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Spirometric Reference Values for Advanced Age from a South German Population

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Key Words
Spirometry · Prediction equations · Ageing · Elderly · Quantile regression

Abstract
Background: The diagnostic use of lung function using spirometry depends on the validity of reference equations. A multitude of spirometric prediction values have been published, but in most of these studies older age groups are underrepresented. ***Objectives:*** The aim of the present study was to establish new spirometric reference values for advanced age and to compare these to recent prediction equations from population-based studies. ***Methods:*** In the present study spirometry was performed in a population-based sample from the KORA-F4 and KORA-Age cohorts (2006–2009, Augsburg, Germany) comprising 592 never-smoking subjects aged 42–89 years and with no history of respiratory disease. Using quantile regression analysis, equations for the median and lower limit of normal were derived for indices characterizing the expiratory flow-volume curve: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow (PEF), and forced expiratory flow rates at 25, 50 and 75% of exhaled FVC (FEF_{25}, FEF_{50} and FEF_{75}). ***Results:*** FEV_1 and FVC were slightly higher, and PEF was lower compared to recently published equations. Importantly, forced expiratory flow rates at middle and low lung volume, as putative indicators of small airway disease, were in good agreement with recent data, especially for older age. ***Conclusion:*** Our study provides up-to-date reference equations for all major indices of flow-volume curves in middle and advanced age in a South German population. The small deviations from published equations indicate that there might be some regional differences of lung function within the Caucasian population of advanced age in Europe.

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Introduction

Spirometry still is the basis of lung function assessment in clinical practice and epidemiology. The adequacy of reference values is essential for the correct interpretation of these measurements and ATS/ERS guidelines have recommended the application of population-specific reference equations in Europe [1]. In the last decade, several studies – among them studies from Switzerland [2] and Germany [3] that include subjects over 70 years of age – have generated up-to-date reference values. These have revealed that, for example, the equations from the European Community of Coal and Steel (ECCS) [4], which still are widely used in Europe, nowadays yield values which are too low, particularly those of FVC and FEV_1 [2, 3, 5–7]. Moreover, an initiative has been started to collate data from a multitude of studies performed worldwide to derive adequate reference values for all age ranges [8].

In many of the existing studies, subjects of advanced age of over 70 years are underrepresented compared to younger individuals. Depending on the applied statistical instruments, this can lead to inadequate reference equations for this age group, which is of relevance in view of the ageing populations in many countries. Of particular value would be validated reference data for the various forced expiratory flow rates in subjects of this advanced age. These measures are often considered as indicative of the beginning of small airway disease [9] but heavily depend on the cooperation of the subjects. It is, therefore, of special importance to achieve a high quality of measurements and of subject characterization.

The present study aims to bridge this gap by providing up-to-date reference equations of flow-volume curves for subjects over the age of 45 years. Data were taken from a random population sample of the Augsburg region in Southern Germany, with an approximately equal representation of middle and advanced age. The results were compared with ECCS [4] predictions and recent equations from population-based studies including a higher number of older adults [2, 3, 5, 6].

Methods

Assessment of Lung Function

Indices of the flow-volume curve were assessed in two studies covering different age ranges. In KORA-F4, 1,321 subjects aged 41–63 years were examined between 2006 and 2008, and in KORA-Age, 935 subjects aged 65–90 years were examined in 2009. Measurement conditions including the major examiners were the same in both studies. KORA-F4 and KORA-Age were based on a representative population cohort from the Augsburg region (KORA, Cooperative Health Research in the Augsburg Region, Germany) and were follow-up studies of the MONICA/KORA surveys S1–S4. Both studies were approved by the Ethics Committee of the Bavarian Medical Association. Details of the KORA platform and surveys have been described previously [10, 11]. The subjects of both studies were recruited in separate age groups to achieve an equal distribution over the age range. There was only a minor gap between 62 and 65 years at the interface between both studies.

Standard spirometry was performed in line with the ATS/ERS recommendations [12] in a sitting position while subjects were wearing noseclips. The procedure was performed using a pneumotachograph-type spirometer (Masterscope PC; CareFusion, Höchberg, Germany) with a resistance of 0.05 $kPa \cdot l^{-1} \cdot s^{-1}$ at 10 $l \cdot s^{-1}$ and a volume accuracy of ± 5 ml. While bronchodilation with 200 μg salbutamol was performed in 71% of subjects from the KORA-F4 cohort, only prebronchodilator results were used for the current combined analysis of both cohorts. We put particular emphasis on obtaining optimal flow-volume curves in up to 8 trials under the guidance of specifically trained and experienced personnel. The participants performed at least three spirometric maneuvers in order to obtain a minimum of two acceptable and reproducible values. During the maneuvers both flow-volume and volume-time curves were monitored online by the examiner. After each test, the curves were visually inspected, artifacts were excluded and the results were selected and evaluated according to the ATS/ERS recommendations [12]. The spirometer was calibrated daily using a calibration pump supplied by the manufacturer. In addition, daily self-testing of the examiners was done.

The indices measured were forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), the ratio FEV_1/FVC, peak expiratory flow (PEF), and forced expiratory flow rates taken from the trial with the largest sum of FEV_1 and FVC at 25, 50 and 75% of exhaled FVC (FEF_{25}, FEF_{50} and FEF_{75}).

Known acute or chronic respiratory diseases and smoking status, as well as the presence of non-lung diseases (cardiac, gastrointestinal, renal, neurological and eye diseases as well as diabetes mellitus and cancer) were assessed by a detailed questionnaire within the comprehensive KORA assessments. Standing height and weight were measured on the day of examination with the subjects wearing light clothes without shoes. After the exclusion of subjects with a history of respiratory diseases such as asthma or COPD and ever-smokers, the final sample for the generation of reference values comprised 311 subjects aged 42–62 years from KORA-F4, and 281 subjects aged 65–89 years from KORA-Age. Descriptive data of the cohorts are shown in table 1a, and the age distribution is shown in table 1b.

Statistical Analyses

Quantile regression models [13] were used to derive reference equations. Prediction equations were derived for both the median and the lower limit of normal (LLN), i.e. the 5th percentile. Since body mass index (BMI, computed as weight over height-squared) has been reported to have a significant influence on spirometric indices [14, 15], a sex-specific quantile regression model was tested with age, height and BMI as predictors. However, in the present study, BMI was nonsignificant for all lung function parameters

Table 1. Samples from KORA-F4 and KORA-Age

a Descriptive data, mean ± SD or percentage

	KORA-F4		KORA-Age	
	men	women	men	women
Subjects, n	114	197	98	183
Age, years	52.3 ± 5.7	52.3 ± 5.9	75.9 ± 6.1	76.5 ± 6.1
Height, cm	176.6 ± 6.6	162.7 ± 5.9	170.8 ± 6.5	157.6 ± 6.3
Weight, kg	85.2 ± 11.9	69.9 ± 12.7	80.6 ± 11.4	69.8 ± 10.9
BMI	27.4 ± 3.7	26.4 ± 4.7	27.6 ± 3.5	28.1 ± 4.2
Prevalence of non-lung diseases, %	19.3	26.4	54.1	68.9

b Age distribution

Age	Men, n (%)	Women, n (%)
40–49 years	45 (21.2)	76 (20.0)
50–59 years	58 (27.4)	100 (26.3)
60–69 years	30 (14.2)	54 (14.2)
70–79 years	51 (24.1)	89 (23.4)
80–89 years	28 (13.2)	61 (16.1)

except for the FEV_1 and FVC median in men, and the FVC and FEV_1/FVC median as well as the FVC LLN in women and had only minor effects on the quality of the fit. These findings are in line with a recent study demonstrating that apart from sex, age and height other determinants explain only a small fraction of lung function variance [16]. The present analysis was thus restricted to sex-specific regression models describing the relationship between lung function indices (LF), age and height.

Two types of regression models were analysed, either additive polynomial, $LF = b_0 + b_1 \times height + b_2 \times height^2 + b_3 \times age + b_4 \times age^2$, or as a power law with various functions of age, $LF = e^{k_1} \times height^{k_2} \times f(age)$, based on the approach by Cole [17]. To perform the regression analysis for the power law model, the logarithm of LF was analysed against the logarithm of height and functions of age. It turned out that different versions of the age relationship did not improve the prediction over that of a linear age term against the logarithm of LF. Regarding the quality of the fit, the power law model was superior to the additive model for all LF. Thus, the multiplicative model with a linear age term was chosen as the final model for prediction [$\ln(LF) = k_1 + k_2 \cdot \ln(height) + k_3 \cdot age$].

In a second step, the spirometric values observed were compared with prediction equations proposed by the ECCS [4] and recent studies [2, 3, 5, 6]. Differences between the predicted and the observed values were expressed as the mean difference in percent of the mean observed values. In addition, the proportion of observed values below the predicted LLN of the respective reference equations was determined. Bland-Altman plots [18] were generated to visualize the differences between predicted values based on the equations from the present study and those from the other studies.

All analyses were performed using the statistical software R, version 2.11.1. [19], and p values <0.05 were considered statistically significant. Additional graphs were generated using the software package Sigmaplot (Systat Software, San Jose, Calif., USA).

Results

Data of flow-volume curves are shown in table 2, separately for the KORA-F4 and KORA-Age cohorts. The equations for the median and 5th percentile (LLN) are provided in table 3a and b. As can be seen in table 4a and b, the values of FEV_1 and FVC in the present study were higher than those in other studies. The differences ranged between 2.6 and 18.3% in men and 2.8 and 21.2% in women. The percentages of values below the LLN also differed from other studies. These percentages mostly ranged below 2% (instead of 5%), with the exception of the FEV_1 in men (8.5%) in the study by Koch et al. [3]. The differences in the prediction equations for FEV_1 and FVC also became obvious in the Bland-Altman plots (fig. 1a, b). The greatest difference in the predicted FEV_1 and FVC occurred in comparison to the study by Smolej-Narancic et al. [6] and the ECCS values [4].

Regarding the ratio FEV_1/FVC, the values observed in the present study were close to the data by Falaschetti et

Table 2. Data of flow-volume curves from KORA-F4 and KORA-Age, median (25th; 75th percentile)

	KORA-F4		KORA-Age	
	men	women	men	women
FVC, l	5.07 (4.57; 5.72)	3.63 (3.23; 4.10)	4.11 (3.72; 4.45)	2.75 (2.41; 3.13)
FEV_1, l	4.14 (3.67; 4.54)	2.87 (2.60; 3.31)	3.17 (2.69; 3.57)	2.10 (1.84; 2.42)
FEV_1/FVC	0.80 (0.77; 0.82)	0.80 (0.77; 0.83)	0.76 (0.73; 0.81)	0.77 (0.73; 0.81)
PEF, l × s^{-1}	9.24 (7.90; 10.62)	6.32 (5.47; 7.15)	7.24 (5.92; 8.15)	4.89 (3.98; 5.94)
FEF_{25}, l × s^{-1}	8.24 (7.18; 9.31)	5.74 (4.97; 6.65)	6.34 (5.39; 7.48)	4.47 (3.64; 5.37)
FEF_{50}, l × s^{-1}	4.78 (4.10; 5.67)	3.60 (3.01; 4.30)	3.51 (2.79; 4.38)	2.49 (1.81; 3.12)
FEF_{75}, l × s^{-1}	1.49 (1.24; 1.89)	1.10 (0.84; 1.43)	0.88 (0.62; 1.22)	0.56 (0.42; 0.77)

Table 3. Reference equations

a For men

50th percentile	
FEV_1, l	exp(−7.0582685 + 1.7333992 × ln(H) − 0.0094511 × A)
FVC, l	exp(−8.0537240 + 1.9555357 × ln(H) − 0.0078653 × A)
FEV_1/FVC	exp(1.3632831 − 0.2818021 × ln(H) − 0.0024269 × A)
PEF, l × s^{-1}	exp(−2.5959640 + 1.0137804 × ln(H) − 0.0083959 × A)
FEF_{25}, l × s^{-1}	exp(−2.9874839 + 1.0779635 × ln(H) − 0.0092600 × A)
FEF_{50}, l × s^{-1}	exp(0.1378636 + 0.4205740 × ln(H) − 0.0137427 × A)
FEF_{75}, l × s^{-1}	exp(−7.4480822 + 1.7448540 × ln(H) − 0.0222180 × A)
5th percentile (LLN)	
FEV_1, l	exp(−8.3950574 + 1.9921763 × ln(H) − 0.0141056 × A)
FVC, l	exp(−8.0982157 + 1.9420799 × ln(H) − 0.0099251 × A)
FEV_1/FVC	exp(2.8334625 − 0.5283780 × ln(H) − 0.0078468 × A)
PEF, l × s^{-1}	exp(−3.5547460 + 1.2103164 × ln(H) − 0.0158704 × A)
FEF_{25}, l × s^{-1}	exp(−4.3742809 + 1.3784100 × ln(H) − 0.0190698 × A)
FEF_{50}, l × s^{-1}	exp(−4.6945760 + 1.3988833 × ln(H) − 0.0270016 × A)
FEF_{75}, l × s^{-1}	exp(−6.0518646 + 1.5263951 × ln(H) − 0.0364690 × A)

b For women

50th percentile	
FEV_1, l	exp(−9.8813308 + 2.2680933 × ln(H) − 0.0111944 × A)
FVC, l	exp(−10.8652593 + 2.4767262 × ln(H) − 0.0085479 × A)
FEV_1/FVC	exp(1.8917901 − 0.3936925 × ln(H) − 0.0020476 × A)
PEF, l × s^{-1}	exp(−5.6346321 + 1.5706259 × ln(H) − 0.0095855 × A)
FEF_{25}, l × s^{-1}	exp(−4.6846464 + 1.3519360 × ln(H) − 0.0086867 × A)
FEF_{50}, l × s^{-1}	exp(0.4949622 + 0.3042329 × ln(H) − 0.0147274 × A)
FEF_{75}, l × s^{-1}	exp(−0.9308838 + 0.4544576 × ln(H) − 0.0253354 × A)
5th percentile (LLN)	
FEV_1, l	exp(−7.9236784 + 1.8464260 × ln(H) − 0.0125501 × A)
FVC, l	exp(−10.8547314 + 2.4425959 × ln(H) − 0.0098406 × A)
FEV_1/FVC	exp(1.6130399 − 0.3287409 × ln(H) − 0.0048989 × A)
PEF, l × s^{-1}	exp(−8.3982765 + 2.0735135 × ln(H) − 0.0129122 × A)
FEF_{25}, l × s^{-1}	exp(−7.1508550 + 1.8017099 × ln(H) − 0.0127377 × A)
FEF_{50}, l × s^{-1}	exp(−1.0823057 + 0.6561240 × ln(H) − 0.0269702 × A)
FEF_{75}, l × s^{-1}	exp(−4.0615846 + 1.0931529 × ln(H) − 0.0366013 × A)

A = Age (years); H = height (cm).

Table 4. Differences between observed values and predictions [2–6]

a For men

Parameter	Study	Mean difference, %	Observed values below LLN, %
FEV_1	Koch et al.	2.5891	8.4906
	Smolej-Narancic et al.	18.0199	0
	Falaschetti et al.	11.1665	1.4151
	Kuster et al.	10.1728	1.8868
	ECCS	13.7025	0
FVC	Koch et al.	7.0920	3.3019
	Smolej-Narancic et al.	18.3201	0
	Falaschetti et al.	9.1528	0.4717
	Kuster et al.	10.5713	0.9434
	ECCS	13.5606	0.9434
FEV_1/FVC	Koch et al.	–6.0986	8.9623
	Falaschetti et al.	–0.3921	1.4151
	Kuster et al.	–0.3264	4.2453
	ECCS	2.9786	1.8868
PEF	Smolej-Narancic et al.	2.1244	5.6604
	Kuster et al.	–16.5507	21.2264
	ECCS	2.3230	12.7358
FEF_{25}	Kuster et al.	–4.8930	5.6604
	ECCS	1.4061	4.2453
FEF_{50}	Kuster et al.	9.1512	3.3019
	ECCS	0.3071	2.3585
FEF_{75}	Kuster et al.	11.5213	1.8868
	ECCS	–18.7135	0

b For women

FEV_1	Koch et al.	2.8317	1.3158
	Smolej-Narancic et al.	18.9824	0.2632
	Falaschetti et al.	11.6610	1.0526
	Kuster et al.	10.6383	1.3158
	ECCS	16.0669	0.2632
FVC	Koch et al.	12.3886	1.0526
	Smolej-Narancic et al.	20.7200	0.2632
	Falaschetti et al.	12.9147	0.2632
	Kuster et al.	11.6468	0.2632
	ECCS	21.2302	0
FEV_1/FVC	Koch et al.	–6.0082	27.1053
	Falaschetti et al.	–1.3395	5.0000
	Kuster et al.	–2.2284	4.2105
	ECCS	1.8187	1.5789
PEF	Smolej-Narancic et al.	12.1155	0.2632
	Kuster et al.	–15.8272	20.2632
	ECCS	–2.3073	13.9474
FEF_{25}	Kuster et al.	–7.2208	8.4211
	ECCS	0.0724	1.0526
FEF_{50}	Kuster et al.	2.7279	3.9474
	ECCS	–11.2562	3.6842
FEF_{75}	Kuster et al.	1.7020	1.5789
	ECCS	–32.1169	0

al. [5] and Kuster et al. [2] (mean differences –0.32% to –2.23%, respectively), but markedly lower than Koch et al. [3]. Importantly, a steeper decrease occurred in both sexes, especially in the LLN. This is illustrated for a specific example in figure 2.

The differences between the forced expiratory flow rates and those of other studies were heterogeneous. While PEF and FEF_{25} were generally in accordance with the ECCS mean values [4], they were markedly lower (about 15% for PEF and 6% for FEF_{25}) than those predicted by Kuster et al. [2]. This difference was lower and even became opposite for FEF_{50} and FEF_{75}, particularly in men. The LLN for PEF in the current study was markedly lower than that predicted by Kuster et al. [2] and the ECCS [4]. For the other forced expiratory flow rates the LLN values of the present study tended to be higher than the ECCS values in late adulthood, but were in good agreement with the values supplied by Kuster et al. [2] for subjects over 65 years of age. This is illustrated by an example in figure 3.

Discussion

The present study provides up-to-date reference values of lung function in middle and advanced age. The equations for the median and LLN for indices of flow-volume curves including forced expiratory flow rates are based on a random population sample of 592 never-smoking subjects without a history of respiratory disease. As the number of subjects thinned out towards the ends of the age and height ranges, thus diminishing predictive reliability, we consider the use of our equations as justified for an age of 45–85 years, and for heights of 160–190 cm in men and 145–175 cm in women.

Reference values for lung function parameters have often been based on standard multiple regression models. However, this approach requires data properties that may be violated for spirometric indices, e.g. a normally distributed outcome variable and homoscedasticity. To avoid these problems, we used quantile regression, a method that has recently been applied to model spirometric data [3, 14]. In contrast to standard regression, quantile regression requires no assumption on outcome distribution and is more robust against data outliers or skewed distributions. It allows an adequate estimation of the percentiles of the target variable even if there is a strong dependence on covariates such as height or age [20]. As an alternative approach, generalized additive models for location, scale and shape (GAMLSS) [21] have

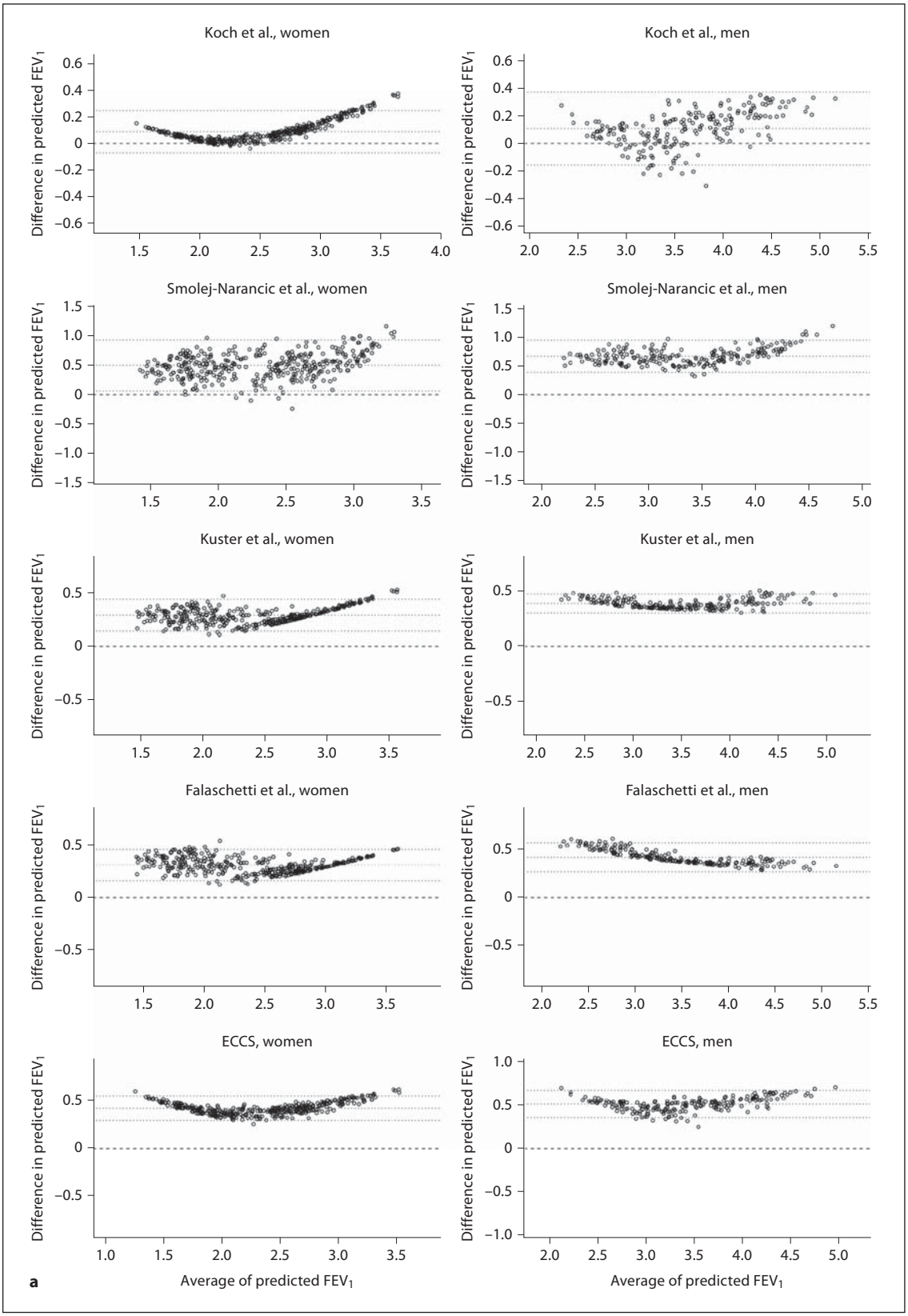

Fig. 1. a Bland-Altman plots for FEV_1 in women and men.

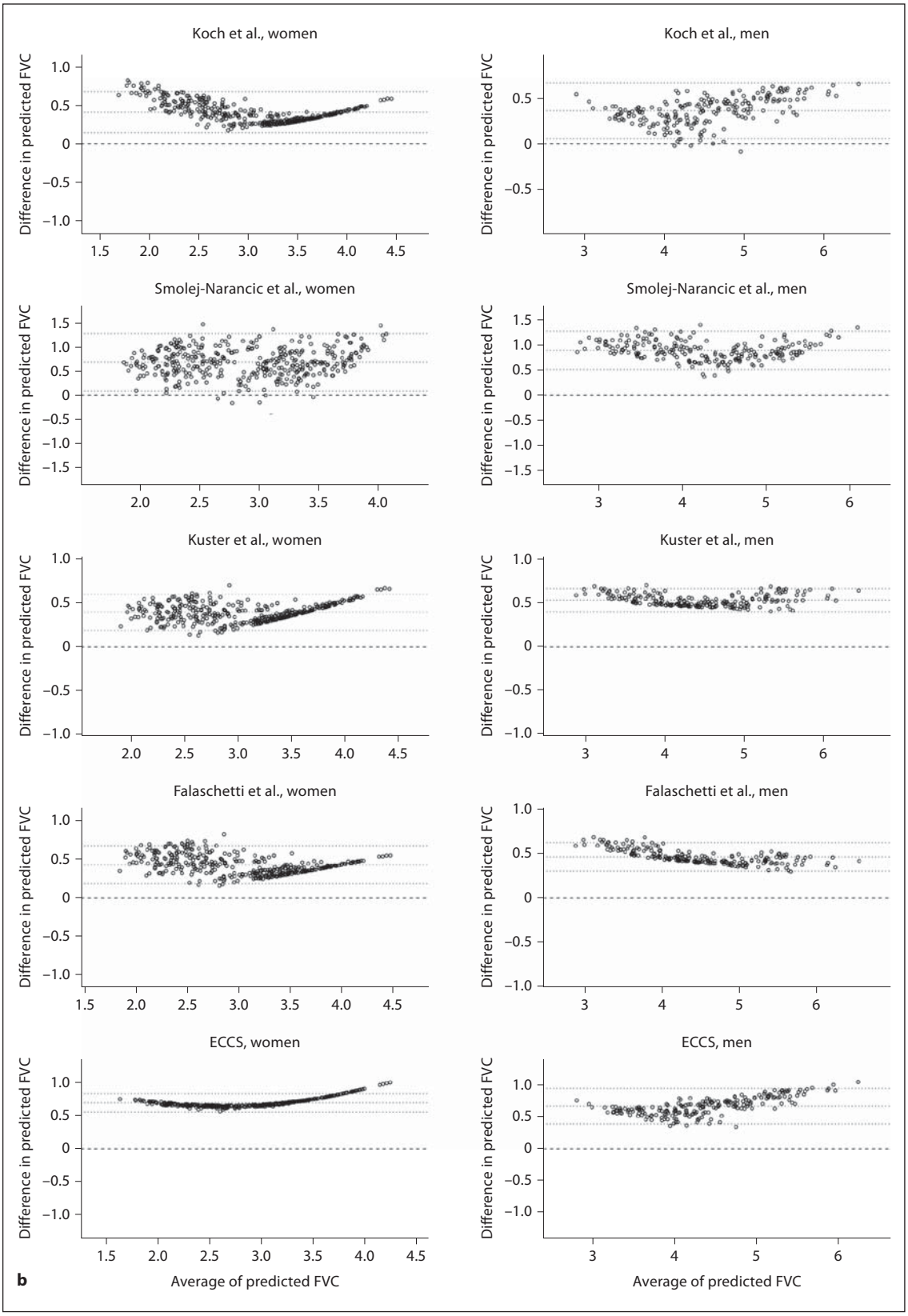

Fig. 1. b Bland-Altman plots for FVC in women and men [2–6].

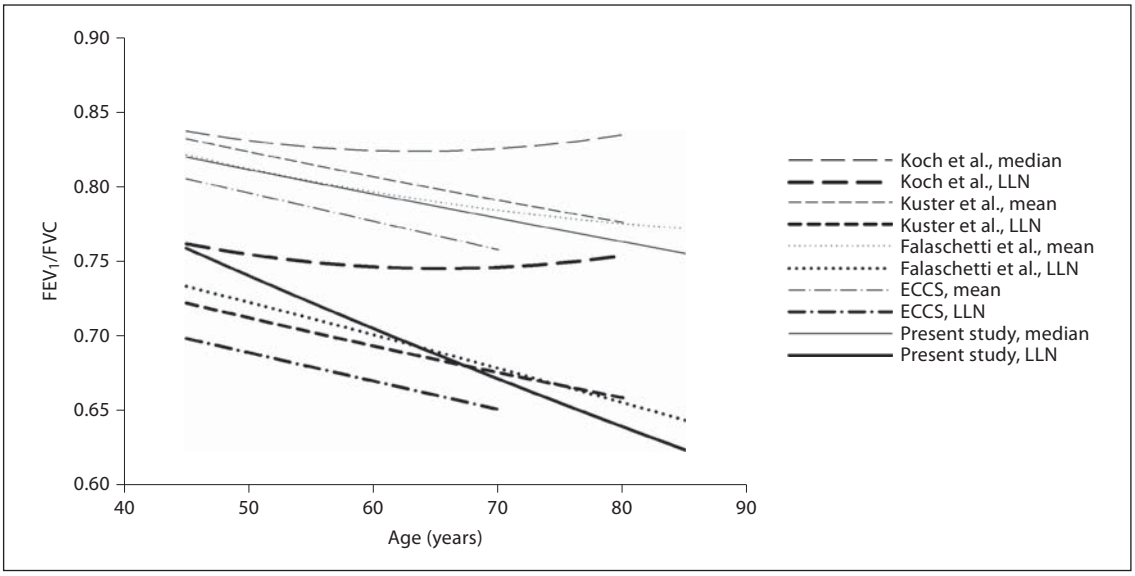

Fig. 2. Plots of the predicted mean/median and LLN for FEV_1/FVC against age in women (height = 160 cm) [2–5].

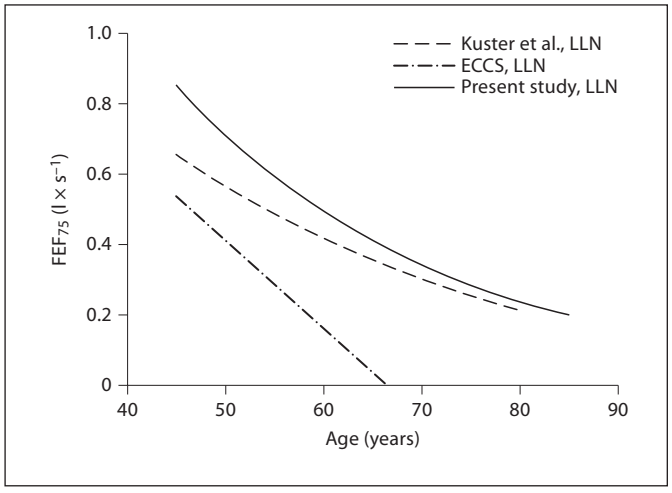

Fig. 3. Plots of the predicted LLN for FEF_{75} against age in women (height = 160 cm) [2, 4].

been applied [22]. This technique requires a distributional assumption for the outcome variable whose parameters are modelled and percentiles derived, as opposed to quantile regression where specific percentiles are modelled separately. While a distributional assumption has been shown to be possibly inadequate in special cases of bimodality [23], comparisons between quantile regression and GAMLSS have demonstrated similar results for both methods [24, 25]. In general, equations resulting from quantile regression may facilitate the interpretation of relationships between variables compared to the rather abstract results generated by GAMLSS.

A major finding of the present study was the observation of higher values for FEV_1 and FVC compared to other reference datasets. While such a difference has been described several times for the ECCS equations, our values are also greater, though to a lesser extent, than recent data [2, 5]. In comparison to the study by Falaschetti et al. [5], this difference was as high as about 300 ml for women at the age of 65 years, equivalent to an age difference of about 12 years. This suggests that from around the sixth decade of life onwards there might be differences in lung function between white Caucasian populations from different regions. The agreement of the present FEV_1 values for men and women with the study by Koch et al. [3], which also describes populations from Germany, is considerably better compared to the other studies whereas in relation to the equations by Kuster et al. [2] there is a clear deviation towards higher values (table 4a, b). On the other hand, our observations for PEF and FEF_{25} on average were markedly below the predictions by Kuster et al. [2]. However, as the distribution of data for these indices was skewed, a comparison of mean values has to be considered with some caution. In addition, the equations by Kuster et al. [2] are based on volunteers who might have introduced a selection bias towards subjects

with a better general health than in the present population sample. It may also be that in advanced age subtle differences in the combination of inherited, environmental and lifestyle factors become more apparent, leading to lung function differences even between geographically proximate regions. This should probably be kept in mind when using prediction equations for this age group. Even if in clinical applications the impact might be not very high, such differences could be misleading in the analysis of large populations with high statistical power and multiple differences in the influencing factors.

One possibility that could have led to rather high values of FEV_1 and FVC in our study is a bias towards healthier subjects of advanced age, since the participants visited the study center for a detailed clinical examination. Conversely, the health status of subjects who did not visit the study center was possibly lower on average, even if they would have been identified as healthy with regard to the lung on the basis of their clinical history. There seems to be no reason to cast doubt on the quality of the equipment used in this and other recent studies as a potential explanation of the differences.

Remarkably, the equations for the ratio FEV_1/FVC not only showed a decrease with age but also a broadening of the normal range for both sexes. This increase in variation might be a manifestation of interindividual differences in lung ageing that become more and more pronounced with age. As our subjects were healthy according to their clinical history, this suggests the need for caution when diagnosing COPD in advanced age. While it has to be kept in mind that we evaluated prebronchodilator values, the postbronchodilator results available in 75% of the KORA-F4 subjects from the above analysis only showed a mean increase of 2% in FEV_1/FVC. The application of the present FEV_1/FVC LLN equations to the complete KORA-F4 and KORA-Age cohorts, for the age and height ranges specified above, results in 17% of subjects below the LLN compared to 10% below the ratio 0.7 in KORA-F4 ($\leq$62 years) and 8% of subjects below the LLN compared to 23% below 0.7 in KORA-Age ($\geq$65 years). These results are in accordance with previous findings, criticizing the use of the fixed ratio for a possible underestimation of bronchial obstruction in the younger age group and, more pronounced, an overestimation in the older age group from the sixth decade of life onwards [26, 27]. On the other hand, the fixed ratio has the advantage of simplicity and is independent of possibly inadequate reference values [28]. To which extent a low value of this ratio can be considered compatible with being 'healthy' could be assessed in studies which aim at the predictive value of lung function independent of lung disease. A recent study found that individuals with a FEV_1/FVC ratio below 0.7 but above the LLN had a worse self-reported health-related quality of life than those with FEV_1/FVC $\geq$0.7, while no differences were found in respiratory exacerbations, dyspnea, physical activity, or six minute walking distance [29]. In the end, for a reliable diagnosis, any spirometric criterion should be complemented by more advanced measurements like body plethysmography as well as information gained from thorough anamnesis and, ideally, individual lung function history.

It also has to be acknowledged that we used cross-sectional data. The relationship between lung function parameters and age might contain secular trends, e.g. towards higher lung function values in general [30]. This would result in a steeper decline in our equations than expected in a follow-up. To explore this relationship, high-quality longitudinal lung function data are needed for the increasing population of advanced age. Recent data, however, do not support the existence of such a secular trend [31].

We put special emphasis on obtaining high-quality data for the whole flow-volume curve, including the flow rates at middle and low lung volume. This was considered important as these indices have often been taken as indicators of changes in small airway function, being indicative of the beginning of airway disease. Although they markedly depend on the cooperation of the subject during the breathing maneuvers, they are still the only widespread available marker of such changes. It is reassuring that the predicted values of FEF_{50} and FEF_{75} were in accordance with those of another recent study. However, they were higher than the ECCS values (see fig. 3). Thus, the use of ECCS values may lead to an underestimation of such changes, which are more subtle than those of the ratio FEV_1/FVC but nonetheless informative provided that the measurements are valid.

In conclusion, our analysis provides reference equations for all common indices of flow-volume curves in never-smoking subjects aged 45–85 years without respiratory disease, according to a comprehensive assessment of their health status. Although generally comparable to published data, the results point towards differences in common measures. This suggests that there might be some regional differences of lung function within the Caucasian population of advanced age in Europe.

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The authors declare that they have no conflicts of interest.

References

1 Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, et al: Interpretative strategies for lung function tests. Eur Respir J 2005;26:948–968.

2 Kuster SP, Kuster D, Schindler C, Rochat MK, Braun J, Held L, Brandli O: Reference equations for lung function screening of healthy never-smoking adults aged 18–80 years. Eur Respir J 2008;31:860–868.

3 Koch B, Schaper C, Ewert R, Volzke H, Obst A, Friedrich N, Felix SB, Vogelmeier CF, Schnabel E, Karrasch S, et al: Lung function reference values in different German populations. Respir Med 2011;105:352–362.

4 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC: Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.

5 Falaschetti E, Laiho J, Primatesta P, Purdon S: Prediction equations for normal and low lung function from the Health Survey for England. Eur Respir J 2004;23:456–463.

6 Smolej-Narancic N, Pavlovic M, Zuskin E, Milicic J, Skaric-Juric T, Barbalic M, Rudan P: New reference equations for forced spirometry in elderly persons. Respir Med 2009; 103:621–628.

7 Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L: Forced spirometry reference values for Norwegian adults: the Bronchial Obstruction in Nord-Trondelag Study. Eur Respir J 2001;18:770–779.

8 Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ: Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008;177:253–260.

9 van den Berge M, ten Hacken NH, Cohen J, Douma WR, Postma DS: Small airway disease in asthma and COPD: clinical implications. Chest 2011;139:412–423.

10 Holle R, Happich M, Lowel H, Wichmann HE: KORA – a research platform for population based health research. Gesundheitswesen 2005;67(suppl 1):S19–S25.

11 Lowel H, Doring A, Schneider A, Heier M, Thorand B, Meisinger C: The MONICA Augsburg surveys – basis for prospective cohort studies. Gesundheitswesen 2005; 67(suppl 1):S13–S18.

12 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al: Standardisation of spirometry. Eur Respir J 2005; 26:319–338.

13 Koenker R: Quantile Regression. New York, Cambridge University Press, 2005.

14 Bottai M, Pistelli F, Di Pede F, Baldacci S, Simoni M, Maio S, Carrozzi L, Viegi G: Percentiles of inspiratory capacity in healthy nonsmokers: a pilot study. Respiration 2011;82: 254–262.

15 Pistelli F, Bottai M, Carrozzi L, Baldacci S, Simoni M, Di Pede F, Viegi G: Reference equations for spirometry from a general population sample in central Italy. Respir Med 2007;101:814–825.

16 Schnabel E, Chen CM, Koch B, Karrasch S, Jorres RA, Schafer T, Vogelmeier C, Ewert R, Schaper C, Volzke H, et al: Regional differences in prediction models of lung function in Germany. Respir Res 2010;11:40.

17 Cole T: Linear and proportional regression models in the prediction of ventilatory function. J R Stat Soc Ser A 1975;138:297–338.

18 Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1: 307–310.

19 R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, R Foundation for Statistical Computing, 2010. http://www.r-project.org.

20 Yu KM, Lu ZD, Stander J: Quantile regression: applications and current research areas. J R Stat Soc Ser D Stat 2003;52:331–350.

21 Rigby RA, Stasinopoulos DM: Generalized additive models for location, scale and shape. J R Stat Soc Ser C Appl Stat 2005;54:507–544.

22 Cole TJ, Stanojevic S, Stocks J, Coates AL, Hankinson JL, Wade AM: Age- and size-related reference ranges: a case study of spirometry through childhood and adulthood. Stat Med 2009;28:880–898.

23 Wei Y, Pere A, Koenker R, He X: Quantile regression methods for reference growth charts. Stat Med 2006;25:1369–1382.

24 Beyerlein A, Fahrmeir L, Mansmann U, Toschke AM: Alternative regression models to assess increase in childhood BMI. BMC Med Res Methodol 2008;8:59.

25 Fenske N, Fahrmeir L, Rzehak P, Höhle M: Detection of risk factors for obesity in early childhood with quantile regression methods for longitudinal data. Technical Report 038. Department of Statistics, University of Munich, 2008.

26 Quanjer PH, Enright PL, Miller MR, Stocks J, Ruppel G, Swanney MP, Crapo RO, Pedersen OF, Falaschetti E, Schouten JP, Jensen RL: The need to change the method for defining mild airway obstruction. Eur Respir J 2011;37:720–722.

27 Miller MR, Pedersen OF, Pellegrino R, Brusasco V: Debating the definition of airflow obstruction: time to move on? Eur Respir J 2009;34:527–528.

28 Vestbo J, Rodriguez-Roisin R: GOLD and the fixed ratio. Eur Respir J 2011;38:481–482, author reply 482–484.

29 Garcia-Rio F, Soriano JB, Miravitlles M, Munoz L, Duran-Tauleria E, Sanchez G, Sobradillo V, Ancochea J: Overdiagnosing subjects with COPD using the 0.7 fixed ratio: correlation with a poor health-related quality of life. Chest 2011;139:1072–1080.

30 van Pelt W, Borsboom GJ, Rijcken B, Schouten JP, van Zomeren BC, Quanjer PH: Discrepancies between longitudinal and cross-sectional change in ventilatory function in 12 years of follow-up. Am J Respir Crit Care Med 1994;149:1218–1226.

31 Quanjer PH, Stocks J, Cole TJ, Hall GL, Stanojevic S: Influence of secular trends and sample size on reference equations for lung function tests. Eur Respir J 2011;37:658–664.