Development and validation of predictive equations for spirometry in Portuguese children

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Background: There are no data on lung function reference values for Portuguese children, and the contribution from the Portuguese data set in the Global Lung Function Initiative (GLI) is scant.

Objectives: We aimed to estimate new up-to-date reference values for Portuguese children by fitting a multivariable regression model to a general population sample. Further, we intended to assess the external validity of the obtained reference values and to compare them to the GLI reference values.

Methods: A random sample of 858 children from 20 primary schools were screened by health questionnaire, physical examination, and spirometry. Spirometric parameters recorded were FVC, FEV_1, and FEF_{25-75}. Multiple regression models were used to derive reference equations.

Results: Overall, 481 children, aged between 7 and 12 years, 267 boys (55.5%), were included. Boys had higher values for FVC and FEV_1 than girls ($P < .05$). The strongest correlation was found for FVC with height ($r = 0.71$ for boys and 0.70 for girls), while the lowest correlation was observed in both sexes for FEF_{25-75} with age ($r = 0.23$). Height was the most significant predictor of FVC, FEV_1, and FEF_{25-75} in our models. Weight and body mass index were not significant predictors for boys but had a significant effect on girls' equations for all spirometry parameters. Compared to obtained reference equations with GLI, they performed better for FVC in boys, FEV_1 in girls, and FEF_{25-75} in both boys and girls.

Conclusion: We offer up-to-date reference values of spirometry for Portuguese children that can be used in clinical practice and research. (J Allergy Clin Immunol Global 2023;2:100084.)

Key words: *Children, spirometry, reference values, lung function, linear regression*

Pulmonary function testing is essential in the diagnosis, assessment, and management of respiratory diseases in both children and adults.[1-4] Like other physiologic measures, the criteria for normality for spirometry relies on a comparison with reference values that are based on healthy subjects with the same anthropometric data and with the same relevant socioeconomic and ethnic characteristics.[5-8] Major predictors of lung function in adults and children are age, sex, ethnicity, and thorax size, which is indirectly measured by approximation using height and weight.[8,9] Currently there is a great availability of reference equations for spirometry that manufacturers can use in their equipment;[10-16] however, these equations should be used with caution if they are based on measures carried out several decades ago. Population anthropometric, health condition, and socioeconomic characteristics are evolutive conditions that affect lung function, and for these reasons, it is important to continually update spirometry reference equations.[17]

In Portugal, many of the equations provided by manufacturers are based on assessments performed over 20 years ago, and from populations with different anthropometric, ethnic, and socioeconomic characteristics. Also, technological developments since then, along with new equipment, software, and techniques, as well as changes in population characteristics, make the need for population-specific and updated equations even more urgent.[18]

In 2012, the European Respiratory Society Task Force, aiming to fulfill the need for standardization, derived continuous predictive equations and their lower limits of normality to be globally applicable.[19] Even across Europe there are significant differences in anthropometric and socioeconomic characteristics of populations, emphasizing the need for population-specific equations.[20,21] This population bias can occur in Portuguese children because the Mediterranean population is shorter than the central and north European populations.[22] Using reference data derived from a population similar to the one to be applied helps reduce misclassification with falsely negative or positive results.[5,23,24]

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Abbreviations used
BMI: Body mass index
CC: Correlation coefficient
GLI: Global Lung Function Initiative

Several studies have addressed spirometry reference values for children and preschool children,[25] but no data for this age group exist in Portugal. Therefore, we aimed to estimate new up-to-date reference values for Portuguese children by fitting a multivariable regression model to a general population sample. Further, we intended to assess the external validity of the obtained reference values and to compare them with the Global Lung Function Initiative (GLI) reference values.

METHODS

Ethics statement

This study enrolled participants from 2 different cohorts: derivation and validation. In both, data collection was approved by the University of Porto ethics committee, and written informed consent was obtained from each participant's caregiver. Children were also asked permission to perform the tests; because spirometry in particular depends on the subject's cooperation, participants who refused or who were afraid for any reason were not forced to continue.

Assessments and lung function testing

All participants underwent complete anthropometric measurements. Lung function values included FEV_1, FVC, and FEF_{25-75}. Reproducibility of FVC and FEV_1 was considered acceptable when the highest FVC and FEV_1 values did not exceed the second highest value by more than 5%. Each child's best flow–volume curve was selected. More details about our lung function testing methodology are available in the Online Repository at www.jaci-global.org.

Derivation cohort participants—ARIA study

Derivation cohort data were obtained from a cross-sectional analysis of 1602 children, aged 8 to 12 years, from 20 elementary schools in Porto (ARIA study). From the 1602 questionnaires that were sent, 688 parents did not return the consent forms, and of the remaining 914 children, 56 (6.1%) were excluded because of refusal to be assessed. Of the 858 children who underwent spirometry, 481 (56.1%) had full expiratory curves, according to the American Thoracic Society/European Respiratory Society recommendations. A total of 481 children were included in the final analysis, with age between 7 and 12 years and 267 boys (55.5%). Detailed data of the included children are provided in the Online Repository at www.jaci-global.org.

For the selected subjects, no significant differences were found between boys and girls in age (mean [SD] 8.8 [0.8] years; $P = .95$), height (135.7 [7.7] cm; $P = .44$), or weight (33.6 [8.5] kg; $P = .81$). On average, boys had higher values for FVC and FEV_1 than girls ($P < .05$), with mean (SD) FVC 2.06 (0.34) L for boys and 1.97 (0.33) L for girls; and FEV_1 1.85 (0.29) L for boys and 1.78 (0.30) L for girls. For the FEV_1 and FVC ratio, girls showed slightly higher values ($P = .04$), with a mean (SD) value of 90.8 (4.63) in girls and 90.0 (4.65) in boys. When analyzing differences between sexes in FEF_{25-75}, no significant differences were found ($P = .91$), with a mean (SD) FEF_{25-75} of 2.27 (0.53) L/s.

Validating cohort participants—G21

The validating cohort was a sample of 2986 children, who enrolled a cohort of 8647 newborns from 2005 (www.geracao21.com). No significant differences were found between boys and girls in age (mean [SD] 10.0 [0.3] years; $P = .32$) or height (140.5 [6.4] cm; $P = .8$), but girls were heavier than boys (weight for girls was 37.7 [8.9] vs 37.0 [8.2] for boys; $P = .04$). As in the derivation cohort, boys had average higher values for FVC and FEV_1 than girls ($P < .05$), with mean (SD) FVC 2.31 (0.37) L for boys and 2.28 (0.35) L for girls; and FEV_1 2.03 (0.30) L for boys and 1.96 (0.29) L for girls. When analyzing differences between the sexes in FEF_{25-75} and FEV_1/FVC, significant differences were found ($P < .05$ for both), with mean (SD) FEF_{25-75} for boys 2.28 (0.49) L/s and girls 2.35 (0.50) L/s, and FEV_1/FVC 88.1 (6.1) for boys and 90.2 (5.5) for girls.

When comparing derivative and validating cohorts, we found that the latter had significant higher FVC and FEV_1 values; however, these differences could be explained by age and anthropometric data once this group is slightly older. When applying the Levene test for homogeneity of variance, we found no differences between groups in lung function parameters. Significant differences were also found for FEV_1/FVC ratio and FEF_{25-75} ($P < .05$). Again, this difference can be explained by age, since it is known that the FEV_1/FVC ratio varies with age.[26] The Levene test showed no differences in variance for FEF_{25-75}, but a significant variance ($P < .05$) was found for FEV_1/FVC. Results are presented Fig 1.

Statistical analysis

Descriptive analysis was performed; data are presented as means (SDs). Two-sample *t* test was used to compare data between the 2 groups when appropriate. The Levene test for homogeneity of variance was used to test if the 2 groups had equal variances. The Pearson correlation coefficient was calculated for each pulmonary function parameter with height (cm), weight (kg), age (years), and body mass index (BMI). Multiple linear regression models were calculated for each pulmonary parameter and chosen on the basis of the rationale presented below. The parameters used were height, weight, age, BMI, and all possible combinations of these 4 parameters (the order in which they appear in equations does not matter), totaling 14 options of linear models. A Bland-Altman plot was used to assess the degree of agreement between the results obtained from the validation cohort and the 2 sets of equations (new derived ARIA equations and GLI 2012). R v4.0.2 (R Project; www.r-project.org) and RStudio IDE v1.3.1093 (rstudio.com/) were used for data analysis and for drawing all the graphs. All statistical data with $P < .05$ were considered significant.

RESULTS

Deriving predictive equations

Spirometry parameters FVC, FEV_1, and FEF_{25-75} correlated positively and significantly with height, weight, age, and BMI in both boys and girls, but no significant correlations were found for FEV_1/FVC (Fig 2).

The rationale for best linear model selection was applied to determine the best model fit. Height was the most significant predictor of FVC, FEV_1, and FEF_{25-75} in all sex-specific models. Using only height, weight, age, and the compounded effect of weight and height (BMI), none of the models showed to be good enough to be used to predict FEF_{25-75}. For this reason, and because FEF_{25-75} is a parameter calculated from FVC, we included measured FVC as a variable to predict FEF_{25-75}, which helped greatly improve this model. The FVC parameter as a predictor in the multiple linear regression was added to the best model obtained using the previous methods.

The final equations suggested for boys are:

$$\begin{aligned} FVC &= -2.322603 + (0.030837 \times Height) \\ &\quad + (0.003058 \times Weight) + (0.009612 \times Age) \\ FVC_1 &= -2.03101 + (0.02710 \times Height) \\ &\quad + (0.02203 \times Age) \\ FEF_{25-75} &= 0.4493680 + (-0.0001922 \times Height) \\ &\quad + (0.0510957 \times Age) + (0.6790825 \times FVC) \end{aligned}$$

And for girls:

$$\begin{aligned}
\text{FVC} &= -3.897335 + (0.040381 \times \text{Height}) \\
&\quad - (0.024744 \times \text{Weight}) + (0.067408 \times \text{BMI}) \\
\text{FEV}_1 &= -3.012830 + (0.030310 \times \text{Height}) \\
&\quad - (0.015603 \times \text{Weight}) + (0.049651 \times \text{BMI}) \\
&\quad + (0.035593 \times \text{Age}) \\
\text{FEF}_{25-75} &= -1.23855 + (0.01240 \times \text{Height}) \\
&\quad + (-0.01284 \times \text{Weight}) + (0.04417 \times \text{BMI}) \\
&\quad + (0.74267 \times \text{FVC})
\end{aligned}$$

Because no model proved good enough to predict reference values for FEV_1/FVC ratio, we suggest using mean (SD) to access normality criteria in this group age; the proposed values are thus 89.96 (4.65) for boys and 90.81 (4.63) for girls.

External validation

When assessing the mean differences between measured FVC, FEV_1, and FEF_{25-75} in the validating cohort and the values predicted by GLI equations and our equations, we found similar results, with GLI having slightly lower mean differences but with lower standard deviation found for ARIA models.

The mean differences between measured and predicted spirometry values were also evaluated for GLI models and ARIA models. A *z*-score transformation was applied separately for boys and girls for all spirometry parameters involving the 3 source values (measured, GLI predicted, our models' predictions), and a correction factor using the absolute value of mean differences between predictive models (ARIA and GLI) and measured values were applied. Graphical visualization of the results can be found in Fig 3.

It is possible to see that GLI equations tend to overestimate FVC values in boys while an underestimation is seen for the ARIA model, and GLI underestimates FEF_{25-75} in both boys and girls while our equations tend to overestimate. No differences were noted for the predicted values of FVC in girls and FEV_1 in both boys and girls.

When assessing correlations between predicted models from ARIA and GLI and the measured values, the predicted values from ARIA showed a higher correlation coefficient (CC = 0.652) for FVC in boys, FEV_1 in girls (CC = 0.670), and FEF_{25-75} in both boys and girls (respectively, CC = 0.416 and CC = 0.396). Predicted values from GLI showed better correlations with measured FEV_1 in boys (CC = 0.618), and the same correlation coefficient as ARIA predicted values with measured FVC in girls (CC = 0.698).

DISCUSSION

The modeling approach we used allowed us to establish reference standards of forced expiratory indices for Portuguese school-age children. Furthermore, the results indicate high external validity. This is the first study establishing reference equations for spirometry for Portuguese children, which is of particular importance because the Portuguese contribution in the GLI project comprised only 137 measurements (from a total of 74,187),[22] and the age range is not specified. Scarcity of reference values for spirometry in children is a commonplace in south Europe; to our knowledge, only 2 such works have been published in the last 20 years.[15,16]

Our findings have a few limitations. First, the narrow intervals of participants' ages limit the usefulness of our reference equations, making them suitable to use only within our age and height range. However, because age has been shown to have a lower effect on pulmonary function parameters than height, reference-equation priority must be given on the basis of a height range. Second, the provided reference equations are not continuous to adolescence and adulthood, which causes interpretation problems when switching references. Nonetheless, it is important to continue this first study and to develop continuous spirometry reference equations for Portuguese children to adult age, and future studies should address this need.

Our study also has important strengths. Most spirometry reference equations are derived from healthy, nonsmoking individuals who generally comprise a small subsample and have higher lung function values than the general population, but in accordance to the American Thoracic Society/European Respiratory Society guidelines, predictive equations can also be derived from a "large group of volunteers, provided that criteria for normal selection and proper distribution of anthropometric characteristics are satisfied."[5] By not applying exclusion criteria other than acceptability and reproducibility, we were able to include a more representative sample of the general population. Other studies have shown that children with mild or moderate asthma, or even with the common cold, do not differ from healthy children regarding spirometry indices.[27,28] Also, more inclusive criteria when deriving reference equations for spirometry has been shown to result in a higher R^2 value with no significant differences in the regression models.[29]

The best prediction models for all spirometry parameters for boys rely on standing height and weight, with age to decimal only accounting for FEV_1. For girls, all best models include BMI as an important factor in addiction to height and weight (except for FVC). The correlations between spirometry parameters with height, weight, and age are well known.[30] However, they have been differently associated with predicted spirometry parameters. Higher weight coefficients for girls than boys have been reported in a few studies,[31-33] while others only account for height in both sexes.[34-39] Another study found results opposite to ours, where weight only accounted for prediction of FVC and FEV_1 in boys.[40] In our study, weight assumes a positive signal when predicting FVC for boys but a negative signal for all parameters in girls. This has been reported before, in a study from Saudi Arabia, where weight accounted positively for all parameters in boys and negatively for all parameters in girls.[33] Overall, the most recent reports from European countries on spirometric prediction equations in children and preschool children use height and weight or age as predictors in their regression models,[16,19,35,40-43] and in our models, adding BMI into girls' equations improved their predictive power.

We have found that at the same age, height, and weight, boys have higher FVC ($P = .01$) and FEV_1 ($P = .04$). These findings have also been reported in other studies in similar populations. An important study that reported these differences between sexes and the effect of puberty stage was that of Rosenthal et al,[12] which studied 772 White children aged 4 to 18 years and found that in children under 152 cm tall, there was no difference in peak expiratory flow, middle expiratory flow at 50% of FVC (MEF_{50}), or MEF_{25} between sexes. However, small but significant differences in FEV_1, FVC,

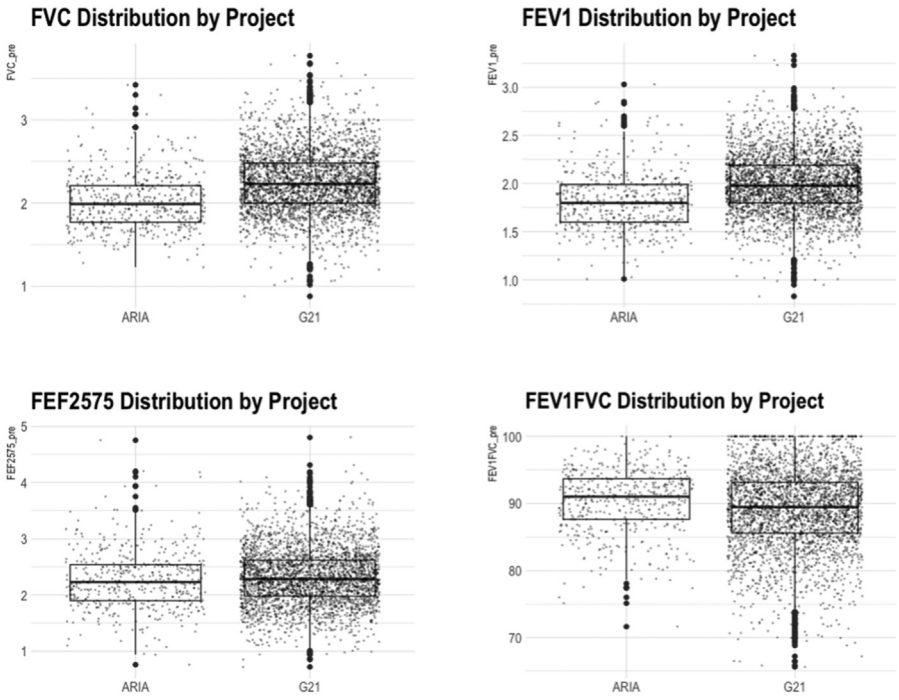

FIG 1. Distribution of lung function parameters by project.

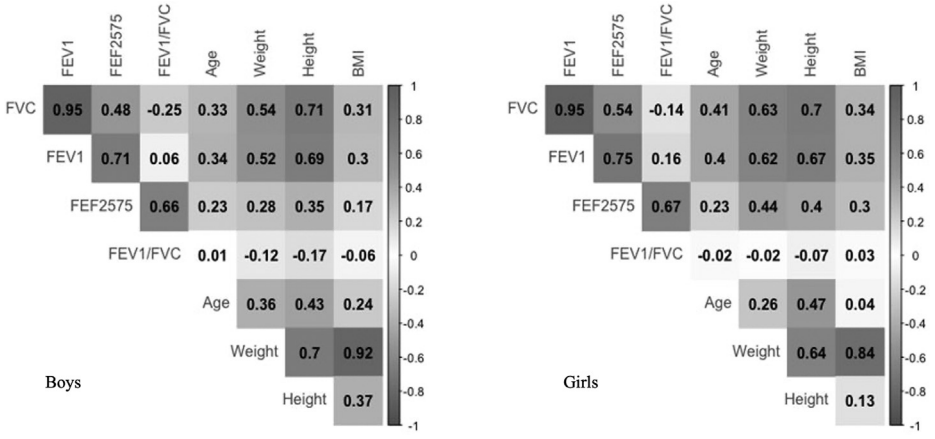

FIG 2. Pearson correlation coefficients between spirometric parameters and height, weight, and age in included subjects.

and FEV_1/FVC were found, with boys having 6% (5.8-6.3%), 8.5% (8.3-8.7%), and 2.4% (2.3-2.55%) higher absolute values than girls, respectively. This difference was uniform over the height range 107 to 152 cm. Studies reporting similar lung function values at preschool age can be easily found,[44,45] but the age when these differences start has not been established and depends on puberty status, which can vary between populations. Alexandraki et al[35] found that up to age 13, there are no statistically significant differences between boys and girls concerning FVC, FEV_1, FEF_{25-75}, and peak expiratory flow, but at the age of 13, boys' measurements start to increase rapidly and become statistically significantly higher than girls' values. On the one hand, one study found that these differences in FVC and FEV_1 between sexes start at about age 10, then increase with age.[46] On the other hand, statistically significant differences between boys and girls at preschool age, but with girls having higher static and dynamic lung volumes, have also been reported.[16]

We found that adding BMI as a factor in all equations only improved the model's goodness of fit in girls. Because mean BMI was similar in both the development and validation groups, and because no significant difference was found, we can only hypothesize that this difference between boys and girls is the result of differences in development once girls are expected to grow differently from boys at this age range. An earlier study documented the effect of BMI in children's lung function but only addressed the effect of BMI above the 90th percentile.[47] Although they found similar results to ours for FVC, other spirometric parameters do not seem to be affected. Given that the 3 predictors necessary for BMI calculation (height, weight, and age) are common and easy to obtain in routine clinical practice, we think

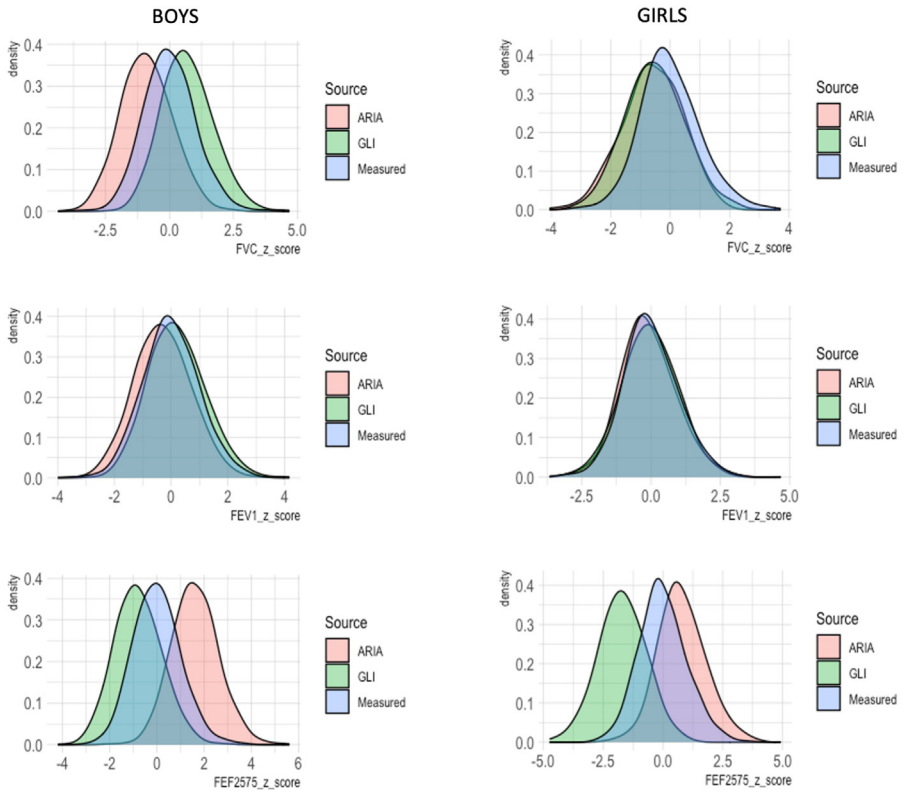

FIG 3. Comparison between normalized measured values and GLI models and ARIA models, with mean differences corrections for GLI and ARIA.

including BMI in girls' equations can be easily implemented and will only improve estimation.

When comparing the reference equations obtained from ARIA with the GLI equations, we found that ARIA equations perform better for FVC in boys, FEV_1 in girls, and FEF_{25-75} in both boys and girls, and had similar performance as GLI equations for girls' FVC and boys' FEV_1. Nevertheless, equations derived from the population to which they will be applied are expected to perform better. A previous work aiming to derive reference values for total lung capacity in a Brazilian population subgroup found that local equations have a lower standard error of estimate and therefore increased sensitivity to detect reduced or increased total lung capacity.[48] Regardless of GLI group efforts, it is not yet safe to say that GLI references can be applied worldwide, as our study shows. This better performance obtained from population-specific equations has been reported before, in a Brazilian study, where the authors found that their new derived equations performed better when predicting FVC and FEV_1 for children aged 3 to 12 years from a population of 1990 children.[49] A German study also found that GLI equations overestimate lung volumes for boys aged between 9 and 19 years.[50] Another study from Jordanian researchers showed that locally developed spirometry equations for children have better performance compared to GLI, and that GLI equations systematically exceed the cutoff point of 0.5 *z* score in more than 1 parameter in both boys and girls.[51] Studies aiming to compare new derived population-specific reference values and GLI references are scarce. Other studies have successfully attempt to validate GLI's 2012 reference values for specific populations; however, that purpose is beyond the scope of the present study.

In conclusion, the present study reports the first set of predictive equations for pulmonary function in Portuguese schoolchildren. The new reference equations have a slightly better fit than GLI equations, and therefore we recommend the use of ARIA equations for spirometry interpretation in this age range.

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Key message

- **This first set of predictive equations for pulmonary function in Portuguese schoolchildren indicates that our new reference equations have a slightly better fit than GLI equations, and we therefore recommend using ARIA equations for spirometry interpretation in this age range.**

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