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A physiologically based model for spirometric reference equations in adults

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Summary

A spirometric reference equation consists of a mathematical model with constants and coefficients optimized to fit a specific data set from healthy individuals. Commonly applied models are selected on statistical rather than physiological considerations. A predetermined model with constants and coefficients optimized to various populations would enable interpretable and interesting comparisons between populations. Lubiński and Gólczewski recently presented a piecewise linear model with constants and coefficients claimed to be physiologically interpretable (Lubiński model). Three questions were addressed: Is the Lubiński model as useful clinically as other models: multiple linear, piecewise polynomial and exponential with splines? Will reference equations based on the Lubiński model and optimized to a Swedish and to a Polish population allow for interpretable comparisons? Are three well-known reference equations clinically useful in the Swedish adult population? A recent Swedish random population sample with high-quality spirometric measurements enabled the present analyses. When optimized to fit the Swedish population sample, the Lubiński model and two other models provided accurate predictive normal values. Interesting differences were demonstrated between the Polish and Swedish populations. The proportion of subjects below lower limit normal was adequate for the piecewise polynomial equations but too low and not clinically useful for the advocated exponential equations with splines. It is concluded that the Lubiński model is clinically as useful as other models, and it adds important value and is recommended for future spirometric reference equations for adults. The advocated exponential equations with splines are not recommended for Swedish adults because of too wide normal limits.

Introduction

The primary objective of a spirometric reference equation is to provide accurate predictive values and lower limits normal (LLN) for clinical decision making. A spirometric reference equation is constructed by applying a mathematical model to measured spirometric data from a population sample of healthy people. Although all reference equations share the same goal, they are based on rather different mathematical models. Spirometric reference equations published during the last decades were based on a multiple linear model (the 'ERS' equations) (Quanjer *et al.*,1993), a piecewise polynomial model (Hankinson *et al.*, 1999), a piecewise linear (Lubiński & Gólczewski, 2010) and exponential models (Brändli *et al.*, 1996; Langhammer *et al.*, 2001; Falaschetti *et al.*, 2004; Kuster *et al.*, 2008). More recently, the Global Lung Function Initiative (GLI) collated data from materials all over the world and presented reference equations (the GLI 2012 equations) based on a model having an exponential form with age-dependent splines (Quanjer *et al.*, 2012). The GLI 2012 equations were derived by sophisticated statistics and because of extensive data and stability of the equations, GLI advises against continued use of popular older equations and claims that collection of further normative Caucasian data is not required (Quanjer *et al.*, 2012;).

Despite the tremendous endeavour of the GLI, more useful models cannot be excluded. In common with other recently published reference equations for spirometry (Brändli *et al.*, 1996; Langhammer *et al.*, 2001; Falaschetti *et al.*, 2004; Kuster *et al.*, 2008), the GLI authors selected the mathematical model much because of statistical performance ('the goodness of model fit'), that is, explaining the measured spirometry variables by sex, age and height. The physiological considerations underlying the different chosen models seem to be basic

assumptions about taller persons having larger lungs, lung ventilation declining by age and differences by sex. Of the recently published spirometric reference equations, the piecewise polynomial model (Hankinson *et al.*, 1999) has variables age and height squared, exponential models (Brändli *et al.*, 1996; Langhammer *et al.*, 2001; Falaschetti *et al.*, 2004; Kuster *et al.*, 2008) also have variables age and/or height squared or at higher potencies and logarithmic-transformed variables. The GLI model has logarithmic-transformed variables and age-dependent splines (Quanjer *et al.*, 2012). This makes constants and coefficients of these models hard to interpret and to compare. The multiple linear ERS model (Quanjer *et al.*, 1993) is simple with interpretable constants and coefficients but has a preset starting age of the age-dependent decline at age 25 which may not be a physiologically valid assumption.

If reference equations for spirometry had been based on one given model, particularly if that model had been based on more elaborated predetermined physiological assumptions, important knowledge of various populations could have been gained apart from predictive values. A common model applied to various populations would allow for interpretations of population characteristics such as effects of ethnicity, age, height or sex by direct comparison of constants and coefficients.

Recently, a model for reference equations for adults was presented by Lubiński and Gólczewski claiming that the constants and coefficients were physiologically interpretable (Lubiński model) (Lubiński & Gólczewski, 2010). The model is based on physiological assumptions that forced vital capacity (FVC) and forced expired volume in one second (FEV_1) of relatively young normal adults are uninfluenced by age until a certain age when the annual decline begins and that the age-dependent annual decline is adequately described as a linear effect when entered into force. These assumptions are expressed by a model of simple piecewise linear equations where constants and coefficients of any given population have an easily interpretable physiological meaning such as the average value of FVC, FEV_1 and height of young adults, the age at which the decline begins and the rate of the age-dependent decline. Lubiński & Gólczewski (2010) applied their model to a Polish population sample, reporting constants and coefficients. Important knowledge of differences between population characteristics might be gained by applying the Lubiński model and comparing constants and coefficients of the derived equations.

In the clinical context, an optimal mathematical model must be completed by a lower limit of normal variation (LLN). According to the ERS/ATS convention (Pellegrino *et al.*, 2005), LLN is defined as 5% of measured values of a normal, healthy population.

The present analysis aims at (i) comparing the predictive power of the Lubiński model (Lubiński & Gólczewski, 2010) with the three other models mentioned above, that is the exponential model with age-dependent splines (Quanjer *et al.*, 2012), the piecewise polynomial equations by Hankinson *et al.* (Hankinson *et al.*, 1999) and the multiple linear ERS equations (Quanjer *et al.*, 1993), (ii) comparing spirometric population characteristics between Polish and Swedish population samples by the Lubiński model and (iii) analysing the proportion of subjects of the present Swedish population sample with measured spirometric values below the LLN according to published equations.

Materials and methods

ADONIX (ADult Onset asthma and NItric oXide) was a general population-based study between 2001 and 2007. The population consists of men and women aged 25–75 randomly selected from the population register in Gothenburg, Sweden (Olin *et al.*, 2006, 2007). Subjects completed a postal questionnaire and underwent clinical examinations, including spirometry. Subjects were asked whether they were born in or outside Europe.

The response rate was 42% of those invited. Subjects gave written consent to the study, and the protocol was approved by the ethics committee of University of Gothenburg. The total study sample was 6128, but for the purpose of this study, only those who never had smoked were selected (n = 2926). Further, 1028 subjects reporting ever having asthma, ever wheezing or whistling in the chest, physician's diagnose of COPD or emphysema, breathlessness, cough within the last 12 months with or without phlegm were excluded. Also, subjects born outside Europe (n = 87) or having low spirometry quality (n = 138) were excluded. Hence, after these exclusions, the final study population comprised 1673 subjects with complete recordings. Age- and sex-specific height and weight are shown in Table 1.

Spirometry was performed with a dry-wedge spirometer (Vitalograph, Buckingham, UK) by 1592 subjects and with a flow sensing spirometer (Easy-One, ndd, Zürich, Switzerland) by 81 subjects. Calibration check of volume with a three-litre (Vitalograph), or a one-litre (Easy-One), syringe was performed daily. A volume calibration check of linearity was per-

Table 1 Height, FVC and FEV_1 of the present material by sex and age class.

Age class (years)	*n*	Height (cm)		FVC (L)		FEV_1 (L)	
		Mean	Range	Mean	Range	Mean	Range
Females							
25–34	82	169	154–186	4·1	3·0–5·2	3·4	2·4–4·3
35–44	201	168	152–182	4·1	2·3–5·9	3·3	2·0–4·6
45–54	224	167	147–184	3·8	2·7–5·5	3·0	2·1–4·3
55–64	200	165	148–178	3·4	2·2–4·9	2·6	1·7–3·6
65–75	130	163	146–176	3·0	1·9–5·1	2·3	1·3–3·4
Males							
25–34	81	182	161–198	5·7	4·0–7·7	4·7	3·3–6·9
35–44	204	182	156–203	5·5	3·1–7·7	4·4	2·6–6·5
45–54	242	180	161–201	5·2	3·5–7·1	4·1	2·8–5·4
55–64	190	179	163–193	4·7	2·8–7·1	3·7	2·1–5·1
65–75	119	177	161–194	4·3	2·4–7·1	3·3	1·8–5·2

formed weekly. Evaluation of leaks was performed daily for the Vitalograph. All spirometry technicians (n = 7 during 2001–2002, n = 5 during 2003–2006) underwent training before the study began and had reoccurring training during the study period. Spirometry was performed in sitting position, wearing a nose clip. At least three and up to seven forced expirations were performed to obtain a minimum of three acceptable and reproducible recordings. Acceptability variables were shape of curves; start, duration, plateau and effort of expiration; leakage and presence of cough. Reproducibility criteria were ≤100 ml between the best two tests for both FEV_1 and FVC. Technicians performed immediate evaluation of acceptability and reproducibility. If all acceptability criteria were accomplished and reproducibility was ≤100 ml, the reading was classified as quality score 3. Quality score 2 implied reproducibility of >100 ml but <200 ml and all other quality criteria accomplished or the technician's minor comment on performance. Quality score 1, if reproducibility was >200 ml or if overall test performance was classified as non-acceptable by the technician. Recordings with quality score 1 were excluded.

The largest FVC and FEV_1 were registered, regardless of the manoeuvre. The FEV_1/FVC ratio was calculated, multiplied by 100 and entered in analyses without decimal.

Standing height without shoes was measured to the nearest centimetre. Weight was measured with light indoor clothing to the nearest kg. Age was years at last birthday. Temperature was registered daily and kept at 20–24°C.

Table 1 presents sex and age-class specific height, FVC and FEV_1.

Spirometry extended quality control

The database was scrutinized for improbable values which were checked with original records and corrected. Moreover, 50 spirometries were randomly selected for extended quality control, stratified for quality score and reclassified blindly by an experienced spirometry technician. There was a good agreement with original records: 48 records kept same quality scores as in original; two primarily classified as score 2 were reclassified as score 3.

Models and equations

In this study, we use three important concepts: *models*, *optimized equations* and *published equations*. A *model* in this context implies the mathematical structure behind an equation. Table 2 presents the four models we choose to study. The constants and coefficients are not numerically determined in the models, only the mathematical structure. When a model is applied to a population sample, the constants and coefficients are *optimized* to best fit the measured spirometry values of the population sample by an iterative statistical process. All *published spirometric* reference equations are developed in this way. The choice of mathematical model is by tradition usually based on previous publications, statistical testing and other considerations. In this study, we applied various models to measured spirometry values from the Swedish population sample, and the optimized equations were developed to best fit the measured spirometry values, that is, in the same way as all published reference equations were developed. Thus, the only difference between *published reference equations* and *optimized equations* is the measured spirometry values used for determining the constants and coefficients of a given model.

Table 2 Tested mathematical models. Constants and coefficients are expressed as letter b with a number.

GLI	Log (FVC or FEV_1 or FEV_1/FVC) = b0 + b1*log (age) + b2*log(height) + age-spline + b3*ethnic group
Lubiński[a]	FVC or FEV_1 = BV_{LFV}*(1 + 0·5*(abs (*A* − A0) + (*A* − A0))*b1 + b2*ΔH) FEV1/FVC = BV_{LFV} + b1**A* + b2*ΔH
Hankinson	FVC or FEV_1 = b0 + b1*age + b2*age^2 + b3*$height^2$ FEV1/FVC = b0 + b1*age
ERS[b]	FVC or FEV_1 = b0 + b1*age + b2*height FEV_1/FVC = b0 + b1*age

[a]Lubiński model; BV_{LFV} is the average value of FVC or FEV_1 of young subjects whose age-dependent decline has not begun, *A* is the subject's age, A0 is the onset age of decline, b1 is the coefficient of cross-sectional annual decline in FVC or FEV_1 and b2 is the coefficient for height difference, that is ΔH, the difference between measured and predicted height (see table 5). The model of Lubinski for FEV1/FVC (%) was modified due to no onset age of decline.
[b]ERS model; if no published coefficients for FVC, then VC was used instead.

We tested the GLI 2012 exponential model with splines (Quanjer *et al.*, 2012), piecewise linear reference models by Lubiński & Gólczewski (2010), piecewise polynomial models of Hankinson *et al.* (1999) and multiple linear models ('ERS') (Quanjer *et al.*, 1993) (Table 2) by applying these models to the present material to find the optimized constants and coefficients. These equations, 'optimized' to the present material, will be referred to as GLI, Lubiński, Hankinson and ERS respectively in the text and in tables.

For the Lubiński model, piecewise linear equations were developed for height by a first step and subsequently also for FVC and FEV_1 according to Lubiński (Lubiński & Gólczewski, 2010). Regarding FEV_1/FVC no onset age of decline was found and therefore a conventional linear equation was applied (Table 2).

The predictive power was assessed in three steps: (i) applying the mathematical models to the present general population sample of healthy adults and optimizing the constants and coefficients, (ii) applying the resulting optimized equations and calculating predicted normal values and (iii) calculating the goodness of fit of the various predicted normal values.

Thus, the mathematical models shown in Table 2, (GLI, Lubiński, Hankinson and ERS) were applied to the present material and the constants and coefficients were optimized statistically by an iterative process yielding best model fit. SAS Software for Windows (version 9.3: SAS Institute, Inc., Cary,

NC, USA) and Excel were used for most analyses, but R software for Windows (version 2.15.1; www.r-project.org) was used to optimize the GLI equation by GAMLSS package. In SAS, Proc Reg was used for applying the ERS and Hankinson models and Proc Nlin for the Lubiński model. Correlation between age and height was tested by Pearson's correlation coefficient.

Goodness of fit of the predicted normal values according to the various optimized reference equations could not be compared by on the commonly used R^2 (coefficient of determination) which is inappropriate for nonlinear models. Mathematical models may be compared using their mean squared errors (MSEs) as a measure of how well they explain a given set of observations: The model with the smallest MSE has the best predictive power (Lehmann & Casella, 1998;). Thus, the various optimized reference equations were applied to the present material, and the MSEs for predicted normal FVC, FEV_1 (in litres) and FEV_1/FVC (in per cent) in females and males were determined. As a further illustration of the goodness of fit, predicted normal values based on the various optimized equations are compared to the corresponding measured values of the present material in five age classes and separately for females and males.

Lower limits normal of the three commonly used published reference equations was estimated according to published procedures (Quanjer *et al.*, 1993, 2012; Hankinson *et al.*, 1999).

Results

For current spirometry, considerable care was taken to achieve tests with good technical quality. The goal was three acceptable recordings with a reproducibility of ≤100 ml which was achieved in 90·7% of all spirometries. 1·4% was acceptable with reproducibility >100 but ≤200 ml. An extended spirometry quality check implied that nearly all tests remained without misclassification of spirometry quality. Therefore, we regard data to be representative for a healthy Swedish population.

By the Lubiński model, individual predicted height and ΔH (the difference between measured and predicted height) were calculated as a first step (Table 5). Measured height was dependent on age in both sexes ($P<0{\cdot}0001$ for both), while ΔH was independent of age ($P = 0{\cdot}98$) in the present material. In Fig. 1, the measured values of FVC and FEV_1 for women and men are plotted against age. The lines represent the applied optimized Lubiński piecewise linear equations assuming ΔH to be zero.

Predictive power

The predictive powers of different models are shown in Tables 3 and 4. Table 3 shows MSEs as calculated using optimized equations. Differences between models were small when comparing within sex and spirometric variable. The optimized Lubiński reference equations ranked first (smallest MSE) in five cases, Hankinson and ERS in two each and GLI in one case. The differences between measured values of the present material and the corresponding predicted values according to optimized equations are presented in Table 4. These differences were extremely small with few exceptions regarding the ERS predicted values in some age classes, for example FVC and FEV_1 in females 25–34 years and FVC in males 45–54 years with differences >100 ml between measured and predicted values.

Population comparison

The comparison based on the Lubiński model of a Swedish and a Polish population is presented in Table 5. In particular, the age at which the age-dependent decline is higher in the Swedish population.

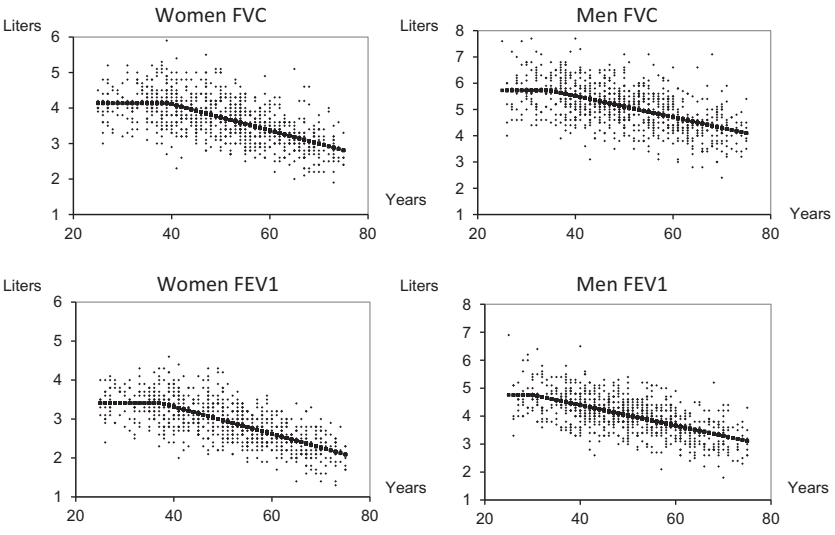

Figure 1 Measured values in litres of FVC and FEV_1 for women and men plotted against age. The dotted lines represent the applied piecewise linear equations according to the Lubiński equations assuming ΔH to be zero.

Table 3 Mean square errors (MSE)[a] of the models optimized to fit the present Swedish population. Lowest MSE = ranked first.

	Females		Males	
	MSE	**Rank**	**MSE**	**Rank**
FVC (L)				
GLI	0·174	1	0·313	4
Lubiński	0·175	2	0·311	1
Hankinson	0·176	3	0·311	1
ERS	0·182	4	0·311	1
FEV_1 (L)				
GLI	0·118	2	0·210	4
Lubiński	0·116	1	0·208	1
Hankinson	0·119	3	0·208	1
ERS	0·121	4	0·208	1
FEV_1/FVC (%)				
GLI	24·5	2	27·8	2
Lubiński	24·4	1	27·6	1
Hankinson	24·7	3	28·1	3
ERS	24·7	3	28·1	3

n, number of observations; df, degrees of freedom.
[a]MSE = Mean Squared Error = $1/(n - \mathrm{df} - 1)\sum_{i=1}^{n}(Y_i\,\mathrm{predicted} - Y_i\mathrm{observered})^2$.

Proportion below lower limits normal

When the LLN of the tested published equations were analysed, the GLI and ERS equations resulted in low proportions of subjects below the LLN as presented in Table 6.

Discussion

The power of the four different mathematical models to predict FVC, FEV_1 and FEV_1/FVC of the present material of healthy Swedish adults appears surprisingly all to be excellent except the ERS models for FVC and FEV_1 in some age classes. Applying the Lubiński model revealed the substantial difference in spirometric characteristics between Swedish and Polish healthy population, which should be taken into account for future study as these two populations often belong to one common group as Caucasian. Percentage of subjects below the LLN varied by the used reference equations, and ERS and GLI equations were are not adequate to make a clinical decision for a Swedish population.

The study population was derived from a large general population age 25–75, with a participation rate of 42%. The participation rate may introduce bias if determinants of spirometric values were associated with participation. The final study sample was selected to be 'healthy with European origin', that is, excluding persons with known determinants of spirometric values such as smoking, respiratory symptoms and inability to perform an acceptable test. We did not control for socio-economic and environmental characteristics. Bias may be introduced if 'healthy' responders distinctly differed from 'healthy' nonresponders regarding socio-economic characteristics and environmental exposures affecting spirometry. Previous studies showed that long-term exposure to ambient air pollution affects spirometry in children and adults (Götschi *et al.*, 2008). Also occupational exposure to pollutants such as vapours, gas, dust or fumes have impact on spirometry (Blanc, 2012). It is not clear whether occupational exposures affect spirometry in such a selected sample of healthy persons, after exclusions due to health criteria. There was no significant effect of occupational exposures to vapours, gas, dust or fumes in a Norwegian study after exclusion of persons with cardinal respiratory symptoms (Johannessen *et al.*, 2007).

In the current study, the predictive power of different mathematical models was judged by both MSE in Table 3 and the mean difference between the measured and the predicted

Table 4 Mean values of the individual differences between measured values in the present Swedish population and corresponding predicted normal values according to optimized mathematical models by GLI 2012, Lubiński, Hankinson and ERS. Differences of FVC and FEV1 are in ml and FEV1/FVC in per cent units.

	Females					Males				
	25–34	**35–44**	**45–54**	**55–64**	**65–75**	**25–34**	**35–44**	**45–54**	**55–64**	**65–75**
FVC (ml)										
GLI 2012	−15	3	18	−9	−10	−13	−26	27	−11	16
Lubiński	−18	−7	30	−18	−2	0	−57	61	−4	−19
Hankinson	−57	45	11	−54	29	10	−36	35	−19	16
ERS	−184	58	76	25	−63	3	20	114	44	25
FEV_1 (ml)										
GLI 2012	−16	5	12	2	−19	6	−17	13	−9	11
Lubiński	1	−13	27	−14	−19	−14	−34	46	−2	−26
Hankinson	−44	33	11	−35	11	34	−37	23	−8	7
ERS	−130	42	54	−16	−52	−1	−33	40	−1	−18
FEV_1/FVC (%)										
GLI 2012	−0·2	0·0	0·1	0·3	−0·6	0·2	−0·1	0·1	0·2	−0·4
Lubiński	0·1	−0·1	−0·1	0·3	−0·3	0·7	−0·3	−0·1	0·2	−0·1
Hankinson	0·1	−0·1	−0·1	0·3	−0·3	0·7	−0·3	−0·1	0·2	−0·1
ERS	0·1	−0·1	0·0	0·3	−0·4	0·6	−0·2	−0·1	0·2	−0·1

Table 5 Constants and coefficients of the Lubiński model (see Table 2) optimized to fit the Swedish and Polish populations. For predicted height (Hpred), constants and coefficients for the Swedish population are given as foot note, the corresponding figures for the Polish population are published (Lubiński & Gólczewski, 2010).

	FVC		FEV_1	
	Swedish	**Polish**	**Swedish**	**Polish**
BV females (L)	4·14	4·13	3·41	3·37
BV males (L)	5·73	5·94	4·76	4·71
A0 females (years)	39·3	31·4	37·4	29·0
A0 males (years)	34·7	30·1	30·0	30·2
b1 females (1/years)	−0·00898	−0·00992	−0·01028	−0·01070
b1 males (1/years)	−0·00706	−0·00968	−0·00767	−0·01098
b2 females (1/cm)	0·01231	0·00843	0·01067	0·00741
b2 males (1/cm)	0·01187	0·00965	0·01014	0·00859

ΔH was the difference between measured and predicted height (Hpred). Hpred = BVheight *(1 + 0.5*(abs(A - A0) + (A - A0))*b1) where BVheight (cm) is the average height of subjects whose age-dependent decline has not begun, abs is the absolute value, A (years) is the subject's age, A0 (years) is the onset age of height decline and b1 (1/year) is the age-dependent decline rate in height.
For the Swedish population, BVheight for females was 169.0 cm, for males 181.7 cm. A0 for females 34.0 years, for males 41.0 years. b1 for females was −0.00088, for males−0.00089.

spirometry values in Table 4. MSE has the disadvantage of heavily weighting outliers – a result of the squaring of each term. Visual inspection of Fig. 1 indicates that measured FVC and FEV_1 are approximately normally distributed about the regression line against age and with few extreme outliers. In any case, the corresponding regression lines of the other models are similarly influenced why we consider MSE a valid comparator of the predictive power of the tested mathematical models. The interpretation of differences of MSEs between variables and sex is not straightforward, but depend primarily on the different magnitudes of the variables FVC, FEV_1 and FEV_1/FVC and the fact that the differences between measured and predicted values are squared. The comparison is more straightforward when the MSE differences depend entirely on the equations, that is, separately for each variable and sex. Then, the MSEs are very similar and almost certainly without any practical value possibly with the exception of ERS in females. Also, the mean differences between predicted and measured values were fairly small in all the models except the ERS which had relatively large deviation. This is presumably due to lack of consideration of age-varying declination slope in the model, that is the model forced to have decreased values for even young adults, which is unlikely to occur physiologically.

However, these differences in predictive power by the quite different mathematical models are neglectfully minor in clinical aspect, indicating that the choice of mathematical model is surprisingly not critical. The exception is the model for the ERS equations which performed inadequately in some age classes. This is in line with the notion that the ERS equations predict too low values for FVC and FEV_1 (Langhammer *et al.*, 2001; Falaschetti *et al.*, 2004).

As most models describe the present population sample equally well, then which model to recommend? The GLI 2012 equations cover the age span between 3–95 years and consider various ethnic groups. But is that important? Is it desirable with one set of equations covering all ages and various ethnic belongings? Computerized calculations by software in clinical spirometry systems using different equations covering different age spans and ethnic groups may, however, be as efficient as one unifying equation, for example GLI. For clinicians, the primary interest is the accuracy of calculated predicted values and of the LLN. Five per cent of normal subjects below LLN is the accepted standard and from Table 6, it is obvious that GLI equations have too low LLN. It is presumably an effect of collating material from many different sources with somewhat different population characteristics, somewhat different inclusion criteria, somewhat different technical methods and somewhat different procedures. Thus, locally derived materials, preferably using the Lubiński model, are still worthwhile.

Lubiński & Gólczewski (2010) claim that their mathematical model has physiologically interpretable constants and coefficients allowing for meaningful comparisons between populations. For example, the constant BV (basal value) is a meaningful and easily understandable constant representing the average value of healthy young adult subjects. Is it useful when comparing populations? Will different BVs of FVC or FEV_1 of different populations merely reflect different basal heights? The present study enables comparison between a Swedish and a Polish population (Lubiński & Gólczewski, 2010). Table 5 shows the constants and coefficients of the original equations published by Lubiński and Gólczewski, that is optimized to the Polish population and the same model opti-

Table 6 Percentage of subjects of the present material below the LLN according to GLI, Hankinson and ERS published reference equations. Published Lubiński reference equations were not applied as they are not in common international use.

	FEV_1				FVC				FEV_1/FVC			
	Females		**Males**		**Females**		**Males**		**Females**		**Males**	
Age class	25–49	50–75	25–49	50–75	25–49	50–75	25–49	50–75	25–49	50–75	25–49	50–75
GLI 2012	2·6	1·8	2·2	1·4	1·6	0·4	3·4	1·9	2·9	1·8	3·7	2·6
Hankinson	3·4	4·0	3·9	3·5	2·4	4·4	6·4	5·8	3·7	3·3	4·2	3·0
ERS	1·6	0·7	1·2	0·9	0·5	0·0	0·7	0·9	2·6	1·5	2·5	2·3

mized to the Swedish population. The Polish study is based on a population sample of 2745 healthy Polish never smokers 18–85 years of age. The BV_{FVC} and BV_{FEV1} of females are quite similar to those of the Swedish material. The heights, however, differ. The Swedish healthy young adult women were on average about 5 cm taller than Polish (169·0 versus 164·5 cm) in spite of the fact that basal FVC and FEV_1 were very similar. Thus, the relation between spirometric variables and stature appeared to be different between Swedish and Polish young adult women, but the effect of age (A0 and b1) was similar. The corresponding comparison among males showed that BV_{FVC}, BV_{FEV1}, BV_{height} and A0 were fairly similar, indicating similar relation to stature among young healthy adult Swedish and Polish men. The cross-sectional annual decline (b1) was, however, about 40% higher among Polish men. Thus, although Sweden and Poland are geographically close, interesting differences were demonstrated that raise questions about possible mechanisms. Comparing females and males of the Swedish material showed that FVC and FEV_1 of young adult females remained unaffected for a longer period of time, but when the cross-sectional annual decline began, the rate is higher among females. In the Lubiński material, the effect of age on FVC and FEV_1 was rather similar among females and males. It would be interesting to compare less equal populations than the Swedish and Polish. It would also be interesting to study decline in spirometry by age in longitudinal cohort studies by the Lubiński model. If the large population studies of spirometric variables presented during the last decades had applied the Lubiński model of equations, important knowledge might have been gained. As far as we understand the corresponding comparison based on, for example, the GLI equations would not have resulted in as useful information.

Furthermore, an advantage with the Lubiński model is avoidance of dependence between height and age, thereby allowing for physiological interpretation of their separate effects. A relationship between height decline and age has been shown in longitudinal population studies (Sorkin *et al.*, 1999). The dependence problem is avoided using the difference between measured and predicted height (ΔH) in the reference equations. Another qualification of the Lubiński equation is that the cross-sectional annual decline is relative to the basal value. Commonly, the cross-sectional annual decline is expressed in millilitre per year, that is, without considering various sizes of FVC and FEV_1. It is plausible that the cross-sectional annual decline should differ between small and large lungs. According to the Lubiński equations the rate of age decline, when entered into force, is roughly 1% of the basal value per year.

Although Quanjer *et al.* (2012) have stated that collection of further Caucasian normative data is not required, one should have in mind that as science tends to constantly pursue new knowledge, we have most probably not seen the end of research into modelling ventilatory lung function. New insights in determinants of FVC and FEV_1 might be given by applying the Lubiński model in spirometry data sets from different populations and extracting interpretable coefficients and constants. Exposures in general as well as occupational environments have been shown to affect ventilatory function in humans (Götschi *et al.*, 2008; Blanc, 2012). Effects of environmental exposures and ethnicity could be explored by comparing interpretable coefficients and constants in the Lubiński model.

To our knowledge, the approach to optimize mathematical models to a present study sample and compare results as MSEs has not been reported in the literature before. An other strength of the present study is the well-defined study sample derived from a large general population and spirometries of high quality. Selection of the study sample is important, and we adhered to published recommendations (Medical Section of the American Lung Association, 1991; Pellegrino *et al.*, 2005; Johannessen *et al.*, 2007).

It is concluded that the mathematical model of spirometric reference equations is not critical. The Lubiński model predicts normal values as accurately as any of the tested models and is recommended for future spirometric reference equations for adults because the model enables interesting comparisons between populations. There were several unexplained differences in spirometric characteristics between a Swedish and a Polish population. The advocated GLI equations are not recommended for Swedish adults because of too wide normal limits.

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Conflict of interest

None of the authors has any conflict of interest.

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