral airways obstruction compared to FEV_1 or FVC. However, they are highly variable. Adjusting the FEF by dividing it by FVC may partially solve this. We therefore provide FVC-adjusted FEF reference equations.

Abstract

Background

The forced expiratory flows (FEFs) towards the end of the expiration may be more sensitive in detecting peripheral airways obstruction compared to the forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC). However, they are highly variable. A partial solution is to adjust the FEFs for FVC (FEF/FVC). Here we provide reference equations for these adjusted FEFs at 25, 50, 75, and 25-75% of FVC, which are currently lacking.

Methods

We included pulmonary healthy, never-smoker adults, 14,472 subjects from Lifelines, a biobank for health research, and 338 subjects from the department's control cohorts (NORM and Fiddle). Reference equations were obtained by linear regression on 80% of the Lifelines dataset and validated on the remaining data. The best model was defined as the one with the highest adjusted R^2-value. The difference in variability between adjusted and unadjusted FEFs was evaluated using the coefficient of variation.

Results

For all adjusted FEFs, the best model contained age, height, and weight. The adjustment improved the coefficient of variation of the FEF_{75} from 39% to 36% and from 43% to 40%, respectively in males and females. The highest percentage of explained variance by the reference equation was obtained for FEF_{75}/FVC, 32%-38% for males, and 41%-46% for females, depending on the validation set.

Conclusion

We developed reference equations for FVC-adjusted FEF values. We demonstrated minimally, yet significantly improved variability. Future studies in obstructive airway diseases should demonstrate whether it is worthwhile to use these (predicted) adjusted FEF-values.

Introduction

Worldwide, spirometry is the most frequently used pulmonary function test, with the main goal to assess expiratory airflow obstruction in chronic diseases, like asthma and chronic obstructive pulmonary disease (COPD). Airflow obstruction is usually assessed with the ratio between the forced expiratory volume in the first second (FEV_1) and the forced vital capacity (FVC) in combination with flow-volume curves. These flow-volume curves are visually attractive and offer pattern recognition in certain situations[1]. They also allow visual representation of the adequacy of a subject's effort in the early, mid, and late phase of forced expiration. Unfortunately, the corresponding numerical values for the forced expiratory flows at 25%, 50%, 75% and 25% to 75% of the FVC (FEF_{25}, FEF_{50}, FEF_{75}, and FEF_{25-75}) demonstrate considerable variability in the healthy population [1, 2]. Therefore, the global standards use the more reproducible and well-defined reference values of FEV_1 and (F)VC to define, grade and monitor airflow obstruction [3, 4]. However, the FEV_1 is deemed not a sensitive parameter to detect small airways disease, as the volume and flow rate of exhaled air in the first second of expiration depends mainly on the diameter and resistance of the large airways. In contrast, the FEFs, towards the end of the expiration, are more sensitive to peripheral airway narrowing, so it would be worthwhile to reduce their variability.

One important source of the high variability in the FEFs originates from their dependency on the FVC. By definition, the FEF_{25}, FEF_{50}, FEF_{75} and FEF_{25-75} values depend on FVC, so small changes in FVC may translate in considerable changes in FEF values. In clinical practice this may have important consequences. For example, if a patient shows a good response in both flow and volume on a bronchodilator, a positive effect on flow at a certain percentage of the FVC may be underestimated due to a higher FVC. The variability of the FEF values can be reduced by adjusting the FEF values for FVC (FEF/FVC). In 1974, Green and colleagues [5], described this calculation when they tried to reduce the

large intersubject variability of flow, by what they called, size compensation. In their opinion, the uneven growth between lung size and airway calibre (called dysanapsis) was an important contributor to intersubject variability. Since then, several studies have indicated that this adjustment of FEFs leads to clinically meaningful outcome variables. For example, lower FEF_{25-75}/FVC ratios were associated with a higher familial risk to develop COPD after smoking [6], with higher airway reactivity and sensitivity to methacholine [7, 8], and with higher airway reactivity to eucapnic hyperventilation with cold air [9].

In a recent editorial, Thompson [10] recommended a revival of the above-described dysanapsis concept. He pointed out that the adjusted FEFs lack normal reference values and are now subject to arbitrary cut-off values. Unfortunately, the 2012 Global Lung Initiative (GLI), in their capacity as European Respiratory Society (ERS) task force, updated only the reference values for FEF_{75} and FEF_{25-75}, but refrained to provide reference equations for FVC adjusted FEFs [11]. We agree with Thomson that reference values with lower and upper limits of normal may speed up the understanding, validation, and implementation of the FEF/FVC outcomes.

In this study, we provide reference equations for the adjusted FEFs (FEF_{25}/FVC, FEF_{50}/FVC, FEF_{75}/FVC, and FEF_{25-75}/FVC). Furthermore, we provide an update of the unadjusted FEF equations and compare these with the equations from Quanjer (1993) [12] and GLI (2012) [13].

Methods

Subjects

Lifelines is a population-based prospective cohort (inclusion between 2003 and 2016), representative of the population of the Netherlands [14, 15], with an intended total follow-up of at least 30 years and a follow-up frequency of 5 years for measurements and 1.5 years for questionnaires. For this study, we used the baseline data of the 152,180 adult subjects who were 18 years or older and

performed spirometry. We selected never smokers, without any pulmonary complaints, who used no pulmonary medication, nor reported any allergies, and had a body mass index (BMI) between 18 and 30. A further selection was performed based on normal pulmonary function (FEV_1, FVC and FEV_1/FVC above the lower limit of normal [16]) and reliable spirometry, as judged by the pulmonary research technician obtaining the spirometry or a pulmonologist (Figure 1 and supplement). For external validation we used 338 healthy never-smokers, without any past or present pulmonary complaints, and a normal pulmonary function. This was a combination of the unpublished Fiddle dataset approved by the ethical committee of the University Medical Center Groningen (UMCG)(n=282, see supplement) enriched with the healthy never-smokers of the NORM study (n=56) [17].

Data collection

The spirometry measurements were based on a full FVC manoeuvre performed according to the standardized operating procedure of the American Thoracic Society (ATS)/European Respiratory Society (ERS)-task-force [18]. In line with these guidelines, the best effort set was used. All Lifelines data (including weight, height, and spirometry) is obtained according to standardized protocols, by trained technicians. Spirometry measurements were obtained on a PC-based SpiroPerfect with CardioPerfect software (Welch Allyn). The unpublished Fiddle dataset and the NORM study's dataset were obtained in the pulmonology department of the University Medical Center Groningen, using the MasterScreen® PFT (Vyaire).

Definition

The FVC-adjusted forced expiratory flow at 25%, 50%, 75%, and mean 25%-75% of FVC were obtained by dividing FEF_{25}, FEF_{50}, FEF_{75}, and FEF_{25-75} by the actually recorded FVC (Equation 1). This is expressed in reciprocal time [19].

$$\text{adjusted } FEF_x\,(s^{-1}) = FEF_x\,(Ls^{-1})/FVC\ (L) \qquad \text{[Eq. 1]}$$

Statistical analyses

To obtain reference equations for the adjusted and unadjusted FEFs, multiple linear regression was performed with explanatory variables age, weight, and height. This regression was stratified by gender. All combinations of the explanatory variables were assessed, and the model with the highest adjusted R^2 was chosen as best model. Models were built on a random sample of 80% of the data (training set), using 10-fold cross-validation (R version 3.5.2, R-package: caret [20]). The obtained model was consecutively evaluated on the remaining 20% of the dataset (internal validation set) and on the Fiddle-Norm dataset (external validation set).

To check if the adjustment of the FEF decreased the variability of the FEFs, the coefficients of variation of the unadjusted and adjusted FEFs were compared using an asymptotic test (R-package: cvequality [21]).

To investigate to what extent the equations (our newly developed equations and the existing equations from Quanjer [12] and GLI [13]) predict the unadjusted FEFs, the adjusted R^2 (explained variance) was used. The adjusted R^2 for the existing equations was calculated using R-package: rspiro [22] and subsequently adjusted for the number of variables in the equation and the sample size of our dataset.

Results

A total of 14,472 healthy subjects were included from Lifelines, 6,054 males and 8,418 females (Table 1 and supplement S2). The external validation set contained 338 subjects, 170 males and 168 females (supplement S2). The variability of the adjusted FEFs is depicted numerically in Table 1b and visually in Figure 2a and Figure 2b. The coefficient of variation of the adjusted FEFs was significantly lower than that of the unadjusted FEFs, except for FEF_{25}/FVC (Table 2).

Table 1a: Characteristics of groups used to train the reference equations

	Male n=4846	Female n=6736
Age (years)*	42 (11.6)	42 (12.4)
Height (cm)	183 (6.7)	170 (6.4)
Weight (kg)	84 (9.8)	69 (8.9)
BMI (kg/m^2)	24.9 (2.5)	23.9 (2.8)
FEV_1 (L)	4.40 (0.63)	3.19 (0.49)
FEV_1 percentage predicted (%)	99 (9.1)	98 (9.2)
FVC (L)	5.58 (0.74)	3.99 (0.56)
FVC percentage predicted (%)	100 (9.0)	101 (9.4)
FEV_1/FVC	78.9 (4.9)	79.8 (5.2)
FEF_{25} (L/s)	8.50 (1.56)	6.10 (1.13)
FEF_{25} percentage predicted (%)	#	#
FEF_{50} (L/s)	4.87 (1.22)	3.67 (0.91)
FEF_{50} percentage predicted (%)	#	#
FEF_{75} (L/s)	1.63 (0.63)	1.25 (0.54)
FEF_{75} percentage predicted (%)	101 (29.7)	96 (30.2)
FEF_{25-75} (L/s)	4.03 (1.10)	3.03 (0.86)
FEF_{25-75} percentage predicted (%)	96 (22.3)	92 (20.5)

Table 1b: Overview of adjusted FEF for all groups

	Male n=4846	Female n=6736
FEF_{25}/FVC (s^{-1})	1.54(0.30)	1.54(0.29)
FEF_{50}/FVC (s^{-1})	0.88(0.21)	0.92(0.21)
FEF_{75}/FVC (s^{-1})	0.29(0.11)	0.31(0.12)
FEF_{25-75}/FVC (s^{-1})	0.72(0.19)	0.76(0.19)

Data are presented as mean (standard deviation). Predicted values are according to the GLI equations[13],
#=no reference equations available from the GLI. For characteristics of internal- and external validation sets see supplement S2.
* Age range (min-max, (years)) 18-80 (interquartile range (IQR) 34-49) and 18-85 (IQR 33-48) for males and females, respectively. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.

Table 2: Coefficient of variation for adjusted and unadjusted FEFs, for a.) males and b.) females.

A.

Males	Coefficient of variation (%)		Coefficient of variation (%)	p-value
FEF_{25}/FVC (s^{-1})	19.2	FEF_{25}	18.3	0.00027
FEF_{50}/FVC (s^{-1})	23.9	FEF_{50}	25.1	0.00097
FEF_{75}/FVC (s^{-1})	36.0	FEF_{75}	38.7	$5.81 \cdot 10^{-5}$
FEF_{25-75}/FVC (s^{-1})	25.4	FEF_{25-75}	27.2	$6.23 \cdot 10^{-7}$

B.

Females	Coefficient of variation (%)		Coefficient of variation (%)	p-value
FEF_{25}/FVC (s^{-1})	18.7	FEF_{25}	18.6	0.739

FEF_{50}/FVC (s^{-1})	22.9	FEF_{50}	24.9	$1.24 \cdot 10^{-13}$
FEF_{75}/FVC (s^{-1})	39.8	FEF_{75}	43.2	$1.51 \cdot 10^{-10}$
FEF_{25-75}/FVC (s^{-1})	25.8	FEF_{25-75}	28.6	$9.46 \cdot 10^{-19}$

FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.

Visual inspection of the data showed a fairly linear relationship between the adjusted FEFs and each of the explanatory variables, age, weight, and height separately. Comparison of the eight possible (multiple) linear regression models showed that the best fit, defined as the highest adjusted R^2, was obtained by including age, weight, and height in all models for the adjusted FEFs, for both males and females (supplement S3). The best models for the adjusted FEFs (Table 3a) were internally and externally validated and showed numerically comparable fits in all datasets (Table 3b). Notably, the fit in the external validation set was better than in the training and internal validation set.

Table 3: Generated reference equations for adjusted FEF values

A. Equations

	Males		Females	
	Reference equation	RSD	Reference equation	RSD
FEF_{25}/FVC (s^{-1})	3.56+0.001A+0.003W-0.013H	0.286	3.52-0.0005A+0.003W-0.013H	0.278
FEF_{50}/FVC (s^{-1})	2.02-0.004A+0.001W– 0.006H	0.205	2.05-0.005A+0.001W-0.006H	0.201
FEF_{75}/FVC (s^{-1})	0.68-0.005A–0.0009W–0.0005H	0.084	0.73-0.006A-0.001W-0.0004H	0.095
FEF_{25-75}/FVC (s^{-1})	1.70-0.007A+0.0005W-0.004H	0.169	1.76-0.008A+0.00009W-0.004H	0.170

B. Percentage of explained variance for the FEF/FVC equations

	Males			Females		
	Training	Internal validation	External validation	Training	Internal validation	External validation
FEF_{25}/FVC (s^{-1})	6.79%	6.48%	13.16%	6.21%	5.82%	4.56%
FEF_{50}/FVC (s^{-1})	6.17%	4.76%	4.04%	8.64%	9.54%	9.32%
FEF_{75}/FVC (s^{-1})	35.9%	32.1%	37.8%	41.0%	41.5%	46.0%
FEF_{25-75}/FVC (s^{-1})	16.6%	13.8%	14.9%	23.6%	24.1%	25.2%

Lower limit of normal = value - 1.64x RSD, Upper limit of normal = value + 1.64x RSD.
A=age (years); W= weight (kg); H=height (cm); and RSD= residual standard deviation.
FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.

For the unadjusted FEFs, the best models were obtained when all explanatory variables were included (Table 4a). Internal- and external validation showed numerically comparable fits (adjusted R^2)

in all datasets (Table 4b). These unadjusted FEF equations show similar fits on the training, internal- and external validation sets compared to the 1993 equations from Quanjer (Table 5a) and the GLI equations (Table 5b).

Table 4: Generated reference equations for unadjusted FEF values

A. Equations

	Males		Females	
	Reference equation	RSD	Reference equation	RSD
$FEF_{25}(Ls^{-1})$	0.50-0.021A+0.019W+0.040H	1.478	1.21-0.026A+0.015W+0.029H	1.039
$FEF_{50}(Ls^{-1})$	0.14-0.038A+0.008W+0.031H	1.099	0.51-0.033A+0.007W+0.024H	0.778
$FEF_{75}(Ls^{-1})$	0.14-0.034A-0.005W+0.018H	0.469	0.35-0.028A-0.005W+0.014H	0.375
$FEF_{25-75}(Ls^{-1})$	0.37-0.048A+0.003W+0.029H	0.903	0.74-0.041A+0.0015W+0.023H	0.654

B. Percentage of explained variance for the unadjusted FEF equations (table 3a)

	Males			Females		
	Training	Internal Validation	External Validation	Training	Internal Validation	External Validation
$FEF_{25}(Ls^{-1})$	9.73%	12.1%	11.6%	15.6%	17.0%	15.4%
$FEF_{50}(Ls^{-1})$	19.5%	19.8%	20.7%	27.1%	27.7%	29.8%
$FEF_{75}(Ls^{-1})$	46.8%	44.7%	55.0%	51.4%	52.0%	56.8%
$FEF_{25-75}(Ls^{-1})$	32.6%	31.9%	39.2%	42.3%	42.6%	44.1%

Lower limit of normal = value - 1.64x RSD, Upper limit of normal = value + 1.64x RSD.
A=age (years); W= weight (kg); H=height (cm); and RSD= residual standard deviation.
FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.

Table 5: Percentage of explained variance of existing reference equations on our datasets

A. Quanjer 1993 equations

	Males			Females		
	Training	Internal Validation	External Validation	Training	Internal Validation	External Validation
$FEF_{25}(Ls^{-1})$	8.49%	10.1%	7.01%	14.5%	15.6%	11.2%
$FEF_{50}(Ls^{-1})$	19.1%	19.3%	18.0%	26.7%	27.4%	27.6%
$FEF_{75}(Ls^{-1})$	43.4%	43.0%	55.1%	50.9%	51.3%	56.3%
$FEF_{25-75}(Ls^{-1})$	32.3%	30.6%	37.2%	41.9%	42.3%	42.1%

B. GLI-equations

	Males			Females		
	Training	Internal Validation	External Validation	Training	Internal Validation	External Validation
$FEF_{75}(Ls^{1})$	47.4%	46.3%	55.1%	53.0%	53.6%	58.3%

$FEF_{25-75}(Ls^{1})$	32.8%	32.0%	38.2%	42.5%	42.7%	42.9%

FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.

Discussion

In this study, we derived reference equations for the adjusted FEF values (FEF/FVC) and provided upper- and lower limits of normal. Predicting the adjusted FEFs by using all tested explanatory variables (age, weight, and height) resulted in the best reference equations, as based on the highest adjusted R^2. Furthermore, we showed that FVC adjustment of the FEF reduces the variability statistically. Finally, we calculated new reference equations for unadjusted FEF values and demonstrated similar predictive value compared to existing reference equations (presented by Quanjer in 1993 [12] and the GLI-task force in 2012 [13]).

We compared the coefficient of variance of the adjusted FEFs to those of the unadjusted FEFs and found that the adjustment significantly decreased the variability of this parameter (Table 2), except in the FEF_{25}/FVC values. The magnitude of this reduction, however, was small and may therefore surpass clinical value. In 1974, Green [5] *et. al.* adjusted flow (FEF) for the actual lung size (using VC) in order to reduce the large intersubject variability. To their surprise, and in line with our findings, the variability only marginally decreased by this adjustment. As this result was non-significant in their small-sized study (n=56) they theorized that the FEFs are subject to substantial intersubject differences in airway size and function, independent of lung size (FVC). This independency is supported in later studies by showing that larger and central airway size is unrelated to lung size in normal adults, based on different imaging and functional techniques [23–25]. Regardless of the small reduction of the variability we propose to use the adjusted FEFs. Its value is in the improved comparability between measurements due to making it less dependent on FVC performance.

We checked the validity of the obtained reference equations on an internal and external dataset. The numerical comparison of the adjusted R^2 of the training set showed comparable adjusted R^2 values as compared to the internal and external validation set (Table 3), demonstrating the validity of the equations in other populations. As the Lifelines dataset is a representative and generalizable sample of the Dutch population [15], we consider the obtained reference equations useful for the Dutch and comparable Caucasian populations.

Notwithstanding the similarity in the fit of the equations among the datasets, the reference equations of the adjusted FEFs had only weak to modest fits, expressed as the percentage of explained variance (adjusted R^2). These were considerably lower than for the unadjusted values. We considered whether the overall relatively low predictive values of adjusted FEFs may be explained by the dependency of the FVC on age, weight, and height. Via the FVC adjustment, the FEFs are indirectly already adjusted for age, weight, and height, as the FVC also depends on these. In other words, these explanatory variables theoretically lose explanatory value when introduced in a model that predicts the adjusted FEF. If FVC would completely depend on age, weight, and height, a prediction model for the adjusted FEF could even be independent of these explanatory variables, which would result in a fixed model. We therefore investigated whether a prediction model without explanatory variables would improve the explanatory value. In all cases, the model's adjusted R^2 including the explanatory variables was significantly higher than a model without explanatory variables (supplement S3). Hence, we conclude that a reference equation including age, weight, and height is preferred overusing one constant value as a reference for the adjusted FEFs.

Next to the overall predictive value it is striking that the explanatory value of the equations, for both the adjusted and unadjusted FEFs, increases towards the end of the expiration. This means that the (un)adjusted FEF_{75} is more accurately predicted than the (un)adjusted FEF_{25}. This aligns with the theory

that the end of the expiration is progressively effort independent [26]. At the beginning of the expiration, the (un)adjusted FEF depends more on explanatory variables unaccounted for in our reference models, like muscle strength or coordination. Towards the end of the expiration, factors less influenced by effort and practice, like age, weight, and height, gain importance. Particularly age is an important contributing factor of the adjusted FEF_{75} variability as the models without age had substantially lower adjusted R^2. This is in line with the well-known age-dependency of the unadjusted FEFs. We speculate that at older age, the small airways collapse more easily than at younger age, due to loss of retractile forces on the airways and loss of alveolar wall tension. Also, decreased mucus clearance at higher age may contribute.

Even though the adjusted R^2 is comparable between datasets, the explanatory value of most of the obtained models was slightly higher in the external validation set. The external dataset also had smaller variability in adjusted FEF values (Figure 1), which theoretically may be explained by the level of compliance to ERS/ATS spirometry acceptability criteria [18]: subjects selected for the external validation dataset had to be able to perform a spirometry completely according to these criteria whereas the Lifelines subjects needed to perform clinically reliable and reproducible spirometry. We therefore checked the variability and fit of the adjusted FEFs in the 1258 (of our 14,472) subjects able to perform spirometry completely compliant to the ERS/ATS criteria, and compared them with those of the external validation set (Supplement S4). However, the variability and fit of the adjusted FEFs from this Lifelines subset was not superior (Supplement S5).

Next to adjusted FEF reference equations, we also generated unadjusted FEF reference equations (Table 4). The Quanjer reference equations from 1993 were updated by the GLI-task force in 2012, but only incorporated FEF_{75} and FEF_{25-75} equations and not FEF_{25} and FEF_{50}. Compared to Quanjer, our equations showed only a minor improvement of the adjusted R^2 (Table 5), probably due to a small

cohort effect, indicating that current cohorts have a higher mean pulmonary function compared to older cohorts [27]. In fact, this cohort effect may be a reason to prefer our equations over the unadjusted FEFs equations of Quanjer. To our surprise, the equations presented by the GLI, which were obtained with advanced statistical techniques on a more recent and more healthy cohort (compared to Quanjer), and which incorporate an age-spline [13], only had slightly higher adjusted R^2- values compared to both our equations and the 1993-equations. Apparently, the log-transformation of the explanatory variables age and height, and the age-spline have limited additional value. The need for the age-spline in the dataset used by GLI may originate from the right-skewed age distribution of the sample, with 47% of the subjects aged <20 [13]. In contrast, our Lifelines data was normally distributed around age 42 and the Fiddle dataset was uniformly distributed with regards to age. This may explain the comparability of our linear reference equations to the GLI-equations and it supports our choice to keep the model simple, without the introduction of a spline.

The strength of this study is the large sample size, collected according to the same protocol, using a unified set up by technicians with equivalent training. This ensured a large measurement homogeneity and through the selection process the data was generalizable for the Caucasian population [15]. Furthermore, all spirometries with questionable reproducibility or ERS/ATS compliance were assessed by an independent pulmonologist. In comparison, the GLI-task force had a larger but more heterogeneous dataset, as it consists of a combination of databases from 72 studies from 33 countries [13] and was therefore potentially measured according to different protocols, with several spirometry devises, operated by differently trained pulmonary technicians. Furthermore, combining different databases is likely to introduce differences in data quality. The dataset used by GLI covers a broader spectrum of subjects, which aids generalizability at the cost of introducing a larger variability in the dataset, that subsequently introduces the need for the more complicated statistics.

Conclusion

Using over 14,000 healthy subjects, we developed reference equations for FVC-adjusted FEF values. We demonstrate acceptable fits, both in internal and external data sets. Additionally, we demonstrate minimally, yet significantly improved variability as compared to unadjusted FEF values. A next step will be to evaluate the clinical relevance of the obtained reference equations in subjects with established airway disease.

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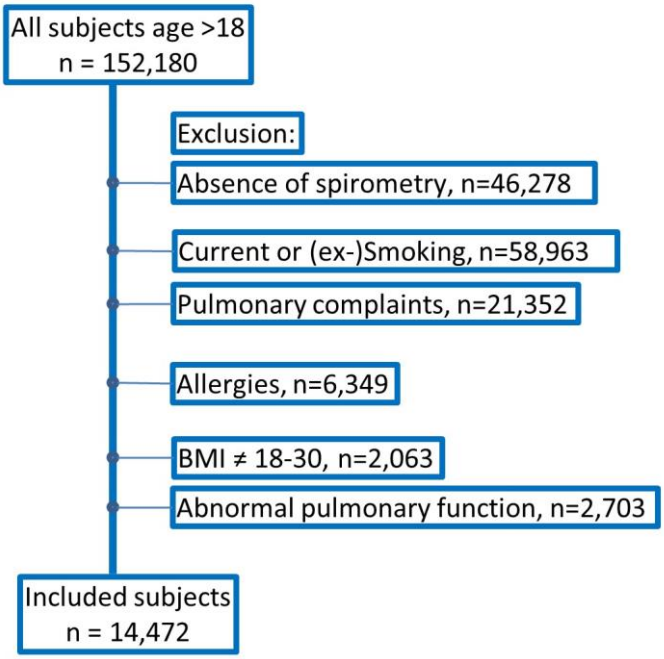
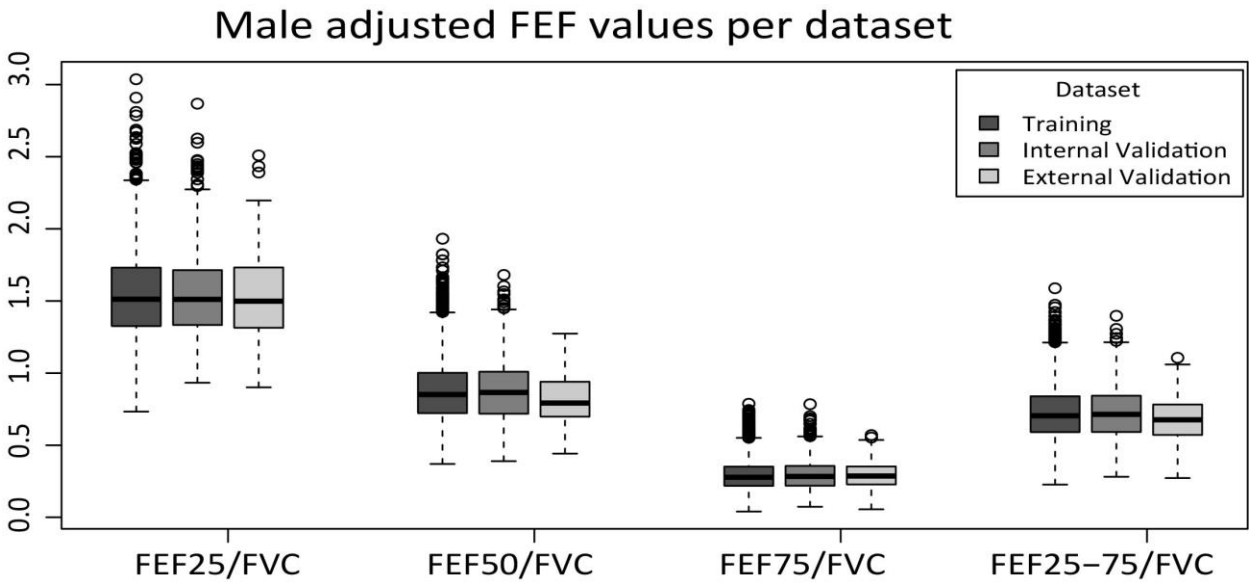
Figures

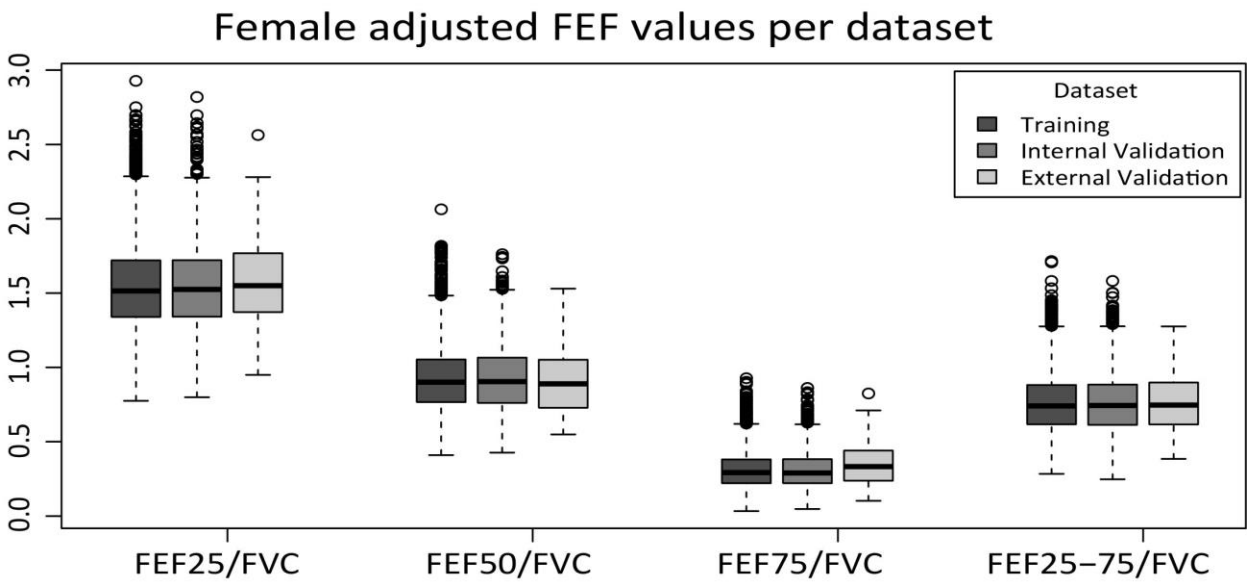
Figure 1: Overview of subject selection from the Lifelines dataset

Figure 2: Variability in the adjusted FEF, for a.) males and b.) females, per datasets

FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.


All subjects age >18
n = 152,180
Exclusion:
Absence of spirometry, n=46,278
Current or (ex-)Smoking, n=58,963
Pulmonary complaints, n=21,352
Allergies, n=6,349
BMI ≠ 18-30, n=2,063
Abnormal pulmonary function, n=2,703
Included subjects
n = 14,472


Male adjusted FEF values per dataset
Dataset
Training
Internal Validation
External Validation
0.0
0.5
1.0
1.5
2.0
2.5
3.0
FEF25/FVC
FEF50/FVC
FEF75/FVC
FEF25−75/FVC


Female adjusted FEF values per dataset
Dataset
Training
Internal Validation
External Validation
0.0
0.5
1.0
1.5
2.0
2.5
3.0
FEF25/FVC
FEF50/FVC
FEF75/FVC
FEF25−75/FVC

Supplement:

Predicted Values for the Forced Expiratory Flow Adjusted for Forced Vital Capacity, a descriptive study

Claire A. Cox, Judith M. Vonk, Huib A.M. Kerstjens, Maarten van den Berge, Nick H.T. ten Hacken

Definitions of selection criteria

From the total dataset (n=152,180) all subject who performed spirometry including a full vital capacity manoeuvre were selected (n=105,902) if their pulmonary function was clinically reliable. Clinical reliability was evaluated by the pulmonary function technician administering the test and in case of doubt the criteria were checked by an independent pulmonologist. From those subjects the pulmonary healthy never smokers were selected based on several criteria (Table S1).

1. Never-smoking; no reported current- or ex-smoker status nor a report of ever having started or stopped with smoking, and 0 calculated packyears.
2. No asthma. Asthma was defined by either a reported doctor's diagnosis of asthma or the use of pulmonary medication (see below at 9) in combination with the presence of two out of three characteristic symptoms (wheeze, a shortness of breath attack in rest during the day, or woken by).
3. No dyspnoea. Dyspnoea was defined by shortness of breath when walking with other people of equal age on level ground.
4. No wheeze. Wheeze was defined by ever wheezing or whistling in the chest
5. No attacks of shortness of breath. Attacks of shortness of breath were defined by sudden shortness of breath at rest during the day.
6. No troubled breathing. Troubled breathing was defined by ever difficulties with breathing
7. No chronic cough. Chronic cough was defined by coughing in winter first thing in the morning, during the day, or at night for most days in three consecutive months.
8. No chronic phlegm. Chronic phlegm was defined as bringing up phlegm in winter first thing in the morning, during the day, or at night for most days in three consecutive months.
9. No use of pulmonary medication. Pulmonary medication was defined as long- or short-acting β2-agonist (LABA, SABA), inhalation corticosteroid (ICS), a combination of ICS and LABA or SABA, anticholinergic, cromoglycate, theophylline, leukotriene receptor antagonist, or omalizumab.
10. No allergy. Allergy defined as self-reported reactions to dust, animals, pollen, foods, medication, contact materials (like metal and latex), and insects.
11. BMI (body mass index) between 18 and 30.
12. Pulmonary function between upper- and lower limit of normal (ULN, LLN) according to the global lung function initiative (GLI) standards [1];
    a. Forced expiratory volume in one second (FEV_1),
    b. Forced vital capacity (FVC),
    c. FEV_1/FVC.

Description of the Fiddle dataset

The Fiddle dataset is designed to generate impulse oscillometry (IOS) reference parameters. The study is registered at the research office of the University Medical Center Groningen (UMCG) under number 201501210. The ethics committee of the UMCG reviewed the study protocol and concluded that compliance to the Dutch Medical Research Involving Human Subject Act (WMO) was not required. The dataset consists of 282 subjects (138 males and 144 females). They were selected among healthy people accompanying patients (usually spouses) visiting the pulmonary function department of the UMCG. To be eligible they had to be healthy; without (self-reported) allergies and respiratory complaints in the past or present, or any pulmonary diagnosis, with <1 packyear of smoking history. This information was assessed with the screenings questionnaire of the European Community Respiratory Health Survey the Netherlands (ECRHS; Europees Luchtweg Onderzoek Nederland (ELON)) [2]. Furthermore, spirometry had to be compliant with ERS/ATS standards, the FEV_1 >80% and FEV_1/FVC >70%. Subjects were included to have a uniform age and sex distribution.

Table S1: Number (#) of subjects fulfilling the criteria used to select healthy subjects

Selection criteria	# cases remaining	# cases in total population
All subjects	152180	152180 (100%)
Performed spirometry*, including FEFs	105902	105902 (69.6%)
Never smokers	46939	67512 (44.4%)
Without dyspnoea	40885	129777 (85.3%)
Without wheeze	34563	117350 (77.1%)
Without shortness of breath attacks	28864	103837 (68.2%)
Without troubled breathing	26898	113447 (74.5%)
Without cough (≥3 months)	26143	136374 (89.6%)
Without phlegm (≥3 months)	25716	138374 (90.9%)
Without pulmonary medication	25587	141614 (93.1%)
Without self-reported allergy	19238	103904 (68.3%)
BMI 18-30	17175	127928 (84.1%)
FEV1 (>LLN, < ULN)	15972	94723 (62.2%)
FVC (>LLN, < ULN)	15436	98771 (64.9%)
FEV1/FVC (>LLN, < ULN)	14472	92352 (60.7%)

* All spirometries which included a full-FVC manoeuvre were clinically reliable, in the entire population 7126 (4.7%) performed clinically unreliable spirometry.
BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FEFs: forced expiratory flows; LLN: lower limit of normal; ULN: upper limit of normal.

S2a: Characteristics per group, the groups used to train and validate the equations.

	Males			**Females**		
	LifeLines Trainings data n=4846	Internal Validation N=1208	External validation n=170	LifeLines Trainings data n=6736	Internal validation n=1682	External validation n=168
Age (years)	42(11.6)	42 (11.6)	43 (15.5)	42 (12.4)	42 (12.7)	40 (14.2)
Age distribution min-max; IQR (years)	18-80; 34-49	18-79; 34-49	18-78; 29-57	18-85; 33-48	18-84; 32-49	18-76; 32-49
Length (cm)	183 (6.7)	184 (6.9)	182 (7.0)*	170 (6.4)	170 (6.4)	170 (6.3)
Weight (kg)	84 (9.8)	84 (9.9)	80 (10.0)*	69 (8.9)	69 (7.8)	67 (9.1)*
BMI (kg/m^2)	24.9 (2.5)	25.0 (2.5)	24.2 (2.61)*	23.9 (2.8)	23.9 (2.7)	23.0 (3.1)*
FEV_1 (L)	4.40 (0.63)	4.42 (0.65)	4.51 (0.72)	3.19 (0.49)	3.19 (0.50)	3.41 (0.56)*

FEV_1 percentage predicted (%)	99 (9.1)	99 (9.4)	105 (11.9)*	98 (9.2)	98 (9.4)	104 (10.7)*
FVC (L)	5.58 (0.74)	5.60 (0.77)	5.77 (0.88)*	3.99 (0.56)	3.99 (0.56)	4.22 (0.57)*
FVC percentage predicted (%)	100 (9.0)	100 (9.3)	107 (12.3)*	101 (9.4)	101 (9.6)	106 (10.0)*
FEV_1/FVC (%)	78.9 (4.9)	79.0 (4.9)	78.2 (4.8)	79.8 (5.2)	79.8 (5.3)	80.7 (5.8)
FEF_{25} (L/s)	8.50 (1.56)	8.52 (1.55)	8.72 (1.64)	6.10 (1.13)	6.12 (1.16)	6.53 (1.24)*
FEF_{25} percentage predicted (%)	#	#	#	#	#	#
FEF_{50} (L/s)	4.87 (1.22)	4.89 (1.22)	4.71 (1.15)	3.67 (0.91)	3.69 (0.94)	3.83 (1.03)*
FEF_{50} percentage predicted (%)	#	#	#	#	#	#
FEF_{75} (L/s)	1.63 (0.63)	1.65 (0.64)	1.70 (0.65)	1.25 (0.54)	1.26 (0.55)	1.49 (0.65)*
FEF_{75} percentage predicted (%)	101 (29.7)	102 (30.6)	111(35.1)*	96 (30.2)	96 (30.7)	109 (34.5)*
FEF_{25-75} (L/s)	4.03 (1.10)	4.06 (1.09)	3.96 (1.03)	3.03 (0.86)	3.04 (0.89)	3.27 (0.98)*
FEF_{25-75} percentage predicted (%)	96 (22.3)	97 (22.2)	99 (22.6)	92 (20.5)	92 (21.0)	98 (22.5)*

Data are presented as mean (standard deviation). Predicted values are according to the GLI equations. # No reference values provided by the GLI. *A significant difference compared to the training data.
BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC, IQR: interquartile range.

S2b: Overview of adjusted FEFs for the groups used to train and validate the equations.

	Males			**Females**		
	LifeLines Trainings data n=4846	Internal Validation n=1208	External validation n=170	LifeLines Trainings data n=6736	Internal validation n=1682	External validation n=168
FEF_{25}/FVC (s^{-1})	1.54 (0.30)	1.54 (0.29)	1.53 (0.31)	1.54 (0.29)	1.55 (0.29)	1.56 (0.28)
FEF_{50}/FVC (s^{-1})	0.88 (0.21)	0.88 (0.21)	0.82 (0.17)*	0.92 (0.21)	0.93 (0.22)	0.91 (0.21)
FEF_{75}/FVC (s^{-1})	0.29 (0.11)	0.29 (0.10)	0.29 (0.10)	0.31 (0.12)	0.31 (0.13)	0.35 (0.14)*
FEF_{25-75}/FVC (s^{-1})	0.72 (0.19)	0.73 (0.18)	0.68 (0.15)*	0.76 (0.19)	0.76 (0.20)	0.77 (0.20)

Data are presented as mean (standard deviation). *A significant difference compared to the training data.
FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.

S3: Regression equations, per adjusted FEF, for all combinations of the selected explanatory parameters (age, weight, and height), including the residual standard deviation (RSD). For all adjusted FEFs the model including all parameters had the highest adjusted R^2. The model with all parameters (last column) was compared to the model with no explanatory parameters (first column).

S3a: Males

FEF_{25}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	1.540	1.427	1.649	3.488	3.327	3.690	1.551	**3.563**
Age		0.0027			0.0152		0.0028	**0.0010**
Weight			-0.0013			0.0034	-0.0015	**0.0032**
Height				-0.0106	-0.0109	-0.0133		**-0.0127**
RSD	0.297	0.295	0.296	0.288	0.288	0.287	0.295	**0.286**
R^2	0.0001	0.011	0.002	0.057	0.061	0.067	0.014	**0.069**
R^2-adjusted	<0	0.011	0.002	0.057	0.060	0.067	0.013	**0.068***

FEF_{50}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	0.878	1.028	0.962	1.473	1.908	1.487	1.086	**2.016**
Age		-0.0036			-0.0041		-0.0035	**-0.0043**
Weight			-0.0010			0.0002	-0.0007	**0.0015**
Height				-0.0032	-0.0047	-0.0034		**-0.0059**
RSD	0.212	0.208	0.211	0.211	0.205	0.211	0.208	**0.205**
R^2	$3.9 \cdot 10^{-7}$	0.038	0.002	0.011	0.059	0.011	0.039	**0.062**
R^2-adjusted	<0	0.038	0.002	0.010	0.059	0.010	0.039	**0.062***

FEF_{75}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	0.291	0.516	0.421	0.172	0.754	0.0298	0.608	**0.684**
Age		-0.0053			-0.0055		-0.0053	**-0.0053**
Weight			-0.0015			-0.0025	-0.0011	**-0.0009**
Height				0.0007	-0.0013	0.0026		**-0.0005**
RSD	0.105	0.085	0.104	0.105	0.085	0.103	0.084	**0.084**
R^2	$4.8 \cdot 10^{-5}$	0.348	0.021	0.0002	0.354	0.040	0.359	**0.360**
R^2-adjusted	<0	0.348	0.021	0.002	0.354	0.039	0.3588	**0.3594***

FEF_{25-75}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	0.723	0.982	0.852	0.974	1.671	0.891	1.067	**1.704**
Age		-0.0061			-0.0066		-0.0061	**-0.0066**
Weight			-0.0015			-0.0014	-0.0010	**0.0005**
Height				-0.0014	-0.0037	-0.0003		**-0.0040**
RSD	0.185	0.171	0.185	0.185	0.169	0.185	0.174	**0.169**
R^2	$2.1 \cdot 10^{-6}$	0.149	0.007	0.002	0.166	0.007	0.152	**0.166**
R^2-adjusted	<0	0.149	0.006	0.002	0.165	0.006	0.152	**0.166***

*: model significantly better than the model without any explanatory variables.
FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.
R^2: proportion explained variance; $R^2_{\text{-adjusted}}$: R^2 adjusted for number of variables in the model.

S3b: Females

FEF_{25}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	1.542	1.492	1.616	3.342	3.355	3.456	1.571	**3.524**
Age		0.0012			-0.0001		0.0012	**-0.0005**
Weight			-0.0011			0.0030	-0.0012	**0.0031**
Height				-0.0106	-0.0106	-0.0125		**-0.0128**
RSD	0.287	0.287	0.287	0.279	0.279	0.278	0.287	**0.278**
R^2	$9.0 \cdot 10^{-5}$	0.003	0.001	0.055	0.055	0.062	0.004	**0.063**
R^2-adjusted	<0	0.003	0.001	0.055	0.055	0.0618	0.004	**0.0622***

FEF_{50}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	0.922	1.099	0.992	1.389	1.977	1.383	1.144	**2.047**
Age		-0.0042			-0.0049		-0.0042	**-0.0050**
Weight			-0.001			-0.0016	-0.0007	**0.0013**
Height				-0.0027	-0.0050	-0.0026		**-0.0059**
RSD	0.210	0.204	0.210	0.209	0.201	0.209	0.203	**0.201**
R^2	0.0003	0.063	0.002	0.007	0.084	0.007	0.063	**0.087**
R^2-adjusted	<0	0.063	0.002	0.007	0.084	0.007	0.063	**0.086***

FEF_{75}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	0.311	0.573	0.443	0.019	0.799	-0.100	0.668	**0.731**
Age		-0.006			-0.0064		-0.0062	**-0.0063**
Weight			-0.0019			-0.0031	-0.0014	**-0.0013**
Height				0.0017	-0.0013	-0.0037		**-0.0004**
RSD	0.123	0.096	0.122	0.123	0.095	0.120	0.095	**0.095**
R^2	0.0001	0.400	0.019	0.008	0.404	0.048	0.410	**0.411**
R^2-adjusted	<0	0.400	0.019	0.008	0.404	0.048	0.4100	**0.4104***

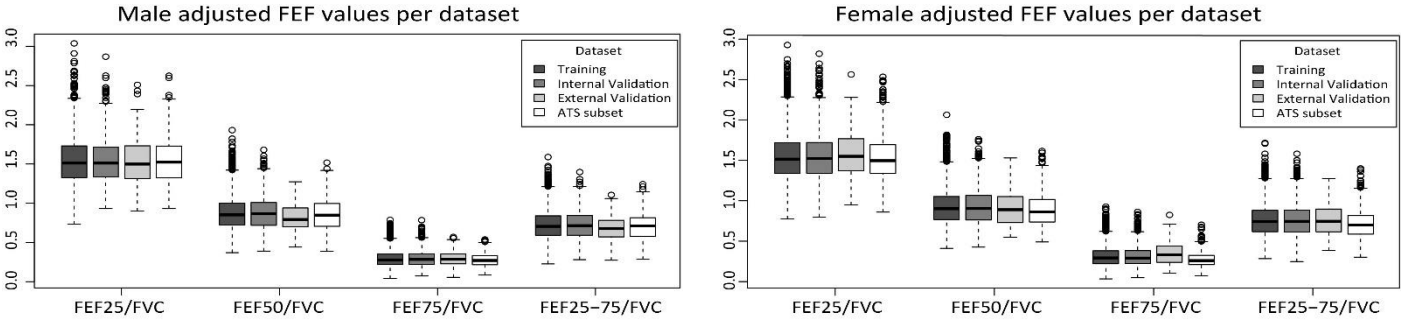
FEF_{25-75}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	0.758	1.065	0.886	0.806	1.755	0.721	1.150	**1.760**
Age		-0.0074			-0.0078		-0.0073	**-0.0079**
Weight			-0.0018			-0.0022	-0.0013	**0.00009**
Height				-0.0003	-0.0039	0.0011		**-0.0040**
RSD	0.195	0.172	0.194	0.195	0.170	0.194	0.171	**0.170**
R^2	0.0005	0.220	0.007	0.00009	0.236	0.008	0.224	**0.236**
R^2-adjusted	<0	0.220	0.007	<0	0.236	0.008	0.223	**0.236***

*: model significantly better than the model without any explanatory variables.

FVC: forced vital capacity; FEF_x: forced expiratory flow at 25%, 50%, 75% and 25-75% of FVC.

R^2: proportion explained variance; $R^2_{\text{-adjusted}}$: R^2 adjusted for number of variables in the model.

S4: Box plots of observed adjusted FEF values per group for a.) males and b.) females, illustrating the dispersion of the data.



S5: Percentage of explained variance per dataset for the FEF/FVC equations

	Males				Females			
	Training	ATS subset	Internal validation	External validation	Training	ATS subset	Internal validation	External validation
FEF_{25}/FVC (s^{-1})	6.79%	5.71%	6.48%	13.16%	6.21%	7.79%	5.82%	4.56%
FEF_{50}/FVC (s^{-1})	6.17%	9.17%	4.76%	4.04%	8.64%	6.20%	9.54%	9.32%
FEF_{75}/FVC (s^{-1})	35.9%	25.9%	32.1%	37.8%	41.0%	29.5%	41.5%	46.0%
FEF_{25-75}/FVC (s^{-1})	16.6%	15.2%	13.8%	14.9%	23.6%	16.0%	24.1%	25.2%

References

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