Bronchodilator response cut-off points and FEV\textsubscript{0.75} reference values for spirometry in preschoolers

Edjane Figueiredo Burity\textsuperscript{1}, Carlos Alberto de Castro Pereira\textsuperscript{2}, Marcus Herbert Jones\textsuperscript{3}, Larissa Bouwman Sayão\textsuperscript{4}, Armèle Donelas de Andrade\textsuperscript{4}, Murilo Carlos Amorim de Britto\textsuperscript{1}

ABSTRACT
Objective: To determine the cut-off points for FEV\textsubscript{1}, FEV\textsubscript{0.75}, FEV\textsubscript{0.5}, and FEF\textsubscript{25-75%} bronchodilator responses in healthy preschool children and to generate reference values for FEV\textsubscript{0.75}. Methods: This was a cross-sectional community-based study involving children 3-5 years of age. Healthy preschool children were selected by a standardized questionnaire. Spirometry was performed before and after bronchodilator use. The cut-off point of the response was defined as the 95th percentile of the change in each parameter. Results: We recruited 266 children, 160 (60%) of whom were able to perform acceptable, reproducible expiratory maneuvers before and after bronchodilator use. The mean age and height were 57.78 ± 7.86 months and 106.56 ± 6.43 cm, respectively. The success rate for FEV\textsubscript{1} was 35%, 68%, and 70% in the 3-, 4-, and 5-year-olds, respectively. The 95th percentile of the change in the percentage of the predicted value in response to bronchodilator use was 11.6%, 16.0%, 8.5%, and 35.5% for FEV\textsubscript{1}, FEV\textsubscript{0.75}, FEV\textsubscript{0.5}, and FEF\textsubscript{25-75%}, respectively. Conclusions: Our results provide cut-off points for bronchodilator responsiveness for FEV\textsubscript{1}, FEV\textsubscript{0.75}, FEV\textsubscript{0.5}, and FEF\textsubscript{25-75%} in healthy preschool children. In addition, we proposed gender-specific reference equations for FEV\textsubscript{0.75}. Our findings could improve the physiological assessment of respiratory function in preschool children.

Keywords: Spirometry; Bronchodilator agents; Reference values; Child, preschool.

INTRODUCTION
Although spirometry with bronchodilator testing is routinely used in order to investigate respiratory diseases in children and adults, it is rarely used in preschool children. In children, only a few studies have defined bronchodilator response cut-off points (for FEV\textsubscript{1}), the established change in baseline FEV\textsubscript{1} and in percent predicted FEV\textsubscript{1}, in response to bronchodilator use having varied across studies, from 9% to 14% and from 9% to 10%, respectively.\textsuperscript{(5-6)} The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have yet to determine the best cut-off points for children. In addition, given the lack of studies, the ATS and the ERS have not been able to determine cut-off points for preschool children.\textsuperscript{(5,6)}

One obstacle is that only a low proportion (34-90%) of preschoolers are able to exhale for 1 s or more.\textsuperscript{(7-12)} Therefore, measurements of FEV\textsubscript{1} during the first 0.5 s of FVC (FEV\textsubscript{0.5}) or during the first 0.75 s of FVC (FEV\textsubscript{0.75}) can be used as surrogates for FEV\textsubscript{1}. According to the ATS and the ERS, FEV\textsubscript{0.5} and FEV\textsubscript{0.75} should always be reported from spirometry maneuvers performed by preschool children.\textsuperscript{(5)} Several studies have shown that FEV\textsubscript{0.5} and FEV\textsubscript{0.75} are reproducible.\textsuperscript{(7,8,10-12,14)} Several reference equations for FEV\textsubscript{0.5} and FEV\textsubscript{0.75} have been established in various populations.\textsuperscript{(13-17)}

In a case-control study,\textsuperscript{(18)} bronchodilator response cut-off points of 14%, 14%, and 33% were found for baseline FEV\textsubscript{1}, FEV\textsubscript{0.75}, and FEF\textsubscript{25-75%}, respectively. In another study,\textsuperscript{(19)} cut-off points of 10%, 11%, and 25% were found for baseline FEV\textsubscript{1}, FEV\textsubscript{0.75}, and FEF\textsubscript{25-75%}, respectively; however, their sensitivity for the diagnosis of asthma was found to be low (12%, 30%, and 41%, respectively), their specificity being 84%, 90%, and 80%, respectively.\textsuperscript{(9)}

Given that spirometry is a low-cost and noninvasive test, and given that several studies\textsuperscript{(7,8,10-12,14)} have demonstrated that preschool children can perform acceptable and reproducible FEV\textsubscript{0.5} and FEV\textsubscript{0.75} measurements, there is a need to determine bronchodilator response cut-off points for children in this age group so that spirometry can be used in daily clinical practice. Only two studies\textsuperscript{(18,19)} have assessed bronchodilator response using spirometry exclusively in preschool children.

In the present study we sought to determine bronchodilator response cut-off points for FEV\textsubscript{1}, FEV\textsubscript{0.75}, FEV\textsubscript{0.5}, and FEF\textsubscript{25-75%} in healthy preschool children (i.e., preschoolers without respiratory symptoms).

Correspondence to:
Edjane Figueiredo Burity, Rua Dr. Geraldo de Andrade, 75/501, Espinheiro, CEP 52021-220, Recife, PE, Brasil.
Tel.: 55 81 3428-1947. E-mail: edjaneburity@hotmail.com
Financial support: None.
METHODS

This was a community-based study of preschool children 3-5 years of age selected from among those attending any one of 18 public day care centers and schools in the city of Recife, Brazil. Data were collected in the period between February and December of 2014.

We selected a convenience sample, giving priority to the schools and day care centers attended by the highest number of children and located in central, northern, and western Recife. We calculated the sample size required to achieve a mean increase in FEV\textsubscript{0.75} after bronchodilator use, of 4.5% and a standard deviation of 5.1%, a value found in a study by Borrego et al.,\textsuperscript{(18)} with 95% confidence, assuming an estimation error of 1%, in accordance with the sample size calculation of Pardos et al.\textsuperscript{(20)} The minimum sample size was calculated to be 100.

In order to characterize the study sample, we used the ATS and Division of Lung Diseases questionnaire for the diagnosis of asthma—designated ATS-DLD-78-C—previously adapted and validated for use in Brazil in children 4 months to 13 years of age.\textsuperscript{(21)} The questionnaire was administered by two of the authors of the present study.

The inclusion criteria were as follows: being 3-5 years of age; having been a full-term infant; having had a birth weight ≥ 2,500 g; and having no respiratory symptoms, i.e., having no symptoms of asthma (dyspnea, wheezing, recurrent cough, or exertional dyspnea) or other respiratory diseases. The exclusion criteria were as follows: respiratory disease at birth requiring the use of oxygen for more than 24 h; chronic respiratory disease (including bronchopulmonary dysplasia, cystic fibrosis, and bronchiolitis obliterans); thoracic and pulmonary malformations; acute viral bronchiolitis in the last 6 months; acute nasopharyngitis; heart disease; and other severe diseases (including immunodeficiencies, neurological diseases, and genetic syndromes). A questionnaire administered up to one week before testing was used in order to determine whether prospective participants met any of the aforementioned criteria. Testing was not performed if there were signs of acute nasopharyngitis at the time of testing.

All tests were performed by the principal investigator, having been performed in the morning in all participating schools and day care centers. A back-extrapolated volume of < 80 mL or 12.5% of FVC was accepted, as recommended for preschool children.\textsuperscript{(22)} The objective was to obtain two acceptable maximal expiratory curves, the variation between the two highest values of FVC, FEV\textsubscript{i}, and FEV\textsubscript{0.75} being equal to or less than 10% and the variation between the two highest values of FEV\textsubscript{0.5} being equal to or less than 5%. Curves with a forced expiratory time (FET) of at least 0.5 s were accepted regardless of whether or not they ended abruptly. Each session of testing lasted a maximum of 25 min. Encouragement screens were used, and each session of testing was preceded by a brief (5-min) session of training. Spirometry was repeated 15 min after administration of 400 µg of albuterol delivered by a metered dose inhaler, as recommended by the ATS/ERS.\textsuperscript{(23)} An aluminum spacer with a face mask was used (inAl-air; RSMed, Belo Horizonte, Brazil). Testing was performed with the children in the sitting position. No nose clips were used in the present study, because the use of nose clips in children undergoing spirometry has been shown to have no clear advantage.\textsuperscript{(22)} Testing was performed with a portable spirometer validated by the ATS (Koko; Ferraris Respiratory, Louisville, CO, USA). Calibration was performed at the testing site, before each session of testing, with the use of a 3-L syringe, within the acceptable range of volume and flow.\textsuperscript{(23)} Room temperature and humidity were measured, and the data collected were entered into the software. In order to obtain acceptable maneuvers, testing sessions were suspended after an average of eight attempts or, before that, if the child showed fatigue or disinterest in continuing.

The following spirometric parameters were assessed: FVC; FEV\textsubscript{i}; FEV\textsubscript{0.5}; and FEF\textsubscript{25-75%}. The values of the aforementioned parameters were obtained from the two best flow-volume curves, both of which were acceptable and reproducible.\textsuperscript{(24)} The criteria for determining the values of FEF\textsubscript{25-75%} were as follows: for curves with a maximum FET of < 0.75 s, FEF\textsubscript{25-75%} was obtained from the curve with the highest FEV\textsubscript{0.5} value and the highest FEV\textsubscript{0.5} + FVC value; for curves with a maximum FET of < 1 s, FEF\textsubscript{25-75%} was obtained from the curve with the highest FEV\textsubscript{0.75} value and the highest FEV\textsubscript{0.75} + FVC value; for curves with a maximum FET ≥ 1 s, FEF\textsubscript{25-75%} was obtained from the curve with the highest FEV\textsubscript{i} value and the highest FEV\textsubscript{i} + FVC value. The variables used in order to determine bronchodilator response cut-off points for FEV\textsubscript{i}, FEV\textsubscript{0.75}, FEV\textsubscript{0.5}, and FEF\textsubscript{25-75%} were the percent change regarding the predicted values, the percent change regarding the baseline values, and the change in absolute values.

Statistical analysis was performed with the IBM SPSS Statistics software package, version 21 (IBM Corporation, Armonk, NY, USA). Numerical variables are expressed as means, medians, and percentiles. Categorical variables are expressed as proportions. The reproducibility of the spirometric measurements was tested by the intraclass correlation coefficient (ICC). Weight, height, and BMI are expressed as Z scores.\textsuperscript{(24)} The Shapiro-Wilk test was used for testing data normality. The Student’s t-test for paired samples was used in order to compare mean baseline and post-bronchodilator values of all spirometric parameters.

The changes in response to bronchodilator use were calculated by the following formulas:

\[(\text{post-bronchodilator value} - \text{baseline value}) \times 100/\text{baseline value}\]
\[(\text{post-bronchodilator value} - \text{baseline value}) \times 100/\text{predicted value}\]
The predicted values were derived from a reference equation for preschool children developed by our research group in a previous study. Because the aforementioned equation does not include reference values for FEV$_{0.75}$, they were calculated in the present study by linear regression.

In order to determine bronchodilator response cut-off points for FEV$_1$, FEV$_{0.75}$, FEV$_{0.5}$, and FEF$_{25-75}$, the 95th percentile of the change in each parameter was calculated for baseline, predicted, and absolute values.

Spearman’s correlation coefficient was calculated in order to evaluate the correlation of the bronchodilator response indices tested with age, height, and baseline FEV$_1$ (FEV$_{0.75}$ and FEV$_{0.5}$).

The study project was approved by the Research Ethics Committee of the Professor Fernando Figueira Institute of Integrative Medicine (Protocol no. 2616-11). The parents or legal guardians of all participating preschoolers gave written informed consent, and the researchers signed a statement of responsibility.

RESULTS

Of the 462 eligible children, 447 completed the questionnaires. Of those 447 children, 41 (9%) met the exclusion criteria and 34 (8%) constituted losses: 26 for missing school on the day of testing and 8 for declining to undergo testing. Of the remaining 372 preschoolers, 266 (71%) were classified as having no respiratory symptoms. Of those 266 children, 56 (21.0%) failed to perform spirometry correctly and 50 (19.0%) failed to perform bronchodilator testing correctly. The final sample consisted of 160 asymptomatic preschool children (60% of the initial sample of 266 asymptomatic children). A flowchart of the sample selection process is shown in Figure 1.

The demographic characteristics of the sample are presented in Table 1. Of the children who performed acceptable measurements, 19 (12%) were 3 years old, 74 (46%) were 4, and 67 (42%) were 5. Curves with a back-extrapolated volume ≤ 5% were obtained in 99% of the tests, and, in 95% of those, the difference between the two highest FVC, FEV$_1$, FEV$_{0.75}$, and FEV$_{0.5}$ values was < 5%, demonstrating a high reproducibility.

We calculated the ICCs for the two highest values of each of the spirometric variables tested. Mean ICCs (and their respective 95% CIs) for FVC and FEV$_1$ were 0.994 (0.990-0.996) and 0.993 (0.989-0.996), respectively. Mean ICCs (and their respective 95% CIs) for FEV$_{0.75}$, FEV$_{0.5}$, and FEF$_{25-75}$ were 0.993 (0.990-0.995), 0.992 (0.990-0.994), and 0.935 (0.913-0.951), respectively.

Among the 3-year-olds in the initial sample of 266 children, FVC, FEV$_1$, FEV$_{0.75}$, and FEV$_{0.5}$ measurements were considered acceptable and reproducible in 5%, 7%, 9%, and 37%, respectively; among the 4-year-olds, they were considered acceptable and reproducible in 23%, 29%, 39%, and 68%, respectively; and among the 5-year-olds, they were considered acceptable and reproducible in 23%, 26%, 44%, and 70%, respectively.

Spirometry was considered unacceptable in 63% of the 3-year-olds, in 32% of the 4-year-olds, and in 30% of the 5-year-olds. Bronchodilator response testing was considered inadequate in 19% of the

**Figure 1.** Flowchart of study sample selection. BD: bronchodilator.
DISCUSSION

This is the first study to establish, by means of spirometry, bronchodilator response cut-off points in preschoolers, the cut-off points being expressed as the change in percent predicted FEV\textsubscript{1}, FEV\textsubscript{0.75}, FEV\textsubscript{0.5}, and FEF\textsubscript{25-75%}. Of the 4-year-olds in the study sample, 67% were able to perform FEV\textsubscript{0.5} measurements and 39% were able to perform FEV\textsubscript{0.75} measurements. Of the 5-year-olds in the study sample, 70% were able to perform FEV\textsubscript{0.5} measurements and 44% were able to perform FEV\textsubscript{0.75} measurements. Therefore, in preschoolers, FEV\textsubscript{0.5} measurements are more useful than FEV\textsubscript{0.75} measurements because the proportion of children who can perform the former is higher. In community-based samples, spirometry is not useful in 3-year-olds due to the high rate of unacceptable tests.

The low proportion of children who were able to perform acceptable and reproducible pre- and post-bronchodilator measurements of FVC, FEV\textsubscript{1}, FEV\textsubscript{0.75}, and FEF\textsubscript{25-75%} can be explained by the fact that ours was a community-based sample, the children therefore being more inexperienced in performing such measurements; in general, children selected from among those treated at respiratory outpatient clinics have previously been evaluated by their physicians regarding their motor coordination to perform such tests. Given that it is difficult for children to perform pre- and post-bronchodilator spirometry, the proportion of preschoolers who can perform it is lower. The high ICCs for the spirometric parameters tested in the present study constitute evidence of the low variability and high reproducibility of the measurements performed, as well as of the technical skills of the professional who performed the tests.

We found no studies evaluating bronchodilator response exclusively in healthy preschool children. The studies that we found involved children with asthma. The mean changes in the percentage of the predicted values of FVC, FEV\textsubscript{1}, and FEV\textsubscript{0.75} in response to bronchodilator use in the present study were 2.3%, 4.5%, and 5.6%, respectively, being similar to those found in another study (2.5%, 4.7%, and 4.5%, respectively).\(^{(18)}\) For FEF\textsubscript{25-75%}, Borrego et al.\(^{(18)}\) found a change of 11.7%, compared with 20.0% in the present study. This difference can be explained by the difference in study sample between the two studies: ours was a community-based sample, whereas that
Bronchodilator response cut-off points and FEV\textsubscript{0.75} reference values for spirometry in preschoolers in the study by Borrego et al.\textsuperscript{(18)} was a case-control sample. In addition, the high reproducibility and, consequently, low variability of FEF\textsubscript{25-75\%} measurements in the present study increase the power to detect differences between pre- and post-bronchodilator values. In the present study, the mean post-bronchodilator percentage changes of FEV\textsubscript{L}, FEV\textsubscript{0.5\%}, and FEF\textsubscript{25-75\%} were 4.5\%, 6.8\%, and 20.0\%, respectively, whereas, in another study\textsuperscript{(19)} they were 8.9\%, 2.9\%, and 8.1\%, respectively. The type of sample used in ours and in that study\textsuperscript{(19)} (community-based and case-control samples, respectively), as well as the fact that dose of albuterol was lower in that study (200 µg),\textsuperscript{(19)} might have contributed to those differences.

Table 3. Percentiles of the changes in FEV\textsubscript{L}, FEV\textsubscript{0.5\%}, FEV\textsubscript{0.75\%}, and FEF\textsubscript{25-75\%} in response to bronchodilator use, the parameters being expressed as percentages of the predicted values, percent changes from baseline, and absolute changes in the preschoolers studied.

| Variable | Percentile   | 5th | 25th | 75th | 95th |
|----------|--------------|-----|------|------|------|
| FEV\textsubscript{L}, L | % of predicted\textsuperscript{a} | 0   | 0    | 7.91 | 11.6 |
|          | % change from baseline | 0   | 0    | 8.80 | 13.0 |
|          | Absolute change, L     | 0   | 0    | 0.09 | 0.13 |
| FEV\textsubscript{0.5\%}, L | % of predicted\textsuperscript{a} | 0.51| 1.18 | 9.66 | 16.0 |
|          | % change from baseline | 0   | 1.07 | 10.74| 20.0 |
|          | Absolute change, L     | 0   | 0.01 | 0.08 | 0.15 |
| FEV\textsubscript{0.75\%}, L | % of predicted\textsuperscript{a} | 0   | 0.57 | 5.35 | 8.50 |
|          | % change from baseline | 0   | 0.85 | 9.20 | 18.0 |
|          | Absolute change, L     | 0   | 0.01 | 0.08 | 0.14 |
| FEF\textsubscript{25-75\%}, L/s | % of predicted\textsuperscript{a} | -2.88| 3.87 | 22.02| 35.5 |
|          | % change from baseline | -4.74| 6.33 | 33.17| 61.0 |
|          | Absolute change, L     | -0.06| 0.09 | 0.44 | 0.74 |

FEV\textsubscript{L}: FEV during the first 0.5 s of FVC; and FEV\textsubscript{0.75\%}: FEV during the first 0.75 s of FVC. \textsuperscript{a}Values according to Piccioni et al.\textsuperscript{(13)} \textsuperscript{b}Values calculated on the basis of the data from the present study.

Figure 2. Scatter plots of FEV during the first 0.75 s of FVC (FEV\textsubscript{0.75\%}) in relation to height and weight in male preschoolers (A and B) and in female preschoolers (C and D).
For FEV₁, the cut-off point found in the present study (a change of 13% from baseline in response to bronchodilator use) was similar to that found in another study (14%) but different from that found by Linares et al. (10%, with a sensitivity of 12% and a specificity of 84%). This low sensitivity suggests that there were no significant differences between the groups regarding bronchodilator response or that the administered dose of albuterol (200 μg) was insufficient to produce a bronchodilator effect. Because the aforementioned study was a case-control study involving patients with moderate to severe persistent asthma, it is more likely that the administered dose of albuterol was insufficient to provide effective bronchodilation. With regard to the change in the percentage of the predicted FEV₁ in response to bronchodilator use in the present study (i.e., 11.6%), we found no other studies evaluating this parameter in samples composed exclusively of preschool children.

For FEV₁, the cut-off point found in the present study (a change of 20% from baseline in response to bronchodilator use) differs from that found by other authors (11%, with a sensitivity of 30% and a specificity of 90%). This low sensitivity suggests that the cut-off point is not the best cut-off point. The high ICCs for the measurements performed in the present study increase its power regarding the reliability of those measurements. It should also be taken into account that the cut-off points for a community-based study should be higher than those for studies evaluating bronchodilator response in children.

For baseline FEV₁, the cut-off point found in the present study (18%) was higher than that found in another study (14%). This difference might be due to the type of study (a case-control study) and how the cut-off point was calculated (mean + 2 standard deviations after bronchodilator use in healthy participants).

With regard to the change in the percentage of the predicted FEV₁ in response to bronchodilator use in the present study (8.5%), the lack of evidence in the literature makes it impossible to make comparisons.

Although some studies have included FEF₂₅-₇₅% in the analysis of bronchodilator response, FEF₂₅-₇₅% is not given weight in studies evaluating bronchodilator response, because it varies widely. For FEF₂₅-₇₅%, the cut-off point found in the present study (a change of 61% from baseline in response to bronchodilator use) is different from those found by Borrego et al. (33%) and other authors (25%, with a sensitivity of 41% and a specificity of 80%). Unlike the present study, the aforementioned studies were conducted in preschool children, and this might explain these discrepancies. The high ICC for FEF₂₅-₇₅% in the present study indicates good reproducibility. With regard to the change in the percentage of the predicted FEF₂₅-₇₅% in response to bronchodilator use in the present study (35%), the lack of studies on this topic makes it impossible to make comparisons. The use of this parameter in the evaluation of bronchodilator response in preschool children will require further studies.

Some studies have shown that, in children, it is best to express bronchodilator response as a percentage of the predicted values, because percent predicted values do not depend on age, height, or baseline FEV₁. However, for preschool children, the present study showed correlations of baseline FEV₁ with the percent change from baseline after bronchodilator use and the percent change in the predicted value after bronchodilator use. With regard to FEV₁, regarding this age group, age correlates with the percent change from baseline after bronchodilator use and the percent change in the predicted value after bronchodilator use. Therefore, in preschool children, there is no difference between the percent change from baseline after bronchodilator use and the percent change in the predicted value after bronchodilator use for the two parameters.

### Table 4. Spearman’s coefficients correlating the bronchodilator response indices with age, height, FEV₁ during the first 0.5 s of FVC (FEV₁₀.₅) and FEV₁ during the first 0.75 s of FVC (FEV₁₀.₇₅) in the study sample.

| Variable | Absolute change from baseline FEV₁₀.₅ after bronchodilator use, L | Percent change from baseline FEV₁₀.₅ after bronchodilator use | Change in percent predicted FEV₁₀.₅ after bronchodilator use |
|----------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Age, months | SCC (p)                                                | SCC (p)                                                | SCC (p)                                                |
|          | 0.04 (0.60)                                               | -0.1 (0.28)                                              | -0.05 (0.50)                                             |
| Height, cm | 0.11 (0.17)                                               | -0.05 (0.50)                                             | -0.03 (0.70)                                             |
| Baseline FEV₁₀.₅, L | -0.16 (0.47)                                           | -3.27 (0.00)                                              | -0.25 (0.02)                                             |

| Variable | Absolute change from baseline FEV₁₀.₇₅ after bronchodilator use, L | Percent change from baseline FEV₁₀.₇₅ after bronchodilator use | Change in percent predicted FEV₁₀.₅ after bronchodilator use |
|----------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Age, months | SCC (p)                                                | SCC (p)                                                | SCC (p)                                                |
|          | -0.17 (0.11)                                               | -0.24 (0.02)                                             | -0.23 (0.03)                                             |
| Height, cm | 0.53 (0.62)                                               | -0.05 (0.66)                                             | -0.01 (0.89)                                             |
| Baseline FEV₁₀.₇₅, L/s | -0.06 (0.60)                                           | -0.18 (0.10)                                             | -0.17 (0.11)                                             |

SCC: Spearman’s correlation coefficient.
REFERENCES

1. Casan P, Roca J, Sanchis J. Spirometric response to a bronchodilator. Reference values for healthy children and adolescents. Bull Eur Physiopathol Respir. 1983;19(6):567-9.

2. Bussama MR, Cukier A, Stemach R, Rodrigues JC. Evaluation of the magnitude of the bronchodilator response in children and adolescent with asthma. Chest. 2005;127(2):530-5. http://dx.doi.org/10.1378/chest.127.2.530

3. Galant SP, Morpeth T, Amaro S, Liao O. Value of the bronchodilator response in assessing controller naive asthmatic children. J Pediatr. 2007;151(6):457-62, e1.

4. Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. Thorax. 2005;60(1):13-6. http://dx.doi.org/10.1136/thx.2004.028934

5. Pellegrino R, Vieggi G, Brusasco V, Copa RO, Burgo F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(6):949-68. http://dx.doi.org/10.1183/09031936.05.0003250

6. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175(12):1304-45. http://dx.doi.org/10.1164/rccm.200605-642ST

7. Burtle EF, Pereira CA, Rizzo JÁ, Sarinho ES, Jones MH. Early termination of exhalation: effect on spirometric parameters in healthy preschool children. J Bras Pneumol. 2011;37(4):464-70. http://dx.doi.org/10.1590/S1808-37122011000400008

8. Nystad W, Samuelsen SO, Nafstad P, Stensrud C, Stensrud T, Jakkola JJ. Feasibility of measuring lung function in preschool children. Thorax. 2002;57(12):1021-7. http://dx.doi.org/10.1136/thorax.57.12.1021

9. Zapieta A, Chalupova J. Forced expiratory parameters in healthy preschool children (3-6 years of age). Pediatr Pulmonol. 2003;35(3):200-7. http://dx.doi.org/10.1002/ppul.10265

10. Aurora P, Stocks J, Oliver C, Saunders C, Castle R, Chaziparasidis I, et al. Quality control for spirometry in preschool children with and without lung disease. Am J Respir Crit Care Med. 2004;169(10):1152-9. http://dx.doi.org/10.1164/rccm.200310-1433OC

11. Eigen H, Bieler H, Grant D, Christoph K, Terri D, Heilman DK, et al. Spirometric pulmonary function in healthy preschool children. Am J Respir Crit Care Med. 2001;163(1 Pt 1):691-23. http://dx.doi.org/10.1164/rccm.163.1.691

12. Crenner O, Berlic M, Bourrier T, Albertini M. Spirometry in children aged 3 to 5 years: reliability of forced expiratory maneuver. Pediatr Pulmonol. 2001;32(1):56-61. http://dx.doi.org/10.1002/ppul.1089

13. Piccioni P, Boraccino A, Fomeris MP, Miglione E, Carena C, Bignamini E, et al. Reference values for Forced Expiratory Volumes and pulmonary flows in 3-6 year children: a cross-sectional study. Respir Res. 2007;8:14. http://dx.doi.org/10.1186/1465-9921-8-14

14. Pesant C, Santschi M, Praud JP, Geoffroy M, Nyonsenga T, Viachos-Mayer H. Spirometry pulmonary function in 2-to 5-year-old children. Pediatr Pulmonol. 2007;42(3):263-71. http://dx.doi.org/10.1002/ppul.20564

15. Jeng MJ, Chang HL, Tsai MC, Tsao PC, Yang CF, Lee YS, et al. Spirometric pulmonary function parameters of healthy Chinese children aged 3-6 years in Taiwan. Pediatr Pulmonol. 2008;44(7):676-82. http://dx.doi.org/10.1002/ppul.21038

16. Pérez-Yarza EG, Villa JR, Cobos N, Navarro M, Salcedo A, Martin C, et al. Forced spirometry in healthy preschool children [Article in Spanish]. An Pediatr (Barc). 2009;70(1):3-11. http://dx.doi.org/10.1016/j.anpedi.2008.10.003

17. Burtle EF, Pereira CA, Rizzo JÁ, Britto MC, Sarinho ES. Reference values for spirometry in preschool children. J Pediatr (Rio J). 2013;89(4):374-80. http://dx.doi.org/10.1016/j.jped.2013.01.002

18. Borrego LM, Stocks J, Almeida I, Stanjevic S, Antunes J, Leiria-Pinto P, et al. Bronchodilator responsiveness using spirometry in healthy and asthmatic preschool children. Arch Dis Child. 2013;98(9):112-7. http://dx.doi.org/10.1136/archdischild-2012-301819

19. Linares Passerini M, Meyer Peirano R, Contreras Estay I, Delgado Becerra I, Castro-Rodrigo JA. Utility of bronchodilator response for asthma diagnosis in Latino preschoolers. Allergol Immunopathol (Madrid). 2014;42(6):553-9. http://dx.doi.org/10.1165/air.2014.02.004

20. Pardos Martínez C, Fuertes Fernández-Espinar J, Neirín De La Puerta I, González Pérez-Yarza E. Cut-off point for a positive bronchodilation test [Article in Spanish]. An Esp Pediatr. 2002;57(1):5-11. http://dx.doi.org/10.1016/S1695-4033(02)77885-5

21. Esteves AR. Adaptation and validation of the questioner “ATS-DLD-78-C” for diagnostic of asthma in children with at least 13 years [dissertation]. São Paulo: Universidade Federal de São Paulo; 1995.

22. Chavasse R, Johnson P, Francis J, Balfour-Lynn I, Rosenthal M, Bush A. To clip or not to clip? Nose clips for spirometry. Eur Respir J. 2003;21(5):876-8. http://dx.doi.org/10.1183/09031936.03.00048303

23. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para testes de função pulmonar. J Pneumol. 2002;28(Suppl 3):S53-S62.

24. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. Coordenação-Geral da Política de Alimentação e Nutrição [homepage on the Internet]. Brasília: o Ministério; [cited 2015 Aug 1]. Incorporação das curvas de crescimento da Organização Mundial de Saúde de 2006 e 2007 no SISVAN. [Adobe Acrobat document, 38p]. Available from: http://www.nutricao.saude.gov.br/docs/geral/curvas_oms_2006_2007.pdf

25. Waalkens HJ, Merkus PJ, van Essen-Zandvliet EE, Brand PL, Gerrets J, Duivenveld EJ, et al. Assessment of bronchodilator response in children with asthma. Dutch CNSLD Study Group. Eur Respir J. 1993;6(6):849-51.

For clinical practice, the recommended bronchodilator response cut-off points for percent predicted FEV1, FEV0.75, and FEV0.5 are ≥ 12%, ≥ 8%, and ≥ 16%, respectively; for baseline FEV1, FEV0.75, and FEV0.5, the recommended cut-off points are ≥ 13%, ≥ 18%, and ≥ 20%, respectively. For percent predicted and baseline FEV25-75%, the recommended cut-off points are ≥ 35% and ≥ 61%, respectively. Given that FEV25-75% showed good reproducibility, it might be useful in the evaluation of bronchodilator response. Further studies are needed in order to test the utility of these cut-off points in samples of patients with respiratory symptoms treated at respiratory outpatient clinics.

ACKNOWLEDGMENTS

We would like to thank Professor José Figueirao Natal, a statistician at the Professor Fernando Figueira Institute of Integrative Medicine, for his invaluable assistance with the statistical analysis in the present study.