Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry

Supplementary material

Graham L. Hall[1,2], Nicole Filipow[3], Gregg Ruppel[4], Tolu Okitika[1], Bruce Thompson[5], Jane Kirkby[6], Irene Steenbruggen[7], Brendan G. Cooper[8] and Sanja Stanojevic[3] on behalf of the contributing GLI Network members

Affiliations: [1]Children's Lung Health, Wal-yan Respiratory Research Centre, Telethon Kids Institute, Perth, Australia. [2]School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia. [3]Translational Medicine, Hospital for Sick Children, Toronto, ON, Canada. [4]Pulmonary, Critical Care and Sleep Medicine, Saint Louis University School of Medicine, St Louis, MO, USA. [5]School of Health Sciences, Swinburne University of Technology, Melbourne, Australia. [6]Respiratory Medicine, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK. [7]Pulmonary Laboratory, Isala Klinieken, Zwolle, The Netherlands. [8]Lung Function and Sleep, University Hospital Birmingham and Institute of Clinical Sciences, University of Birmingham, Birmingham, UK.

@ERSpublications
The GLI Network has developed all-ages reference equations for lung volumes for population of European Ancestry. The unification of GLI lung function reference equations will improve the interpretation of lung function in patients with lung disease. http://bit.ly/3hHZR1N

Cite as: Hall GL, Filipow N, Ruppel G, *et al*. Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry. *Eur Respir J* 2021; 57: 2000289 [https://doi.org/10.1183/13993003.00289-2020].

Results

Data from 17 centres in 11 countries were submitted with a final dataset of 7190 individuals of European ancestry available for analysis. In general, there were more data collected for females compared with males, with fewer relative observations between the ages of 20 and 40 (figure S1). In total there were 987 observations (544 female and 443 males) between the ages of 20 and 40, which alone is bigger than any of the previously published equations. If FRC data were not submitted, we did not report any other lung volume indices.

Initial analyses of the FRC and TLC data demonstrated significant overlap between plethysmography and dilution techniques across all ages (figure S2). In a multivariable model with height, age and technique, we did not identify physiologically relevant differences of technique (table S1). In particular, the range of values observed between the three techniques was the same (figure S2). In addition, comparison of z-scores for each technique using the final equations (figure S3) found that most of the offsets were within 0.5 z-scores.

The European Respiratory Society Global Lung Function Initiative lung volume reference equations were endorsed by the ERS Executive Committee on 2 September 2020, and have also been endorsed by the following respiratory societies: American Thoracic Society (ATS), Australian and New Zealand Society of Respiratory Science (ANZSRS), Thoracic Society of Australia and New Zealand (TSANZ), Pan African Thoracic Society (PATS) and Latin American Thoracic Association (ALAT).

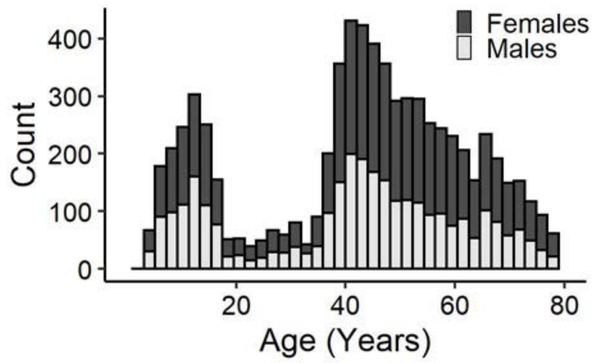

FIGURE S1 Summary of collated data. The submitted functional residual capacity (FRC) data was predominantly in older adults (>40 years). The distribution with age is the same for TLC but the number of observations was reduced to 6815 from 7190.

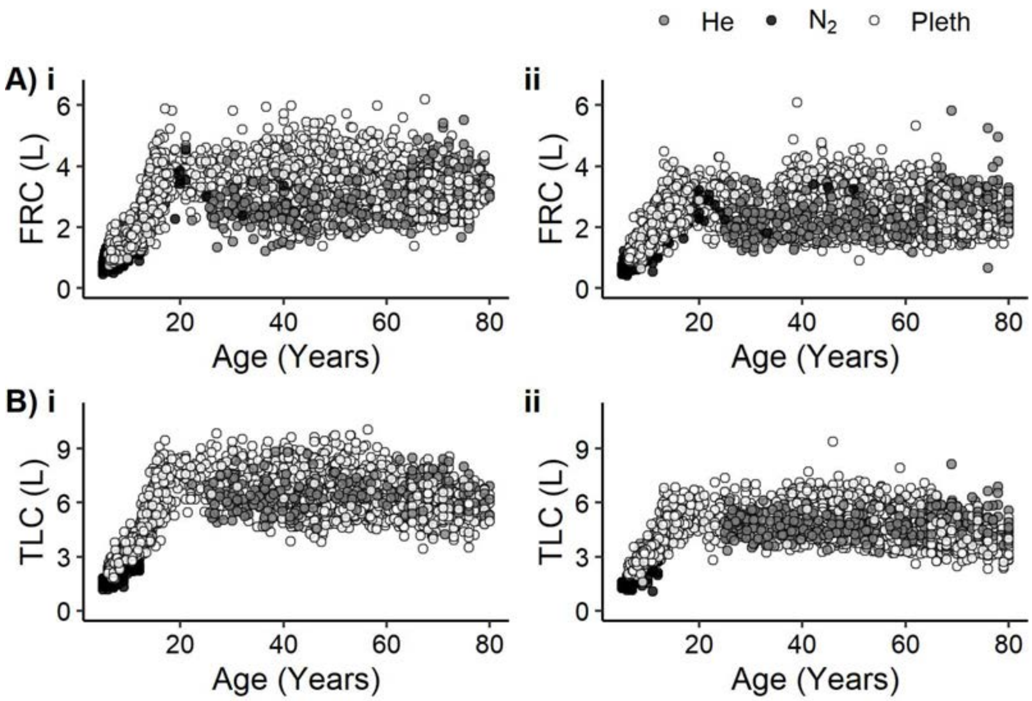

FIGURE S2 Comparison of FRC and TLC data by collection method. Measurements of functional residual capacity (FRC: panel A) and total lung capacity (TLC); panel B for males (i) and females (ii)) demonstrated overlap between the three different measurement techniques: dilution using Helium dilution (He: grey circles) or Nitrogen washout (N_2: black circles) and body plethysmography (Pleth: open circles).

TABLE S1 Regression coefficients of method relative to Plethysmography from the multiple regression analysis of each index

	He Males	He Females	N_2 Males	N_2 Females
FRC	-0.06 (0.01)	-0.02 (0.01)	-0.12 (0.02)	-0.09 (0.02)
TLC	0.01 (0.01)	-0.01 (0.01)	-0.14 (0.02)	-0.16 (0.02)
RV	0.08 (0.2)	0.13 (0.02)	0.13 (0.1)	0.37 (0.09)
RV/TLC	0.06 (0.01)	0.11 (0.01)	0.35 (0.07)	0.49 (0.07)

Positive coefficients indicate by how much the average result (in litres) is greater than that recorded by Plethysmography, whereas negative coefficients indicate by how much the average result is lower than that recorded by Plethysmography.

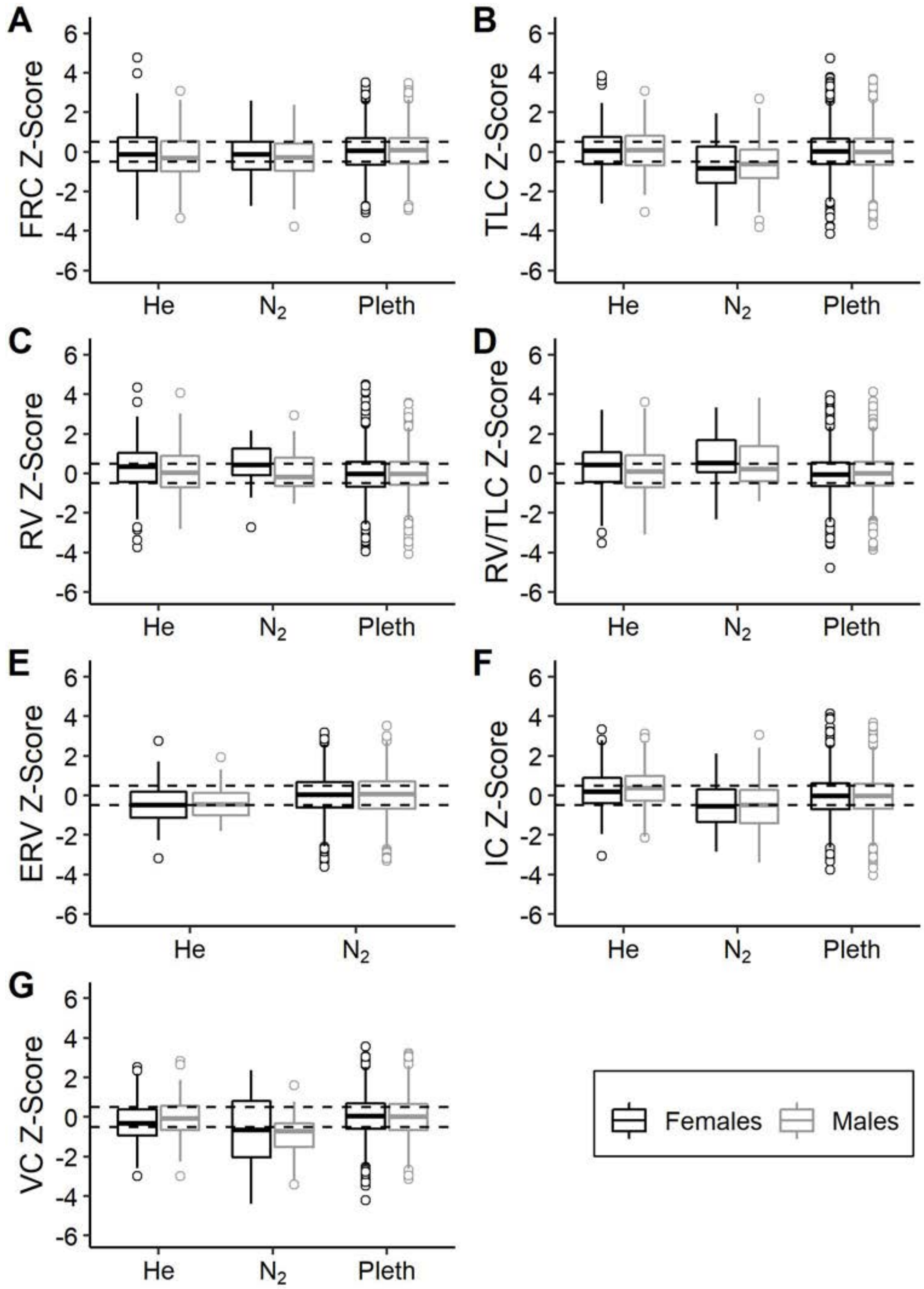

FIGURE S3 Comparison of technique differences for each lung volume outcome developed from predicted reference equations. Comparison of calculated z-scores for A) FRC, B) TLC, C) RV, D) RV/TLC, E) ERV, F) IC, and G) VC for data collected using multiple breath washout (He dilution (He) and Nitrogen washout (N_2)) and plethysmography (Pleth). Boxes represent the first and third quartiles (the 25th and 75th percentiles), and whiskers are 1.5*IQR (IQR is distance between the first and third quartiles). Middle line is the median, and plotted points are outliers >1.5* IQR. Dashed lines correspond to +/- 0.5 Z-scores.

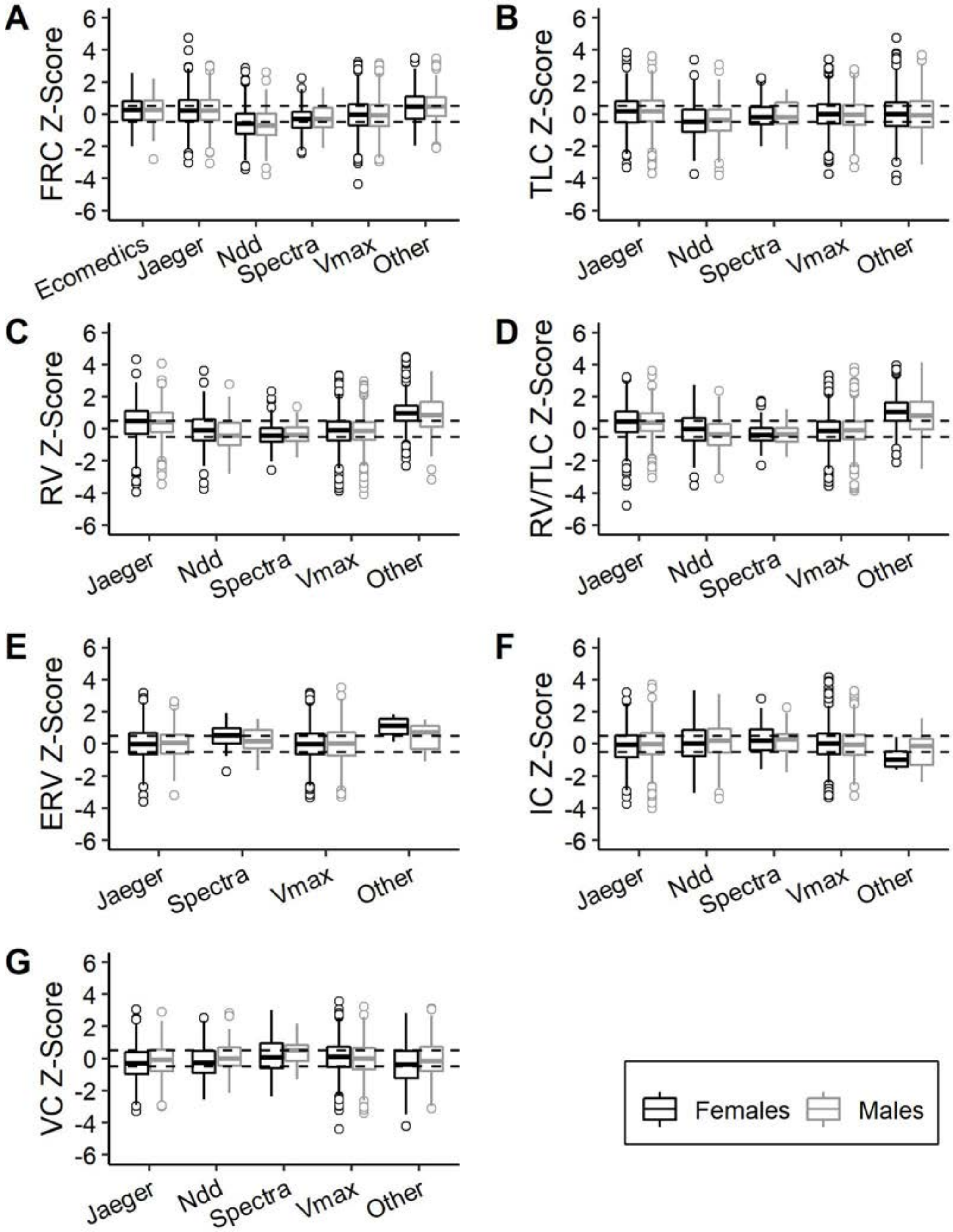

FIGURE S4 Comparison of equipment differences for each lung volume outcome developed from predicted reference equations. Differences in calculated z-scores for A) FRC, B) TLC, C) RV, D) RV/TLC, E) ERV, F) IC, and G) VC in males and females according to the type of equipment that was used to collect the data. Boxes represent the first and third quartiles (the 25th and 75th percentiles), and whiskers are 1.5*IQR (IQR is distance between the first and third quartiles). Middle line is the median, and plotted points are outliers >1.5* IQR. Dotted lines correspond to +/- 0.5 Z-scores.

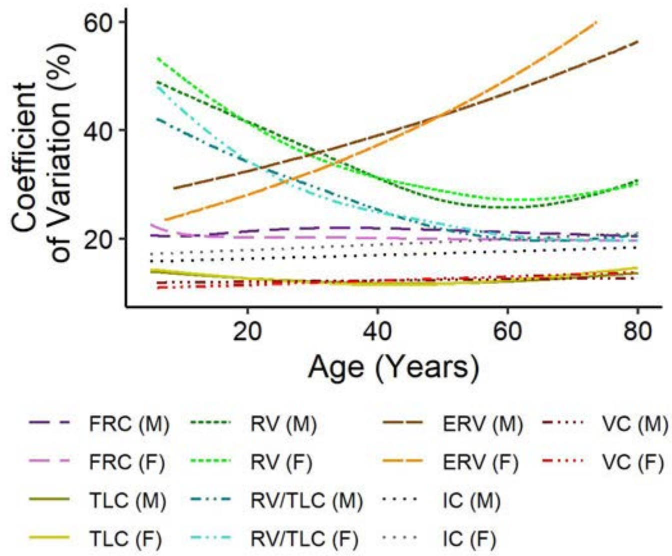

FIGURE S5 Population variability (Coefficient of variation) for FRC, TLC, RV, RV/TLC, ERV, IC and VC individually for males and females.

Population variability

The population variability for FRC was similar between males and females and relatively age independent (figure S5). Other lung volume indices varied with age, highlighting that fixed limits of normality are not appropriate (figures S5 and S6). For TLC, younger children had more variable results than adolescents and adults, with the population variability between males and females being similar. Population variability was markedly increased for RV and consequently RV/TLC in children and adults less than 40 years of age. In contrast population variability was highest in older adults for ERV (figure S5).

Impact of obesity on lung volume outcomes

A weight bias was noted in FRC and ERV in obese males, with no differences observed for TLC and RV or females (Table S2; Figure S7). However, most observations (94.2%) were within +/- 2 z-scores and data from these individuals was retained within the development reference equations (Figure S7). At the individual level the difference between the predicted values was minimal (Table S3).

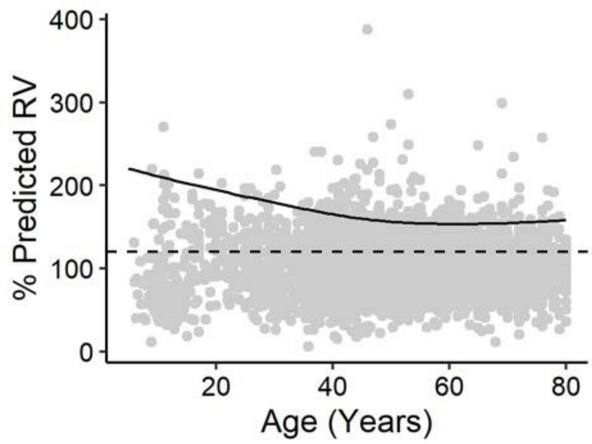

FIGURE S6 Upper limit of normal for the RV relative to the commonly used cut-off of 120% predicted.

TABLE S2 Mean (SD) Lung Volume Z scores for overweight and normal weight subjects

	Overweight and Obese		Normal Weight	
	Male	**Females**	**Male**	**Female**
FRC	-0.19 (1.01)	-0.24 (0.99)	0.27 (0.92)	0.26 (0.95)
n	1805	2122	1271	1967
TLC	-0.05 (1.01)	-0.08 (1.01)	0.08 (0.98)	0.09 (0.98)
n	1771	2088	1148	1783
RV	-0.06 (1.00)	-0.04 (0.99)	0.13 (0.99)	0.07 (1.00)
n	1612	1937	734	1352
ERV	-0.19 (1.00)	-0.25 (0.99)	0.43 (0.86)	0.36 (0.89)
n	1356	1648	599	1113

Data from 25 participants (18 males, 7 females) had missing weight and hence BMI values. All obesity analyses have excluded these 25 individuals.

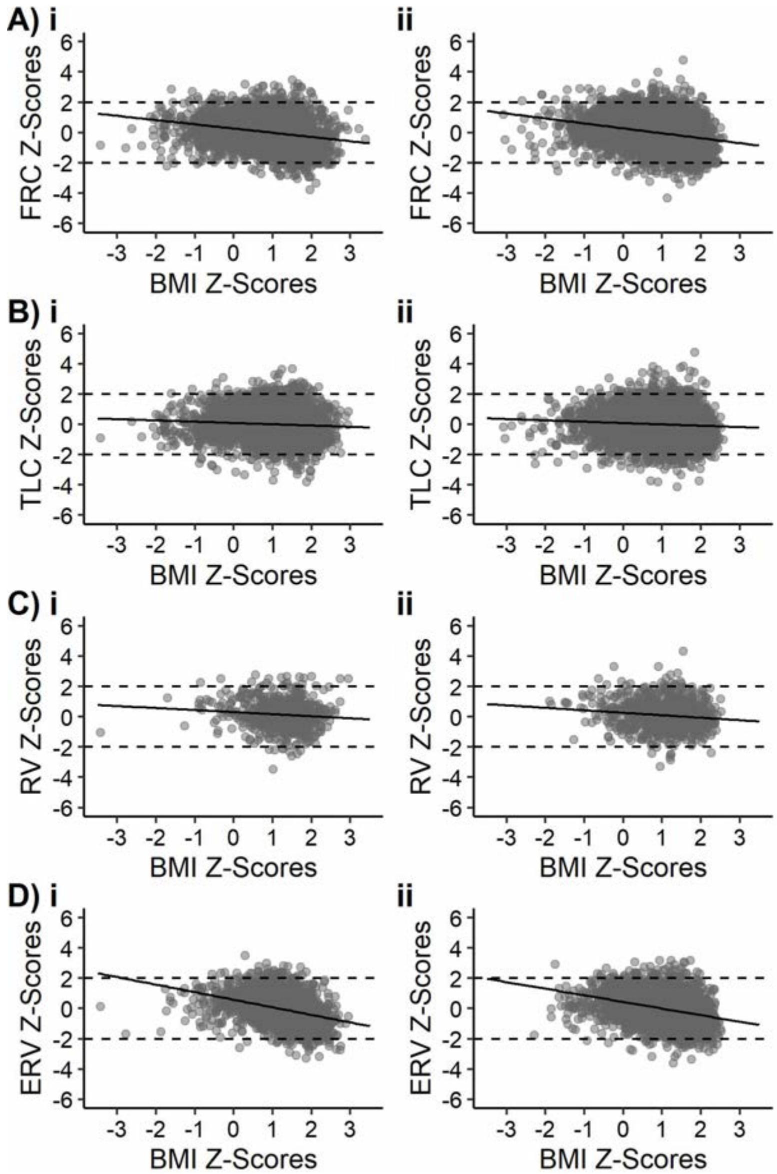

FIGURE S7 Distribution of A) FRC, B) TLC, C) RV, D) RV/TLC, E) ERV, F) IC, and G) VC z-scores against BMI z-scores for males (i) and females (ii) with a linear regression fitted through the data to identify an association with BMI Z-score. Z-scores for BMI were calculated for adults to allow for a continuous outcome across all ages. To facilitate interpretation of BMI across all-ages, BMI z-scores were calculated for adults using the paediatric growth charts at age 19 applied to all adults.

TABLE S3 Comparison of predicted values and the upper limit of normal (ULN) between the equations derived for normal weight individuals only, and those with all observations

Male, 1.75m, 40y BMI	TLC	Predicted Values TLC ULN	FRC	FRC ULN	RV	RV ULN
Equations based on 'normal' body weight	7.032	8.616	3.532	4.954	1.632	2.655
Equations including obese/overweight	6.915	8.517	3.183	4.751	1.533	2.582

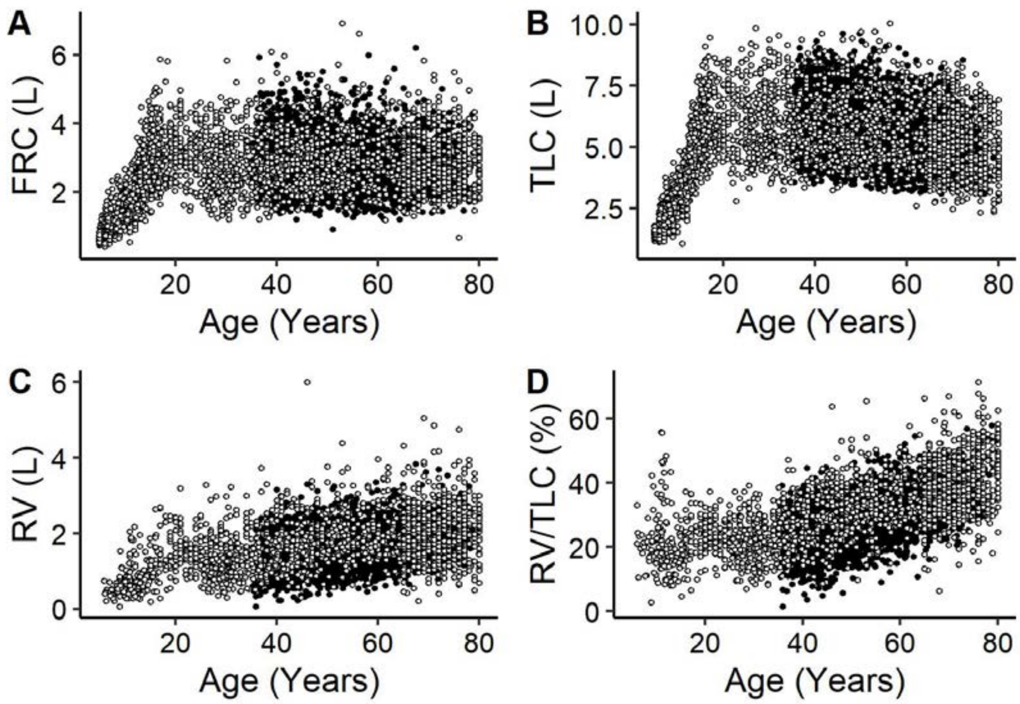

FIGURE S8 Scatter plots showing the degree of overlap between the data from the largest centre (black) and all the other GLI data (white) for a) FRC, b) TLC, c) RV and d) RV/TLC. Sensitivity analyses showed that equations were essentially unchanged if smaller sub-sets of the data from the largest centre were used instead of the full sample size.

Comparison with Existing Reference Values

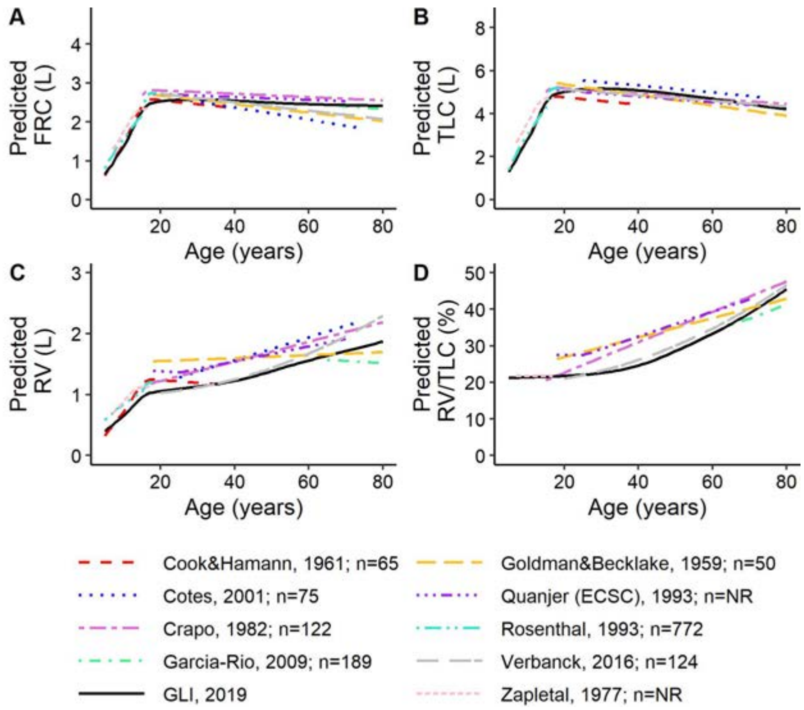

FIGURE S9 Comparison with commonly used reference equations in females.

The VC equations were similar to those of FVC measured by spirometry (Figure S10). However, the VC equations are based on a significantly smaller sample size and limited data in early adulthood which could explain the reported differences (Table S5).

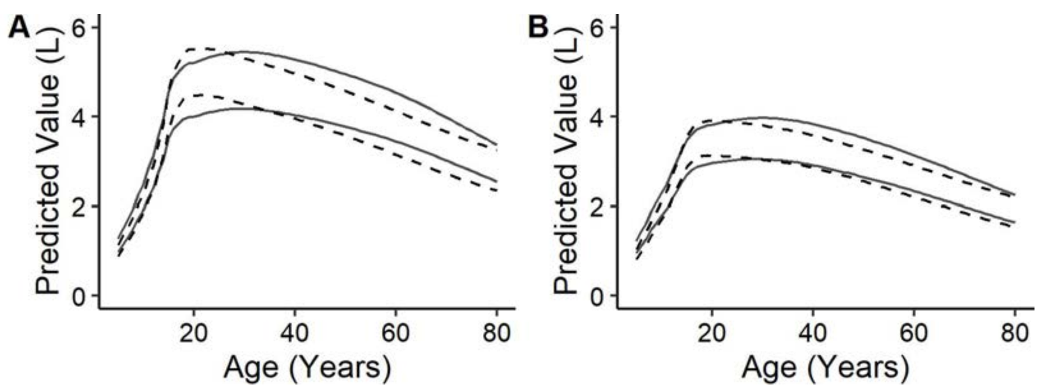

FIGURE S10 Mean and LLN of predicted VC (*Lung volumes*) (solid) and predicted FVC (*Spirometry*) (dashed) for males (A) and females (B).

TABLE S4 Comparison of VC and FVC in a representative male and female

	15y	20y	40y	60y
Male 1.75m				
VC	4.66	5.00	5.37	4.89
FVC	4.67	5.28	5.05	4.47
Female 1.65m				
VC	3.63	3.84	4.06	3.51
FVC	3.72	3.92	3.81	3.28

Worked Example for FRC

Male 30 years old, 178cm, FRC = 3.7 L
Mspline = -0.01119485 Sspline = 0.03213313

M = exp(-13.4898 + 0.1111 · ln(age) + 2.7634 · ln(height) + Mspline)
M = exp(-13.4898 + 0.1111 · ln(30) + 2.7634 · ln(178) – 0.01119485)
M = 3.307587

S = exp(-1.60197 + 0.01513 · ln (age) + Sspline)
S = exp(-1.60197 + 0.01513 · ln (30) + 0.03213313)
S = 0.2190672

L = 0.3416

% predicted = (measured/M) · 100
% predicted = (3.7 / 3.307587) · 100
% predicted = 111.864

Lower limit of Normal (LLN) (5th percentile) = exp(ln(M) + ln(1 - 1.645 · L · S) / L)
Lower limit of Normal (LLN) (5th percentile) = exp(ln(3.307587) + ln(1 - 1.645 · 0.3416 · 0.2190672) / 0.3416)
Lower limit of Normal (LLN) (5th percentile) = 2.251922

Z-score = $((\text{measured}/M)^{L} - 1)/(L \cdot S)$
Z-score = $((3.7/3.307587)^{0.3416} - 1)/(0.3416 \cdot 0.2190672)$
Z-score = 0.5211515

TABLE S5 Derivation of centiles from calculated z scores

Percentile	z-score	Percentile	z-score	Percentile	z-score
1	-2.326	34	-0.412	67	0.44
2	-2.054	35	-0.385	68	0.468
3	-1.881	36	-0.358	69	0.496
4	-1.751	37	-0.332	70	0.524
5	-1.645	38	-0.305	71	0.553
6	-1.555	39	-0.279	72	0.583
7	-1.476	40	-0.253	73	0.613
8	-1.405	41	-0.228	74	0.643
9	-1.341	42	-0.202	75	0.674
10	-1.282	43	-0.176	76	0.706
11	-1.227	44	-0.151	77	0.739
12	-1.175	45	-0.126	78	0.772
13	-1.126	46	-0.1	79	0.806
14	-1.08	47	-0.075	80	0.842
15	-1.036	48	-0.05	81	0.878
16	-0.994	49	-0.025	82	0.915
17	-0.954	50	0	83	0.954
18	-0.915	51	0.025	84	0.994
19	-0.878	52	0.05	85	1.036
20	-0.842	53	0.075	86	1.08
21	-0.806	54	0.1	87	1.126
22	-0.772	55	0.126	88	1.175
23	-0.739	56	0.151	89	1.227
24	-0.706	57	0.176	90	1.282
25	-0.674	58	0.202	91	1.341
26	-0.643	59	0.228	92	1.405
27	-0.613	60	0.253	93	1.476
28	-0.583	61	0.279	94	1.555
29	-0.553	62	0.305	95	1.645
30	-0.524	63	0.332	96	1.751
31	-0.496	64	0.358	97	1.881
32	-0.468	65	0.385	98	2.054
33	-0.44	66	0.412	99	2.326

Z-scores can be converted to percentiles using the standard normal distribution table.