

## AGE- AND HEIGHT-BASED PREDICTION BIAS IN SPIROMETRY REFERENCE EQUATIONS

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## **Abstract**

**Introduction.** Prediction bias in spirometry reference equations can arise from combining equations for different age groups, rounding age or height to integers or using self-reported height.

**Objectives.** To assess the bias arising from these sources.

**Methods.** The fit of 13 prediction equations was tested against the Global Lungs Initiative (GLI) dataset using spirometric data from 55,136 healthy Caucasians (54% female). The effects on predicted values of using whole-year age versus decimal age, and of a 1% bias in height, were quantified.

**Results.** In children, the prediction bias relative to GLI ranged from -22% to +17%. Switching equations at 18 years of age led to biases of between -846 (-14%) to +1309 (+38%) mL. Using age in whole years rather than decimal age introduced biases from -8% to +7%, whereas a 1% over-estimation of height introduced bias that ranged from +1% to +40%. Bias was greatest in children and adolescents, and in short elderly subjects.

**Conclusion.** Using a single spirometry equation applicable across all ages and populations reduces prediction bias. Measuring and recording age and height accurately are also essential if bias is to be minimised.

**Keywords:** reference equations, spirometry, prediction, bias

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## **Introduction**

Height and age are the most important explanatory variables in spirometry reference equations. Guidelines for the measurement of spirometric indices, aiming to maximise accuracy and precision, focus on equipment, measurement procedures and quality control [1]. They do not, however, address the equally important issues of accurate height and age measurement. For example in the Global Lungs dataset [2] only 45% of the heights were recorded to 1 mm accuracy, 12% of heights were self-reported, and 45% of ages were recorded in whole years, many rounded by software. These all have the potential to bias the prediction of spirometric indices, particularly in children.

Both height and age appear consistently in adult prediction equations, but in children height is commonly used without age. Examples are Polgar [3] and Wang [4] (recommended by ATS/ERS [1] in the USA), Rosenthal [5] in the United Kingdom (recommended by British Thoracic Society and Association of Respiratory Technicians and Physiologists [6]) and Zapletal [7] in Europe. Yet it has been shown that during adolescence the relationship between age, height and spirometry changes [8-9], and that this can only be accounted for by including age in the equation [9-10]. Thus the omission of age from the equation will generate bias at certain ages in childhood.

In the past, most prediction equations were developed separately for children and adults, with a disjunction in the prediction at the child-adult age boundary (usually around 18-19 years). Recently, spirometry reference equations have become available for Caucasians [10] and other ethnic groups [2] from childhood to old age, complete with accurate lower limits of normal. These all-age equations avoid the child-adult disjunction, and they inevitably highlight bias due the disjunction in other equations.

This study aims to address four questions, focussing on FEV<sub>1</sub> and FVC in Caucasians relative to the Global Lungs Initiative [2], namely:

How large is the prediction bias:

1. for other commonly used spirometry prediction equations?
2. for paediatric prediction equations that omit age?
3. at the child-adult age boundary?
4. due to biases in age and height measurement?

## **Data**

We used data on 54,866 healthy Caucasian lifelong non-smokers from the Global Lungs Initiative (GLI 2012) [2]; 24,768 males and 30,098 females aged 6-95 years. The paediatric subset comprised of 14,486 boys (height 96.0-198.5 cm) and 14,053 girls (height 100.0-188.0 cm) aged 6-18.99 years. A full account of the GLI dataset has been published previously [2].

## **Methods**

FEV<sub>1</sub> and FVC measurements from the GLI 2012 dataset were expressed as percent of predicted based on each of the following prediction equations:

- Children and adolescents: GLI 2012 [2], Polgar [3], Wang [4], Rosenthal [5], Zapletal [7], Quanjer [9], Stanojevic [10], Hankinson [11], Knudson [12],
- Adults: GLI 2012 [2], Stanojevic [10], Crapo [13], ECSC/ERS [14], Falaschetti [15], and the SAPALDIA study [16-17].

Within the dataset height was recorded to 1 mm accuracy in 57.2% of those < 19 years and 33.8%  $\geq$  19 years (n=28,539 and 26,327, respectively). Similarly age was reported to 1 decimal accuracy in 89.2% of subjects < 19 years and in 16.0% of those  $\geq$  19 years.

The effect of recording age in whole years was explored by comparing predicted values based on decimal age with those based on truncated age. Predicted values were also calculated using a +1% bias in height, to simulate a small measurement error or optimistic self-report (equivalent to ~ 2 cm in a child or 1 cm in an adult. The bias introduced in age was 0.0 to 0.99 years (mean 0.30 in males and 0.26 in females, standard deviation (SD) 0.32 in males and females), while for height the bias was 0.9 to 2.0 cm (mean 1.5, SD 0.24) in males, and 0.8 to 1.9 cm (mean 1.5, SD 0.18) in females. All calculations were performed within the age range specified in published prediction equations, precluding extrapolation beyond valid age ranges.

The ‘18<sup>th</sup> birthday effect’ is the size of the transition from a paediatric equation that may be applied up to 18 years of age to an adult equation in subjects  $\geq$  18 years. This was estimated by identifying 386 boys and 404 girls in the dataset who were 17 years old, and calculating their predicted values for both 17.99 and 18.0 years of age according to the various child and adult prediction equations [2-5,7,9-17]. The same height was used at both ages.

## **Results**

### **Effect of switching to the GLI 2012 equations in children**

Mean deviations of measured values from 100% predicted were calculated for each regression equation. Predictably, the equations for GLI 2012 and Stanojevic [2,10] fitted best as they shared methodology and had many data in common, but are still slightly biased during the growth spurt (Figure 1). The reference equations omitting age as an explanatory variable (Polgar, Rosenthal, Zapletal) [3,5,7] performed particularly poorly (Table 1, Figure 1).

### **Birthday effect in children**

Predicted values from Wang [4] are based on power functions of height which differ for each full year from 6-18 years. We identified 1987 subjects from the GLI dataset (1019 boys, 968 girls) who were within one month of their birthday, and calculated their Wang predicted values for the ages before and after their birthday (Figure 2). The same height was used for both predictions, as height increment over a month is small. In girls and boys the birthday discontinuities varied from -42 to +229 mL in FEV<sub>1</sub>, and -65 to +215 mL in FVC.

When switching to other equations at age 18 years (‘18<sup>th</sup> birthday effect’), the FEV<sub>1</sub> change in boys ranged between -846 mL (-14%) and +1,309 mL (+38%) (Table 2). Findings for FVC and for girls were similar (not shown).

### Biased age and height measurements

Based on the GLI 2012 equations [2] the percentage bias in FEV<sub>1</sub> and FVC arising from truncating age to whole years was largest in preschool children and adolescents, up to 8.5% (Figure 3, Table 3). With the GLI and Stanojevic equations [2,10] a 1% bias in height led to biases in FEV<sub>1</sub> and FVC of 2.1-2.4% (Table 3). Truncating age and exaggerating height reduced the bias in childhood (Figure 3) but increased it in adulthood. The use of other equations led to biases of -9 to +40% across the entire age range (Table 3).

### Discussion

There are several practical considerations that affect the interpretation of lung function values. The current practice to combine reference equations from different populations and different age ranges introduces biases ranging from -14% to 38% at the transition from adolescence to adulthood. This range can be converted to the z-score scale by dividing by the coefficient of variation, which at this age is ~12% [2]. So the bias ranges from -1.2 and +3.2 z-score units, with potentially serious consequences for the clinical interpretation of test results around the lower limit of normal (LLN). Truncating age or using self-reported height leads to further biases. The interpretation of spirometry results could be greatly improved by applying a global reference equation spanning all ages, and using measures of height and age accurate to at least one decimal place.

With two exceptions (which shared many of the data and used the same statistical approach) [2,10], the fit of the prediction equations to the GLI dataset was poor, and there was considerable disparity between equations. This leads to a number of sobering conclusions. The present situation with respect to prediction equations is highly unsatisfactory, particularly in the paediatric age range. There is a plethora of spirometry equations; a non-exhaustive summary lists over 120 such equations [18]. However, the piecemeal approach of dividing the human lifespan into small sections inevitably leads to disjunctions at the age group boundaries (Table 2). These arise mainly from the use of different models, which may fit the data poorly, and from the use of population samples that are often small and only poorly representative of the population [2,19]. Thus there is an urgent need for a consistent evidence-based approach towards the construction and use of reference values. Until recently no statistical techniques allowed accurate and continuous description of pulmonary function from childhood to old age. However, with the advent of new techniques, notably the GAMLSS technique [10,20-23] it is now possible to summarise pulmonary function across the whole age range. In addition, it allows the lower limit of normal (usually the 5<sup>th</sup> percentile), which varies appreciably with age [10,15-16,22], to be modelled properly. It is costly and time-consuming to collect sufficient data covering the entire age range. However, collating good quality data from different studies has been shown to be a valid alternative [9-10,22,24].

With the advent of automated pulmonary function machines, laboratories have to decide which prediction equations to use from the selection provided by the manufacturer. Few laboratories are sufficiently informed about the alternatives, and in practice many use the manufacturer's default choice. Such defaults often include equations that include a transition from adolescence to adulthood. Even in institutions with respiratory disease training programs,

people are often unaware of the reference values used in their institute [25-26]. Changes in reference standards, particularly when unannounced, can have considerable impact on diagnosis, referrals, treatment, preoperative assessments, disability ratings and even lung transplantation referrals, as well as the interpretation of serial measurements [27-29]. There is an urgent need for the use of prediction equations which span childhood to old age [2,10]; the GLI 2012 equations [2] achieve this, and offer the additional advantage of being valid for four ethnic groups, obviating the need for arbitrary ethnic correction factors.

The second major finding is that biased age and height measurements can lead to considerable bias in predicted values, which naturally propagate into the lower limits of normal. For example, using the GLI 2012 reference [2], a 1-year age bias due to truncating age to the last birthday, can lead to a bias in predicted values of up to 8.5% (Table 3). This may be due simply to the common practice of entering age in whole years, or the failure of software to compute decimal age as the difference between test date and birth date. Truncating age biases the predicted value downwards in children, particularly in puberty, and upwards in adults (Figure 3). A bias of only +1% in height results in an increase in predicted FEV<sub>1</sub> and FVC by between 0.9% and 40%. In reality, biases greater than this can easily occur purely due to a poorly calibrated stadiometer, or using self-reported height. Importantly the two biases are cumulative, leading to significant errors in predicted spirometric outcomes.

Errors in height of up to 6.9 cm [30] can arise from the use of self-reported height, and in different ethnic groups [30-34]. Males tend to overestimate their height more than females [35]. Over-reporting height also increases with age; thus on average men and women aged 65 to 79 years over-reported by 2.3 and 1.6 cm, respectively, and those aged 80 years or older by 2.6 and 3.3 cm [35]. In addition errors in height can occur if previously recorded values are used: in children during periods of rapid growth, and in elderly people when height loss has occurred. Note that although the study was limited to Caucasians, the findings also apply to other ethnic groups (results not shown).

For accurate interpretation of lung function it is essential that age and height should be entered into equations accurately. This can be achieved by using software which requires entering the date of birth as well as the date of measurement. Height should be measured with a calibrated stadiometer with the subject standing upright without shoes, shoulders, buttocks and heels flat against the wall or stadiometer, and the head tilted so that the lower orbital level and the external auditory meatus (Frankfurt plane) are level; measurements should be recorded to the nearest 0.1 cm. Ideally the mean of two measurements should be used. Inches should not be used, as the conversion to centimetres may generate error. Accurately recorded height and age (to one decimal accuracy) are also required when deriving new prediction equations.

## **Conclusion**

There are large differences in frequently used predicted values according to different authors. Consequently, a transition from one to another set of reference equations can have profound clinical consequences. Therefore final reports should always name the set of reference values used, so that this can be taken into account when interpreting test results. Also in any institute the transition to new reference equations should always be properly announced, and the consequences clearly explained to medical practitioners. The use of modern prediction

equations valid from childhood to old age, derived from large datasets [2,10] and applicable to different ethnic groups [2], obviates the need to change from one set of equations to another, and so avoids age-related disjunctions. It also provides a world-wide standard for the interpretation of spirometric test results.

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Table 1 – Extent to which measured spirometric outcomes from 6-19 year old Caucasian subjects on average differ from 100 percent predicted according to different authors.

			Males (n=13,368)		Females (n=12,953)	
	Ref.	Equation	Median (%)	Range (%)	Median (%)	Range (%)
<b>FEV<sub>1</sub></b>						
Stanojevic	10	all-age + height	-0.2	-1.7 to 4.2	-0.2	-1.3 to 3.2
GLI 2012	2	all-age + height	-0.3	-2.6 to 0.9	-0.4	-1.8 to 0.8
Quanjer	9	age + height	-2.7	-5.5 to 2.6	-1.5	-3.7 to 4.0
Hankinson	11	age + height	1.2	-5.6 to 4.5	-1.6	-5.3 to 2.2
Knudson	12	age + height	-0.9	-3.0 to 7.8	1.2	-1.5 to 7.8
Polgar	3	height	-3.3	-5.8 to 9.2	-6.5	-9.8 to -2.0
Rosenthal	5	height	1.3	-0.9 to 9.9	1.8	-0.6 to 10.7
Zapletal	7	height	3.1	-0.2 to 14.5	4.5	2.2 to 14.1
Wang	4	height*	2.0	0.4 to 4.1	2.6	1.7 to 5.6
<b>FVC</b>						
Stanojevic	10	all-age + height	-0.3	-1.9 to 1.8	-0.7	-1.1 to 1.2
GLI 2012	2	all-age + height	-0.4	-2.2 to 1.0	-0.4	-1.5 to 0.7
Quanjer	9	age + height	-3.5	-6.8 to 0.6	-2.5	-6.6 to 0.9
Hankinson	11	age + height	-0.4	-3.9 to 3.4	-6.1	-9.0 to -4.3
Knudson	12	age + height	0.0	-2.2 to 8.4	0.0	-3.4 to 6.7
Polgar	3	height	-1.1	-3.8 to 16.9	-6.6	-9.6 to -1.9
Rosenthal	5	height	-1.0	-3.4 to 5.8	1.8	-0.1 to 8.4
Zapletal	7	height	-0.4	-2.6 to 10.8	0.9	-1.1 to 9.1
Wang	4	height*	2.8	-0.1 to 9.5	2.5	0.8 to 5.9

**Footnote:** Minimum and maximum deviations correspond to the full year age cohorts depicted in Figure 1, the median is calculated over the full age range. A positive result means that observed values in the GLI dataset exceed predicted values according to different authors.

\* Height-based equations for each whole year of age.

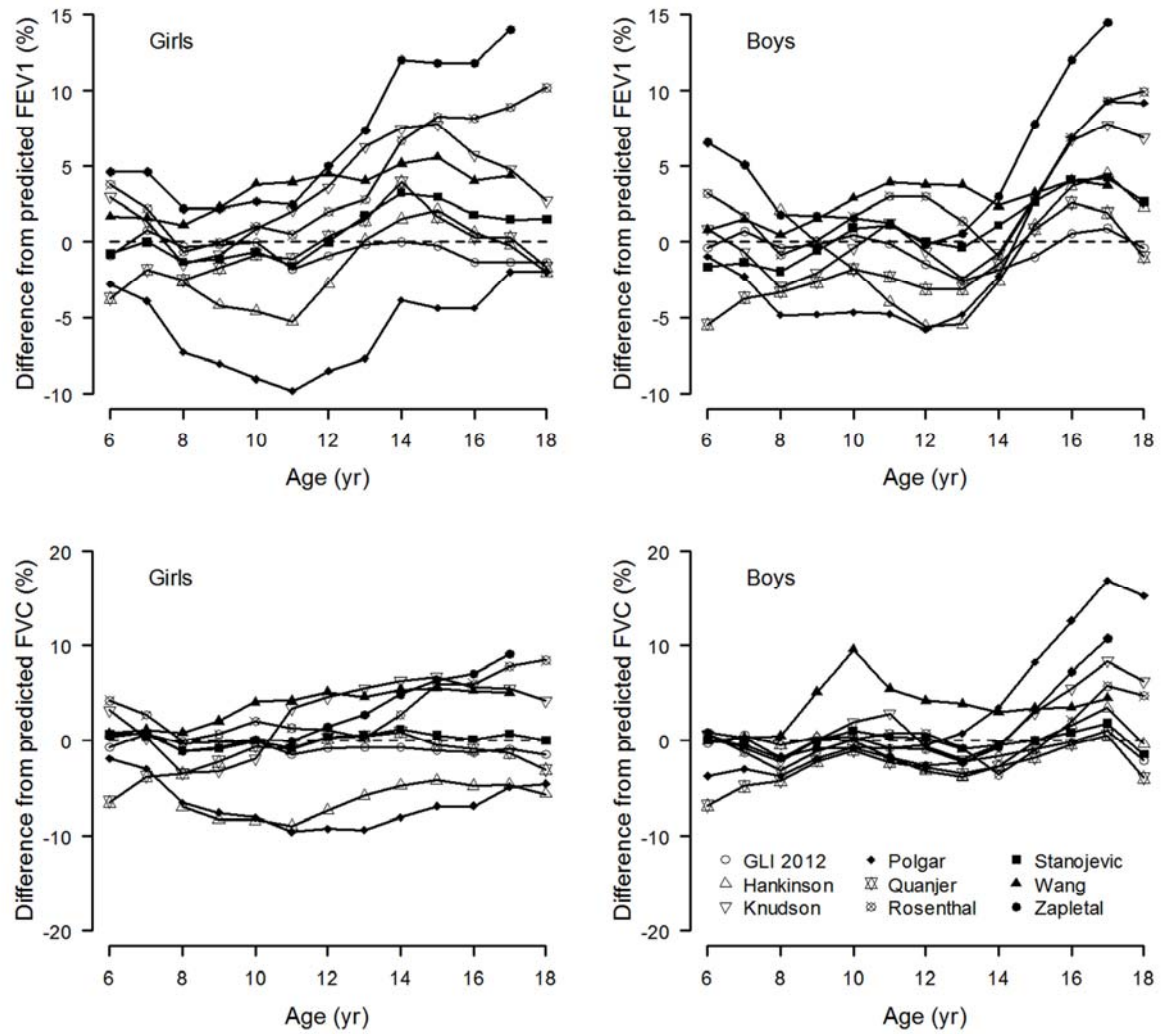


Figure 1

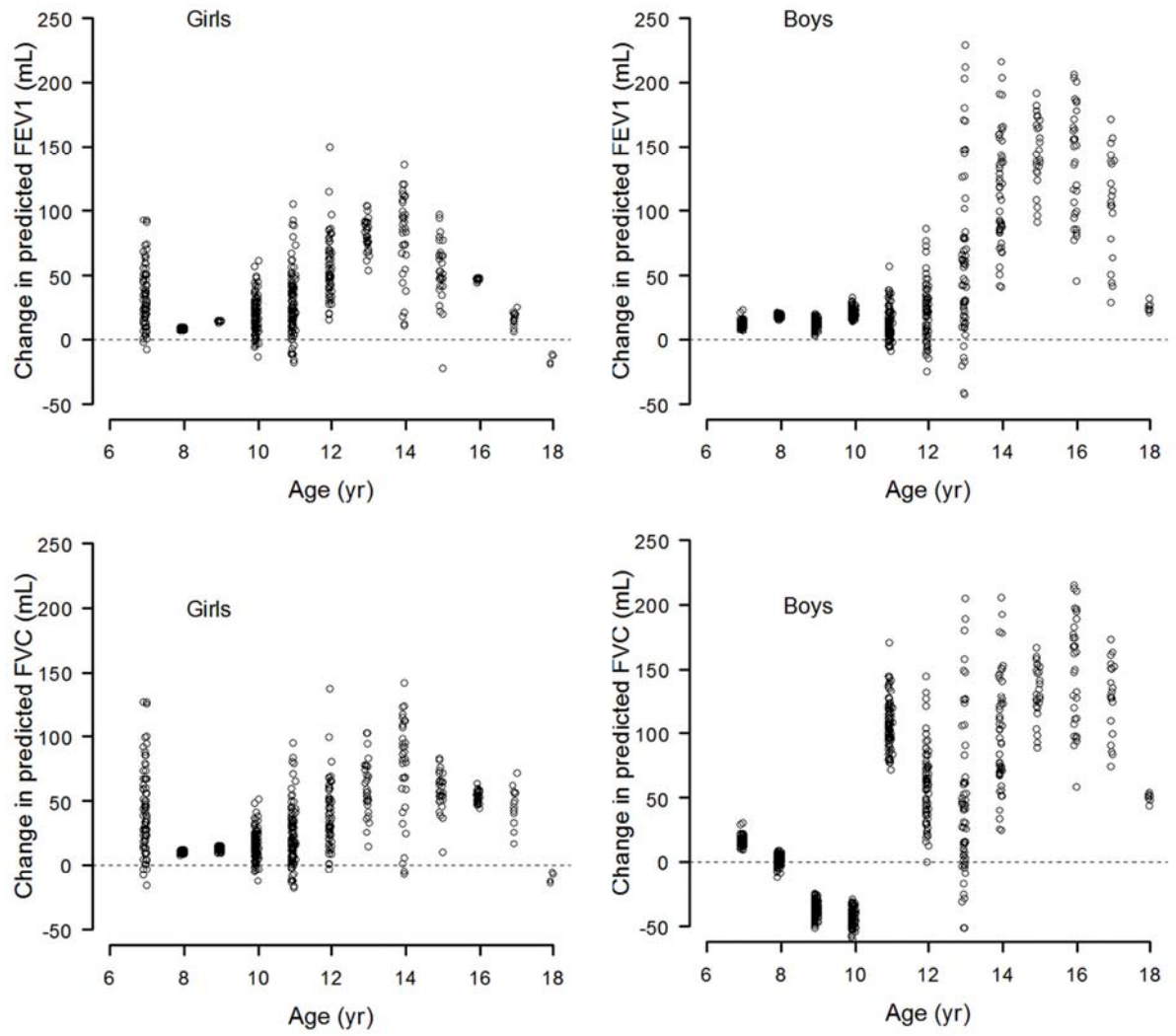


Figure 2

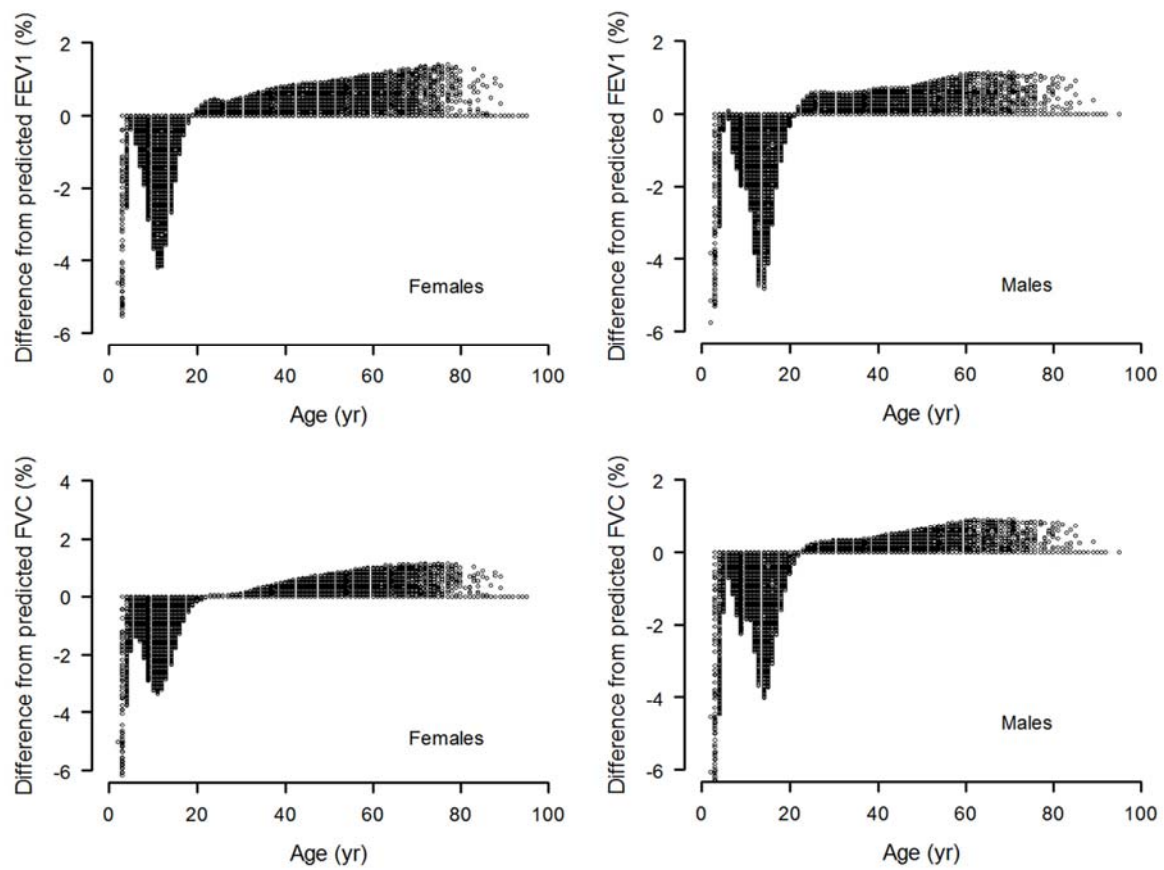


Figure 3

Table 2 – Potential errors in FEV<sub>1</sub> in boys caused by switching reference equations at the 18<sup>th</sup> birthday.

Age 17.99 years	Absolute error	Ref.	Age 18.0 years					
			GLI 2012 [2]	Crapo [13]	ECSC/ERS [14]	Falaschetti [15]	Hankinson [11]	SAPALDIA [16-17]
GLI 2012 <sup>¶</sup>	mL	2	0	-161 to 478	-433 to 127	-49 to 74	-267 to 34	-286 to 118
Hankinson <sup>¶</sup>	mL	11	-33 to 268	107 to 445	-165 to 99	41 to 218	0	-18 to 85
Knudson <sup>¶</sup>	mL	12	263 to 450	289 to 805	16 to 454	299 to 401	164 to 361	164 to 445
Polgar <sup>§</sup>	mL	3	192 to 538	31 to 1017	-241 to 666	143 to 613	-75 to 573	-94 to 656
Quanjer <sup>§</sup>	mL	9	-413 to 181	-574 to 659	-846 to 308	-462 to 255	-680 to 215	-699 to 299
Rosenthal <sup>§</sup>	mL	5	364 to 930	384 to 1309	111 to 982	300 to 979	261 to 898	259 to 959
Wang <sup>§</sup>	mL	4	61 to 313	152 to 539	-120 to 192	135 to 264	46 to 95	27 to 179
Zapletal <sup>§</sup>	mL	7	401 to 681	241 to 1160	-32 to 809	352 to 756	135 to 716	116 to 800

Age 17.99 years	Error as %predicted	Ref.	Age 18.0 years					
			GLI 2012 [2]	Crapo [13]	ECSC/ERS [14]	Falaschetti [15]	Hankinson [11]	SAPALDIA [16-17]
GLI 2012 <sup>¶</sup>	%	2	0	-3 to 16	-8 to 4	-1 to 3	-5 to 1	-5 to 4
Hankinson <sup>¶</sup>	%	11	-1 to 5	-2 to 15	-3 to 3	1 to 4	0	0 to 3
Knudson <sup>¶</sup>	%	12	7 to 12	6 to 31	0 to 17	7 to 15	3 to 14	3 to 17
Polgar <sup>§</sup>	%	3	4 to 22	1 to 42	-4 to 27	3 to 25	-1 to 24	-2 to 27
Quanjer <sup>§</sup>	%	9	-7 to 6	-9 to 24	-14 to 11	-8 to 9	-11 to 8	-12 to 11
Rosenthal <sup>§</sup>	%	5	9 to 34	8 to 54	2 to 38	9 to 35	5 to 34	5 to 37
Wang <sup>§</sup>	%	4	2 to 6	3 to 19	-2 to 6	-5 to 5	1 to 3	1 to 6
Zapletal <sup>§</sup>	%	7	8 to 30	5 to 51	-1 to 35	7 to 33	3 to 31	2 to 35

Footnote: The range of differences between predicted values for FEV<sub>1</sub> at 17.99 and 18.0 years for 282 boys of identical height are shown both in mL and % predicted according to various reference equations. For example, switching from Quanjer's equations at 17.99 years to the GLI 2012

equations at 18.0 years, predicted FEV<sub>1</sub> goes down by as much as 413 mL or up by 181 mL, depending on the subject's height; this represents a change of between -7% and +6% of the predicted value at age 17.99 years. Findings for Stanojevic *et al.* [2] very similar to GLI 2012.

<sup>¶</sup>Equation spanning childhood and adults; <sup>§</sup> Paediatric data only.



Table 3 – Biases in prediction due to age truncated to whole years and/or height biased by +1%; combined results across all age ranges.

		Males			Females		
		Truncated age	Biased height	Truncated age and biased height	Truncated age	Biased height	Truncated age and biased height
		% bias	% bias	% bias	% bias	% bias	% bias
<b>FEV<sub>1</sub></b>	Ref.	min to max	min to max	min to max	min to max	min to max	min to max
Crapo	13	0 to 1	2 to 4	2 to 4	0 to 2	2 to 5	2 to 6
ECSC	14	0 to 1	2 to 3	2 to 4	0 to 2	2 to 5	2 to 6
Falaschetti	15	-2 to 2	1 to 6	0 to 6	0 to 2	2	2 to 4
GLI 2012	2	-7 to 1	2	-5 to 3	-8 to 1	2	-6 to 4
Hankinson	11	-3 to 2	2 to 4	-1 to 5	-5 to 3	1 to 3	-2 to 5
Knudson	12	3 to 2	2 to 16	1 to 16	-3 to 2	2 to 6	-1 to 6
SAPALDIA	16	-1 to 1	1 to 2	0 to 3	0 to 2	2	2 to 4
Stanojevic	10	-5 to 1	2	-3 to 4	-4 to 2	2	-4 to 3

<b>FVC</b>							
Crapo	13	0 to 1	2 to 4	2 to 4	0 to 1	2 to 5	2 to 6
ECSC	14	0 to 1	2 to 3	2 to 4	0 to 1	2 to 4	2 to 5
Falaschetti	15	-3 to 1	1 to 3	0 to 4	-3 to 2	1 to 4	0 to 5
GLI 2012	2	-8 to 1	2	-6 to 3	-9 to 1	2	- to 3
Hankinson	11	-3 to 2	2 to 4	-1 to 6	-5 to 3	2 to 6	-1 to 7
Knudson	12	-3 to 2	2 to 13	2 to 13*	-3 to 7	2 to 40*	0 to 40*
SAPALDIA	16	-2 to 0	1 to 2	1 to 2	-2 to 0	1 to 2	1 to 3
Stanojevic	10	-6 to 1	3	-3 to 4	-5 to 1	2	-3 to 4

Biases are expressed as percent of the accurate prediction. The values shown represent the range across all the various prediction equations relative to the GLI data.

\* The large errors occur in short people older than 70 years.

NB: Analysis has been limited to those equations which include both height and age as predictors.