J Bras Pneumol. 2020;46(3):e20190138
https://dx.doi.org/10.36416/1806-3756/e20190138

ORIGINAL ARTICLE

Reference values for spirometry in Brazilian children

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Submitted: 1 August 2019.
Accepted: 13 October 2019.

ABSTRACT

Objective: To generate reference values for spirometry in Brazilian children 3-12 years of age and to compare those values with the values employed in the equations currently in use in Brazil. **Methods:** This study involved healthy children, 3-12 years of age, recruited from 14 centers (primary data) and spirometry results from children with the same characteristics in six databases (secondary data). Reference equations by quantile regressions were generated after log transformation of the spirometric and anthropometric data. Skin color was classified as self-reported by the participants. To determine the suitability of the results obtained, they were compared with those predicted by the equations currently in use in Brazil. **Results:** We included 1,990 individuals from a total of 21 primary and secondary data sources. Of those, 1,059 (53%) were female. Equations for FEV_1, FVC, the FEV_1/FVC ratio, FEF between 25% and 75% of the FVC ($FEF_{25-75\%}$) and the $FEF_{25-75\%}$/FVC ratio were generated for white-, black-, and brown-skinned children. The logarithms for height and age, together with skin color, were the best predictors of FEV_1 and FVC. The reference values obtained were significantly higher than those employed in the equations currently in use in Brazil, for predicted values, as well as for the lower limit of normality, particularly in children with self-reported black or brown skin. **Conclusions:** New spirometric equations were generated for Brazilian children 3-12 years of age, in the three skin-color categories defined. The equations currently in use in Brazil seem to underestimate the lung function of Brazilian children 3-12 years of age and should be replaced by the equations proposed in this study.

Keywords: Spirometry; Reference values; Child; Child, preschool; Respiratory function tests.

INTRODUCTION

Spirometry is the most widely used complementary test for the assessment of respiratory function in children, and reference values are essential for its clinical application. Healthy individuals, ideally of the same ethnicity as the patients in whom the test will be used, are used in the generation of such reference values.[1]

In Brazil, reference values for spirometry in children were generated between 1989 and 1991 from a sample of individuals in the city of São Paulo. The values were then published in the 2002 *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) Guidelines for Pulmonary Function Tests.[2] The study that generated those values included a total of 602 children (defined as individuals 6-14 years of age) and youths (defined as individuals 14-24 years of age) with self-reported skin color of white, black, or brown. However, the authors did not propose distinct equations for black and brown children; nor did they offer age- and height-adjusted values for the FEV_1/FVC ratio.[2]

In 2009, Stanojevic et al.[3] proposed international spirometric equations for white children, their sample including a small proportion of children in Brazil. In 2012, the Global Lung Function Initiative (GLI) published equations for use in White, Black, Asian, and mixed-race individuals aged 3 to 95 years.[4] However, those equations did not use spirometry data from healthy African or Latin American children and have therefore not been validated for use in Brazil. More recently, reference values for Brazilian children under 6 years of age were obtained in the cities of Recife, in the state of Pernambuco,[5] and Sete Lagoas, in the state of Minas Gerais.[6]

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Financial support: This study was carried out with the financial support of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association), the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development), the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education), and AstraZeneca.

Given the lack of spirometry reference equations for children that have been validated for use in Brazil, the present study aimed to generate reference values for spirometry in Brazilian children 3-12 years of age, who are healthy from a respiratory standpoint, using a large, representative sample. Another objective was to compare the spirometry equations obtained in this study with those currently in use in Brazil.[2,4]

METHODS

Study design, inclusion criteria, and exclusion criteria

This was a multicenter, cross-sectional observational study involving healthy children (defined here as individuals 3-12 years of age) with a self-reported skin color of white, black, or brown. For subject selection, we used a standardized questionnaire containing specific questions about respiratory diseases, based on the American Thoracic Society/Division of Lung Diseases questionnaire for children, known as the ATS-DLD-78-C.[7] This instrument, which is formally recommended for use in epidemiological studies, has been adapted and validated for use in Brazil.[7]

The following exclusion criteria were applied: gestational age < 37 weeks, low birth weight (< 2,500 g), signs and symptoms of chronic respiratory disease, recurrent wheezing (three or more episodes), heart disease, scoliosis, history of thoracic surgery, and any disease that could prevent a forced expiratory maneuver.

Setting up the spirometry database

The data were obtained from a prospective multicenter study conducted in 16 Brazilian cities (primary data) and from spirometry databases generated in other studies of healthy children in the same age group (secondary data).

The primary database was composed of data obtained prospectively through a strict observance of the study protocol. Participants whose data were analyzed in the primary database were recruited in the following Brazilian cities (states): Belo Horizonte (Minas Gerais); Blumenau (Santa Catarina); Campinas (São Paulo); Curitiba (Paraná); Foz do Iguaçu (Paraná); Niterói (Rio de Janeiro); Porto Alegre (Rio Grande do Sul); Recife (Pernambuco); Ribeirão Preto (São Paulo); Rio de Janeiro (Rio de Janeiro); Salvador (Bahia); São Luiz Gonzaga (Rio Grande do Sul); and Sete Lagoas (Minas Gerais).

The secondary database was composed of spirometric data obtained from healthy children 3-12 years of age recruited in other studies, provided that the inclusion criteria and quality control were similar to those established in the original protocol. Those data were obtained in the city of São Paulo, as well as in three cities in the state of Rio Grande do Sul (Porto Alegre, Caxias do Sul, and Rio Grande). The collaborating researchers authorized the inclusion of their databases in the present analysis. Finally, the primary and secondary databases were combined into a single database after we confirmed, by multiple linear regression, that the data source had no significant effect on the variables FVC, FEV_1, FEV_1/FVC ratio, and $FEF_{25-75\%}$.

Spirometry and anthropometry

We collected data on gender, date of birth, birth weight, and skin color. The skin color (white, brown, or black) was self-reported by the participants.

Weight and height were measured on the day of the pulmonary function test. For the anthropometric assessment, we used digital scales with a precision of 100 g and stadiometers with a precision of 1 mm. The height was measured in triplicate, the mode of the three measurements being recorded. Maximum expiratory maneuvers were obtained with a Koko PFT Spirometer (nSpire Health Inc., Longmont, CO, USA), in accordance with the protocols of the American Thoracic Society and European Respiratory Society.[1,8] The spirometry results were registered in an electronic spreadsheet, together with the clinical and the anthropometric data.

Quality control

The flow-volume curves and the results were first analyzed by the researchers at each center at the time of collection and rejected if they did not meet the acceptance and reproducibility criteria previously described.[1] The spirometric curves were also reviewed by two researchers before inclusion in the consolidated database. Finally, spirometric data with extreme values, defined as a difference of more than four standard deviations between what was predicted by the new equations and the observed value, were excluded because of the likelihood that they were technical or typographical errors.

Statistical analysis

Demographic, anthropometric, and spirometric data were transferred to the R computing environment, where statistical calculations were performed.[9]

The lung function, height, and age variables were log transformed to correct the nonlinearity of the relationships and to stabilize the variance.

Reference equations for FVC, FEV_1, the FEV_1/FVC ratio, $FEF_{25-75\%}$, and the $FEF_{25-75\%}$/FVC ratio were generated by quantile regression so as to estimate the predicted value (50th percentile) and the lower limit of normal (5th percentile). To calculate the Z-score, we generated equations by multiple linear regression. Height, age, gender, and skin color were considered independent variables. We used multiple linear regression to compare the lung function variables of individuals by skin color. We considered lung function parameters as dependent variables, adjusted for height and age, and tested the statistical significance of skin color in the model. The same procedure was used in order to compare the primary and the secondary databases.

The results obtained were compared with the predicted values defined in the equations established in the SBPT

guidelines,[2] which propose the same equation for all children, regardless of skin color. For the comparison with the GLI equations[4], we applied the so-called "Caucasian" equations to the self-described white children, the "Black" equations to the self-described black children, and the "other/mixed" equations to the self-described brown children. The statistical analysis of the comparison between the observed and the predicted values was performed with the Mann-Whitney non-parametric test for paired samples. Descriptive statistical analyses were conducted, and linear regression models were created in the R language and environment for statistical computing.[9] The *quantreg* and *ggplot2* packages were also used in order to generate the quantile regression models and plots, respectively.

Ethics

Parents or legal guardians authorized the spirometry and gave written informed consent or assent. The study was approved by the Research Ethics Committee at the Pontifical Catholic University of Rio Grande do Sul (Reference no. 09/04787) and was later approved by the research ethics committee at each participating center. Collaborating researchers who shared their databases consented to the use of their data for generating reference values.

RESULTS

After subjects for whom there were incomplete data, nonreproducible spirometric curves, or extreme values had been excluded, the primary and secondary databases contained information on 936 subjects and 1,054 subjects, respectively. Therefore, the final database contained information on 1,990 subjects, of whom 1,059 (53%) were female and 931 (47%) were male. The various data sources are shown in Table 1. The medians (ranges) for age, height, and weight were, respectively, 9.04 years (3.0-12.9 years), 134.5 cm (85-176 cm), and 30.5 kg (11-89 kg). The age and height histograms are shown as supplementary material (Figure S1). Among the 1,990 subjects included in the analyses, the self-reported skin color was white in 1,353 (68%), black in 184 (9%), and brown in 386 (19%). The remaining 67 subjects (3%) did not report their skin color.

Comparison of lung function between the primary and secondary databases

The multiple linear regression models adjusted for age, gender, skin color, and height revealed no significant differences between the primary and secondary data for FVC, FEV_1, FEV_1/FVC ratio, and $FEF_{25-75\%}$.

Lung function by skin color

After adjusting for height and age through a multiple linear regression model, we found that the white children had significantly higher FVC and FEV_1 values than did the black and brown children. The black and brown children did not differ significantly regarding their FVC ($p = 0.582$), FEV_1 ($p = 0.561$), FEV_1/FVC ratio ($p = 0.900$), or $FEF_{25-75\%}$ ($p = 0.925$) variables. Therefore, for subsequent comparative analyses and the generation of the equations, we divided the subjects into two groups: white children; and black/brown children.

Table 1. Primary and secondary data sources: location and number of participating individuals (N = 1,990).

Data source	City, state	Individuals	
		n	%
Primary	Recife, PE	176	8.8
	Sete Lagoas, MG	164	8.2
	Porto Alegre, RS	156	7.8
	São Luis Gonzaga, RS	76	3.8
	Porto Alegre, RS	68	3.4
	Foz do Iguaçu, PR	48	2.4
	Salvador, BA	42	2.1
	Blumenau, SC	42	2.1
	Campinas, SP	34	1.7
	Ribeirão Preto, SP	32	1.6
	Rio de Janeiro, RJ	32	1.6
	Niterói, RJ	28	1.4
	Curitiba, PR	22	1.1
	Belo Horizonte, MG	16	0.8
Secondary	São Paulo, SP	266	13.4
	Porto Alegre, RS	242	12.2
	Porto Alegre, RS	220	11.1
	Rio Grande, RS	188	9.4
	Porto Alegre, RS	93	4.7
	Caxias do Sul, RS	45	2.3

PE: Pernambuco; MG: Minas Gerais; RS: Rio Grande do Sul; PR: Paraná; BA: Bahia; SC: Santa Catarina; SP: São Paulo; and RJ: Rio de Janeiro.

The black/brown children showed significantly lower FVCs in comparison with the white children, the mean differences (95% CIs) being −4.7% (−6.3% to −3.1%) for girls and −3.2% (−4.8% to −1.6%) for boys ($p < 0.001$ and $p < 0.01$, respectively). Similar differences were found for FEV_1: −4.3% (−5.8% to −2.8%) for girls and −2.2% (−3.8% to −0.7%) for boys ($p < 0.0010$ and $p < 0.050$, respectively). The differences between the two skin-color groups did not achieve statistical significance for $FEF_{25-75\%}$ or for the FEV_1/ FVC ratio. Therefore, skin color was not used as a predictor for these variables in the equations. The black/brown children had higher $FEF_{25-75\%}$/FVC ratios than did the white children ($p < 0.001$ for both genders).

Generating the predicted value equations

The equations for the predicted values and for the lower limit of normal were generated separately for female and male individuals, as shown in Table 2. The variables used in calculating the FVC and FEV_1 logarithms were the natural logarithms of height and age plus skin color, a value of 1 being assigned to the black/brown children group and a value of 0 being assigned to the white children group. For the calculation of the $FEF_{25-75\%}$ logarithm, natural logarithms of height and age were used. To calculate the predicted value for the FEV_1/FVC ratio, only the height logarithm was used, because the models did not show age or skin color to be significant. For the $FEF_{25-75\%}$/FVC ratio model, only the height and skin color logarithms were found to be significant. The adjusted correlation coefficient for the equations ranged from 0.83 to 0.85 for FVC and FEV_1, for both genders. As references, two-dimensional representations of the relationships that FEV_1 and FVC had with height, stratified by gender and skin color, can be seen in Figure 1, whereas the relationships that FEV_1/FVC ratio and $FEF_{25-75\%}$ had with height, stratified by gender, can be seen in Figure 2. The equations for calculating the Z-scores are included in the supplementary material (Table S1).

Comparisons with the SBPT and GLI equations

The comparison between the values observed in our study and those predicted by the SBPT[2] and GLI[4] equations are shown in Table 3. The values predicted by the SBPT[2] equations significantly underestimate FVC and FEV_1, when compared with those observed in our sample. For FVC, the mean amplitude of that difference was 12.5% (230 mL) and 10.2% (205 mL) in white girls and boys, respectively ($p < 0.001$ for both). For FEV_1, the difference was 9.7% (157 mL) and 5.6% (101 mL) in white girls and boys, respectively ($p < 0.001$ for both).

For black/brown children, the differences between the values predicted by the SBPT[2] and the value observed in our sample were smaller, although still considerable. The FVC values in our sample were 134 mL and 181 mL higher than those predicted by the SBPT equation.[2] For girls and boys, the differences were 132 mL and 192 mL, respectively ($p < 0.001$ for

Table 2. Equations for predicted spirometry values children 3-12 years of age in Brazil.[a]

Gender	Predicted value (50th percentile)				Lower limit of normal (5th percentile)			
Female	LN(FVC)	LN(FEV_1)	FEV_1/FVC	LN($FEF_{25-75\%}$)	LN(FVC)	LN(FEV_1)	FEV_1/FVC	LN($FEF_{25-75\%}$)	$FEF_{25-75\%}$/FVC
Intercept	−10.741935	−9.967740	1.437685	−7.385469	5.041747	−10.325884	−8.934018	1.313149	−7.855190	3.919387
LN(Height)	2.261976	2.088950	−0.106215	1.594033	−0.785773	2.098703	1.768038	−0.100805	1.673427	−0.642607
LN(Age)	0.156836	0.150386		0.203576		0.230220	0.290733		0.056126	
Skin color	−0.041015	−0.048582			0.046472	−0.073692	−0.054695			0.027623
Male	LN(FVC)	LN(FEV_1)	FEV_1/FVC	LN($FEF_{25-75\%}$)	$FEF_{25-75\%}$/FVC	LN(FVC)	LN(FEV_1)	FEV_1/FVC	LN($FEF_{25-75\%}$)	$FEF_{25-75\%}$/FVC
Intercept	−11.358191	−10.434226	1.760961	−6.957857	6.185501	−9.327490	−8.960184	1.942780	−5.356269	4.579022
LN(Height)	2.419817	2.207609	−0.176748	1.527303	−1.044205	1.890179	1.820202	−0.231255	1.085145	−0.786610
LN(Age)	0.115477	0.114001		0.138649		0.268924	0.208981		0.211021	
Skin color	−0.028745	−0.031836			0.093297	−0.042377	−0.026383			0.036968

NL: natural logarithm. [a]Height in centimeters; age in years; skin color: white = 0, black/brown = 1.

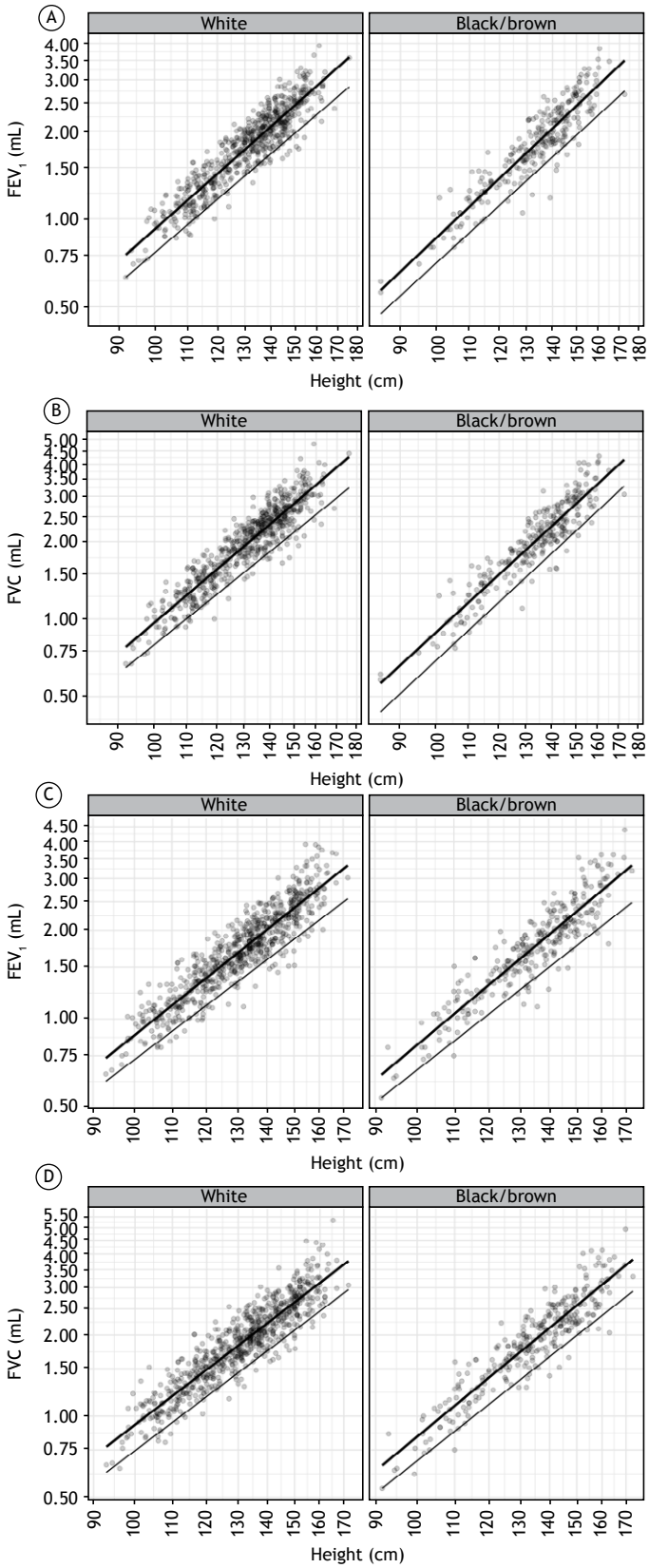

Figure 1. Lung function variables versus height in white children and in brown and black children (male: A and B, female: C and D), showing the 50th percentile (thick line) and the 5th percentile (thin line) for FEV_1 (A and C) and FVC (B and D).

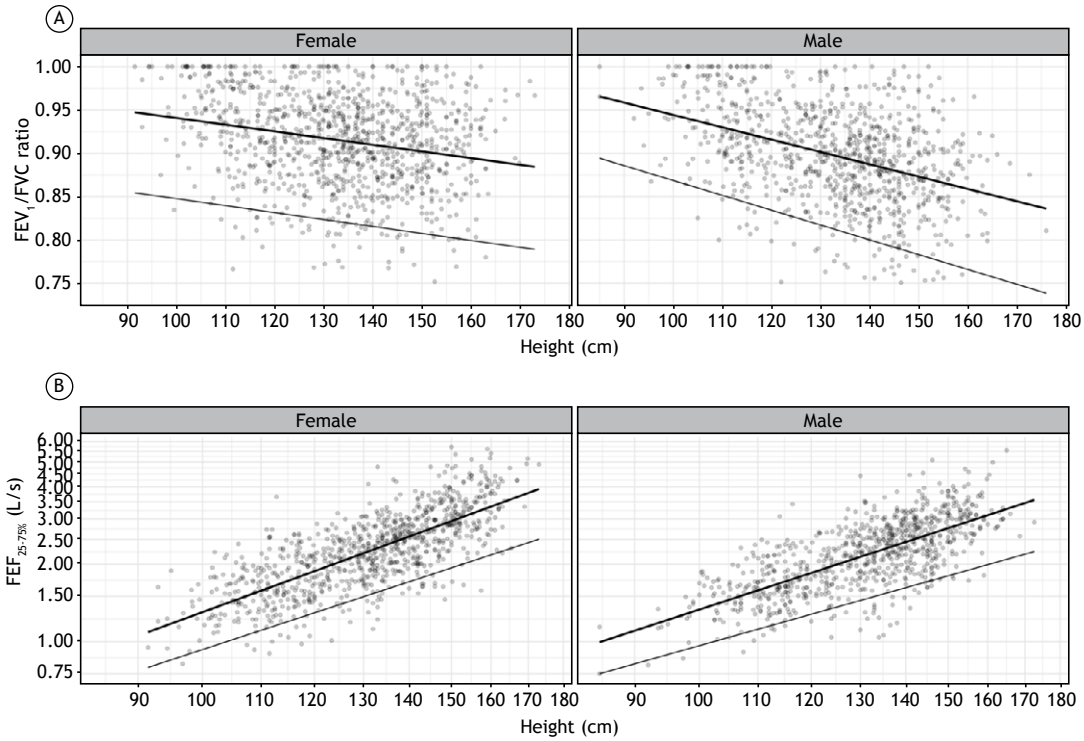

Figure 2. FEV_1/FVC ratio (A) and $FEF_{25-75\%}$ (B) versus height in white and black/brown male and female children, showing the 50th percentile (thick line) and the 5th percentile (thin line).

both). For black children, the differences between the observed FEV_1 values and those predicted by the SBPT equation[2] were smaller and not statistically significant. In our sample, the FEV_1/FVC ratio was approximately 0.04 points lower for boys and 0.02-0.03 points lower for girls when compared with the values predicted by the SBPT equation[2]. When applying the lower limits of normal of 0.83 and 0.81 to the FEV_1/FVC ratios for boys and girls, respectively, as proposed in the SBPT equation[2], 14.6% and 4.9% of the sample, respectively, were classified as "abnormal".

The international GLI equation[4] also underestimates the lung function of Brazilian children, the greatest differences being for black children, for whom the observed FEV_1 was 17.3% (262 mL) for boys and 14.9% (249 mL) for girls, higher than those predicted ($p < 0.001$ for both). Among black children, the mean FEV_1 Z-score was 1.32 for boys and 1.16 for girls. Among brown children, the FEV_1 Z-score was also quite high for boys and girls, with mean values of 0.75 and 0.60, respectively. Among white children, the mean FVC Z-score was 0.10 for boys and 0.16 for girls, compared with 1.13 and 0.61, respectively, among black children and 0.99 and 0.48, respectively, among brown children. The comparison of the FEV_1/FVC ratios found in our sample with those predicted by the GLI[4] also showed discrepancies ranging from 0.011 (not significant) to 0.017 ($p < 0.05$). The mean Z-scores in our sample were 0.32 and 0.33 for white girls and boys and 0.22 and 0.25 for black/brown girls and boys.

Table 4 shows the comparison between the lower limit of normal values proposed by the quantile equations generated in this study and those proposed by the GLI equations.[4] The differences in FVC and FEV_1 were small for white children and significantly larger for black/brown children. The lower limit of normal of the FEV_1/FVC ratio predicted by the GLI[4] was also significantly lower than that predicted by the equations proposed in this study. Those values can be found in the supplementary material (Figure S2).

DISCUSSION

In the present study, lung function data for 1,990 children in 16 Brazilian urban centers, from 21 different databases, were compiled to generate equations for predicted values and lower limits of normal. To our knowledge, this was the largest and most representative study on the lung function of children in Brazil, due to the size and geographic diversity of the sample. The data collected show that Brazilian children have significantly higher lung function values than those predicted by the equations currently used in Brazil,[2,4] emphasizing the clinical importance this study can have in the functional assessment of children in the country.

There are many possible explanations for the fact that we observed lung function values higher than those predicted by the SBPT equations.[2] First, the technological differences in the equipment used and the stricter acceptability criteria, in particular the exclusion criteria for cases of early termination and back-extrapolated

Table 3. Absolute and relative differences between the values obtained in the present study and the values predicted by the equations currently in use in Brazil.[a]

	GLI[4] (N = 1,990)			SBPT[21] (N = 1,624)		
Male	White	Black	Brown	White	Black	Brown
FEV_1 (mL)	55 (3.5%)*	262 (17.3%)*	159 (8.7%)*	101 (5.6%)*	43 (1.9%)	96 (4.8%)*
FVC (mL)	17 (1.3%)	257 (15.0%)*	147 (6.8%)*	205 (10.2%)*	132 (6.1%)*	192 (8.9%)*
FEV_1/FVC ratio	0.017*	0.011	0.012*	−0.042*	−0.043*	−0.038*
$FEF_{25-75\%}$ (mL/s)	114 (6.0%)*	419 (22.4%)*	287 (12.7%)*	17 (1.3%)	68 (2.5%)	82 (3.8%)
Female						
FEV_1 (mL)	67 (4.1%)*	249 (14.9%)*	124 (7.1%)*	156 (9.7%)*	59 (3.6%)	109 (5.8%)*
FVC (mL)	35 (2.2%)*	251 (13.3%)*	114 (5.8%)*	229 (12.5%)*	134 (6.9%)*	181 (9.1%)*
FEV_1/FVC ratio	0.013*	0.008*	0.007*	−0.019*	−0.030*	−0.022*
$FEF_{25-75\%}$ (mL/s)	131 (5.7%)*	313 (14.4%)*	192 (9.2%)*	295 (13.8%)*	165 (7.3%)*	185 (8.5%)*

GLI: Global Lung Initiative; and SBPT: *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Association). *p < 0.05. Mann-Whitney test for paired samples.

Table 4. Differences between the values predicted by the equations proposed in the present study and those predicted by the Global Lung Initiative[4] equations, for the lower limit of normal.

Lower limit of normal	Female		Male	
	White	Brown and black	White	Brown and black
FVC	0.06%	3.00%	0.21%	6.98%*
FEV_1	2.00%	7.20%*	3.34%	11.97%*
FEV_1/FVC ratio	0.028*	0.012*	0.044*	0.027*
$FEF_{25-75\%}$	9.84%*	22.34%*	10.20%*	21.51%*

*p < 0.05. Mann-Whitney test for unpaired samples.

volume, may have contributed to the higher FVC and FEV_1 values observed in the present study. In addition, the prevalence of overweight and obesity has increased considerably in the past 25 years. In children and adolescents, overweight and obesity are associated with an up to 7.5% increase in FVC and FEV_1, and that could also partially explain the differences between the studies.[10] Furthermore, secular changes in lung function may have contributed, in part, to the higher FVC, FEV_1, and $FEF_{25-75\%}$ values observed. Improvements in the general health status and, in particular, the nutritional status of the population included in this study favor changes in body proportions and final height, affecting the predicted lung function values.[11]

Regarding the differences in flows and volumes found in the comparison with the multiethnic equations proposed by the GLI,[4] we must point out that the differences for white children, although statistically significant, are small. However, the values predicted by the GLI[4] for black and brown children, who make up the majority of the Brazilian population, are very far from what was observed in our study sample. We believe this discrepancy is due to the large European genetic contribution in individuals in Brazil who self-report their skin color as black or brown.[12,13]

The quantile equations generated from this sample resulted in values significantly higher than those predicted by the GLI[4] for FVC and FEV_1, and this is particularly important for establishing the lower limit of normal. These findings are in line with the validation studies of the GLI equations[4] conducted in Brazil and in other countries, which also found significant differences between the values observed and those predicted by the GLI equations for adults and children.[14-19] These results, taken together, suggest that there are limitations to the application of international equations and that local reference values are more suitable for lung function assessment.

This study has limitations that merit further discussion. First, we evaluated a convenience sample comprising predominantly white children living in the southern and southeastern regions of Brazil. According to data from the Brazilian Institute of Geography and Statistics,[20] Brazil has a population of 206.1 million, of which 97.3 million (47.2%) self-report their skin color as brown; 90.2 million (43.8%) self-report their skin color as white; and 16.8 million (8.2%) self-report their skin color as black. Therefore, in a fully representative sample of the Brazilian population, white individuals should compose approximately half, the other half comprising black and brown individuals. The absence of individuals from the northern and central-west regions needs to be corrected in subsequent studies. Another limitation is the lack of socioeconomic data, in particular, on parental level of education and income, as well as on environmental factors, because these unquestionably influence lung development and may explain, in part, the differences observed in lung function among the white, black, and brown children in our sample.[21,22] It is also noteworthy that we employed conventional multiple linear regression, in which it is assumed that the variance is homogeneously distributed over the

height and age range. This problem was mitigated by the log transformation of the data and because a narrow age range was assessed.

In summary, this study provides reference equations for FVC, FEV_1, the FEV_1/FVC ratio, $FEF_{25-75\%}$, and the $FEF_{25-75\%}$/FVC ratio for white, brown, and black children 3-12 years of age in Brazil. These new equations differ significantly from those currently in use in Brazil,[2,4] which tend to underestimate FVC and FEV_1 values. We suggest that these equations be revised periodically, with updates that include advances in the lung assessment methodology, the evaluation of larger samples, and improvement of the mathematical model, as well as better characterization of the ancestry and socioeconomic status of the participants.

COLLABORATORS

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