Supplement:

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

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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***

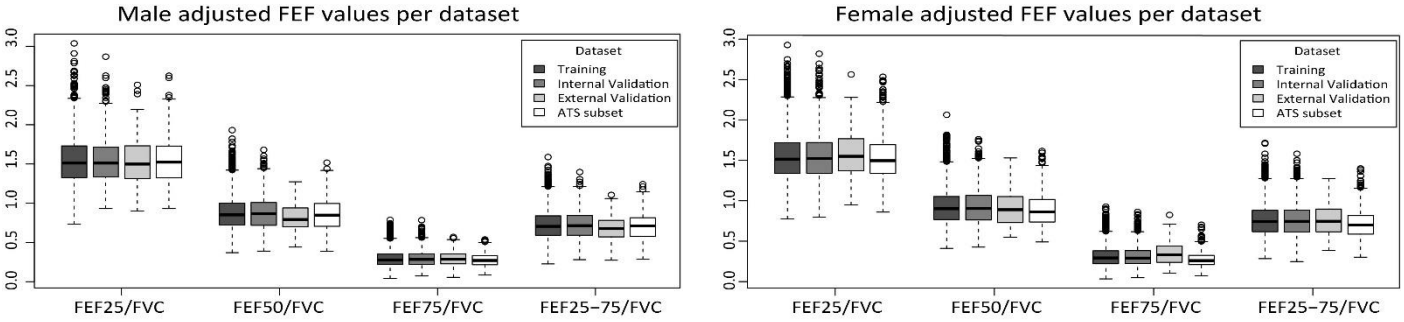
FEF_{25-75}/FVC	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Constant	0.758	1.065	0.886	0.806	1.755	0.721	1.150	**1.760**
Age		-0.0074			-0.0078		-0.0073	**-0.0079**
Weight			-0.0018			-0.0022	-0.0013	**0.00009**
Height				-0.0003	-0.0039	0.0011		**-0.0040**
RSD	0.195	0.172	0.194	0.195	0.170	0.194	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

1. Quanjer PH, Stanojevic S, Cole TJ, Stocks J. Implementing GLI 2012 regression equations. *Eur. Respir. J.* 2013; 2: 1–11.

2. Smit HA, Beaumont M. De morbiditeit van astma en COPD in Nederland; een inventariserend onderzoek ten behoeve van de beleidsondersteuning van het Nederlands Astma Fonds. *RIVM 260855 001* 2000; : 17.