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Bronchodilator response cut-off points and $FEV_{0.75}$ reference values for spirometry in preschoolers

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ABSTRACT

Objective: To determine the cut-off points for FEV_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$ bronchodilator responses in healthy preschool children and to generate reference values for $FEV_{0.75}$. **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 $FEV_{0.5}$ 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_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$, respectively. **Conclusions:** Our results provide cut-off points for bronchodilator responsiveness for FEV_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$ in healthy preschool children. In addition, we proposed gender-specific reference equations for $FEV_{0.75}$. 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_1), the established change in baseline FEV_1 and in percent predicted FEV_1 in response to bronchodilator use having varied across studies, from 9% to 14% and from 9% to 10%, respectively.[1-4] 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.[5,6]

One obstacle is that only a low proportion (34-90%) of preschoolers are able to exhale for 1 s or more.[7-12] Therefore, measurements of FEV during the first 0.5 s of FVC ($FEV_{0.5}$) or during the first 0.75 s of FVC ($FEV_{0.75}$) can be used as surrogates for FEV_1. According to the ATS and the ERS, $FEV_{0.5}$ and $FEV_{0.75}$ should always be reported from spirometry maneuvers performed by preschool children.[6] Several studies have shown that $FEV_{0.5}$ and $FEV_{0.75}$ are reproducible.[7,8,10,12-14] Several reference equations for $FEV_{0.5}$ and $FEV_{0.75}$ have been established in various populations.[13-17]

In a case-control study,[18] bronchodilator response cut-off points of 14%, 14%, and 33% were found for baseline FEV_1, $FEV_{0.75}$, and $FEF_{25-75\%}$, respectively. In another study,[19] cut-off points of 10%, 11%, and 25% were found for baseline FEV_1, $FEV_{0.5}$, and $FEF_{25-75\%}$, 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.[9]

Given that spirometry is a low-cost and noninvasive test, and given that several studies[7,8,10,12-14] have demonstrated that preschool children can perform acceptable and reproducible $FEV_{0.5}$ and $FEV_{0.75}$ 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[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_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$ using the 95th percentile of the change in each parameter and establish reference values for $FEV_{0.75}$ in healthy preschool children (i.e., preschoolers without respiratory symptoms).

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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 $FEV_{0.75}$, after bronchodilator use, of 4.5% and a standard deviation of 5.1%, a value found in a study by Borrego et al.,[18] with 95% confidence, assuming an estimation error of 1%, in accordance with the sample size calculation of Pardos et al.[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.[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.[6] The objective was to obtain two acceptable maximal expiratory curves, the variation between the two highest values of FVC, FEV_1, and $FEV_{0.75}$ being equal to or less than 10% and the variation between the two highest values of $FEV_{0.5}$ 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.[6] 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.[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.[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_1; $FEV_{0.75}$; $FEV_{0.5}$; and $FEF_{25-75\%}$. The values of the aforementioned parameters were obtained from the two best flow-volume curves, both of which were acceptable and reproducible.[6] The criteria for determining the values of $FEF_{25-75\%}$ were as follows: for curves with a maximum FET of < 0.75 s, $FEF_{25-75\%}$ was obtained from the curve with the highest $FEV_{0.5}$ value and the highest $FEV_{0.5}$ + FVC value; for curves with a maximum FET of < 1 s, $FEF_{25-75\%}$ was obtained from the curve with the highest $FEV_{0.75}$ value and the highest $FEV_{0.75}$ + FVC value; for curves with a maximum FET ≥ 1 s, $FEF_{25-75\%}$ was obtained from the curve with the highest FEV_1 value and the highest FEV_1 + FVC value. The variables used in order to determine bronchodilator response cut-off points for FEV_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$ 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.[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.[17] Because the aforementioned equation[17] 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_t (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

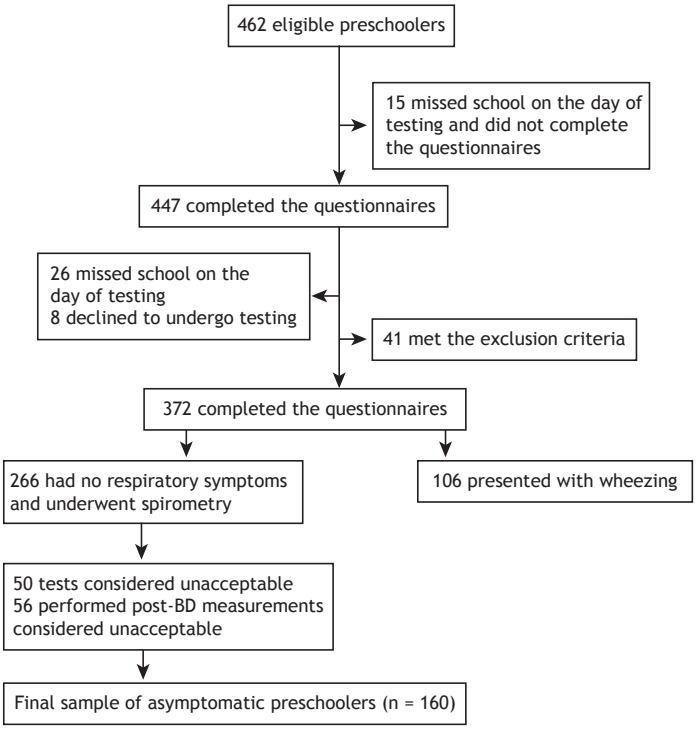

Figure 1. Flowchart of study sample selection. BD: bronchodilator.

3-year-olds, in 20% of the 4-year-olds, and in 20% of the 5-year-olds, proportions that were very similar.

Mean baseline and post-bronchodilator FVC, FEV_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$ values are shown in Table 2. There were significant differences between mean pre- and post-bronchodilator values of the aforementioned parameters ($p < 0.005$). Proportionally, mean and median pre- and post-bronchodilator changes in FVC, FEV_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$ with non-normal distribution can be seen in Table 2.

In order to calculate reference values for $FEV_{0.75}$, gender-specific reference equations were derived by linear regression. For males, the equation and the lower limit (LL) are as follows:

$FEV_{0.75}$ = height × 0.013 + weight × 0.010

LL = predicted value − 0.21(5th percentile of the residual)

For females, the equation and the LL are as follows:

$FEV_{0.75}$ = height × 0.008 + age × 0.008 + weight × 0.013

LL = predicted value − 0.19

The dispersion of $FEV_{0.75}$ values is shown in Figure 2.

Table 3 shows all cut-off points established by the 95th percentile of the change in FEV_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$ in response to bronchodilator use.

Table 4 shows the Spearman's correlations of the bronchodilator response cut-off points for baseline, percent predicted, and absolute values of $FEV_{0.5}$ and $FEV_{0.75}$ with age, height, and baseline FEV_t ($FEV_{0.5}$ and $FEV_{0.75}$).

Table 1. Sociodemographic characteristics of the study population, Recife, Brazil, February-December of 2014.[a]

Variable	Result
Male gender	84 (52.5)
Age, months	57.8 ± 7.8
Race	
White	33 (20.6)
Black	11 (6.9)
Mulatto	116 (72.5)
Weight-for-age (Z score)[b]	0.20 ± 1.18
Height-for-age (Z score)[b]	−0.38 ± 1.03
BMI (Z score)[b]	0.65 ± 1.20

[a]Values expressed as n (%) or mean ± SD. [b]Based on data from the Brazilian National Ministry of Health.[24]

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_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$. Of the 4-year-olds in the study sample, 67% were able to perform $FEV_{0.5}$ measurements and 39% were able to perform $FEV_{0.75}$ measurements. Of the 5-year-olds in the study sample, 70% were able to perform $FEV_{0.5}$ measurements and 44% were able to perform $FEV_{0.75}$ measurements. Therefore, in preschoolers, $FEV_{0.5}$ measurements are more useful than $FEV_{0.75}$ 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_1, $FEV_{0.75}$, and $FEF_{25-75\%}$ 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_1, and $FEV_{0.75}$ 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 $FEF_{25-75\%}$, 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

Table 2. Means and dispersion of baseline and post-bronchodilator spirometric parameters in the preschoolers studied.

Variable	Baseline		Post-BD		Change (pre- and post-BD), %	p*
	n	Mean ± SD	n	Mean ± SD	Mean ± SD (median)[a]	
FVC, L	94	1.06 ± 0.21	52	1.09 ± 0.18	2.3 ± 4.3 (0.71)	< 0.001
FEV_1, L	93	1.00 ± 0.18	61	1.06 ± 0.17	4.5 ± 4.7 (2.67)	< 0.001
$FEV_{0.75}$, L	94	0.94 ± 0.17	92	1.00 ± 0.17	5.6 ± 5.6 (4.32)	< 0.001
$FEV_{0.5}$, L	160	0.80 ± 0.16	160	0.86 ± 0.16	6.8 ± 6.4 (5.47)	< 0.001
$FEF_{25-75\%}$, L/s	94	1.52 ± 0.40	92	1.79 ± 0.42	20.0 ± 20.2 (15.48)	< 0.001

BD: bronchodilator; $FEV_{0.5}$: FEV during the first 0.5 s of FVC; and $FEV_{0.75}$: FEV during the first 0.75 s of FVC. [a]Mean and median of the changes observed after bronchodilator use (variables with non-normal distribution). All parameters had a normal distribution. The greatest differences between mean and median values are due to a lower n of FVC and FEV_1 measurements after bronchodilator use. *Student's t-test for paired samples.

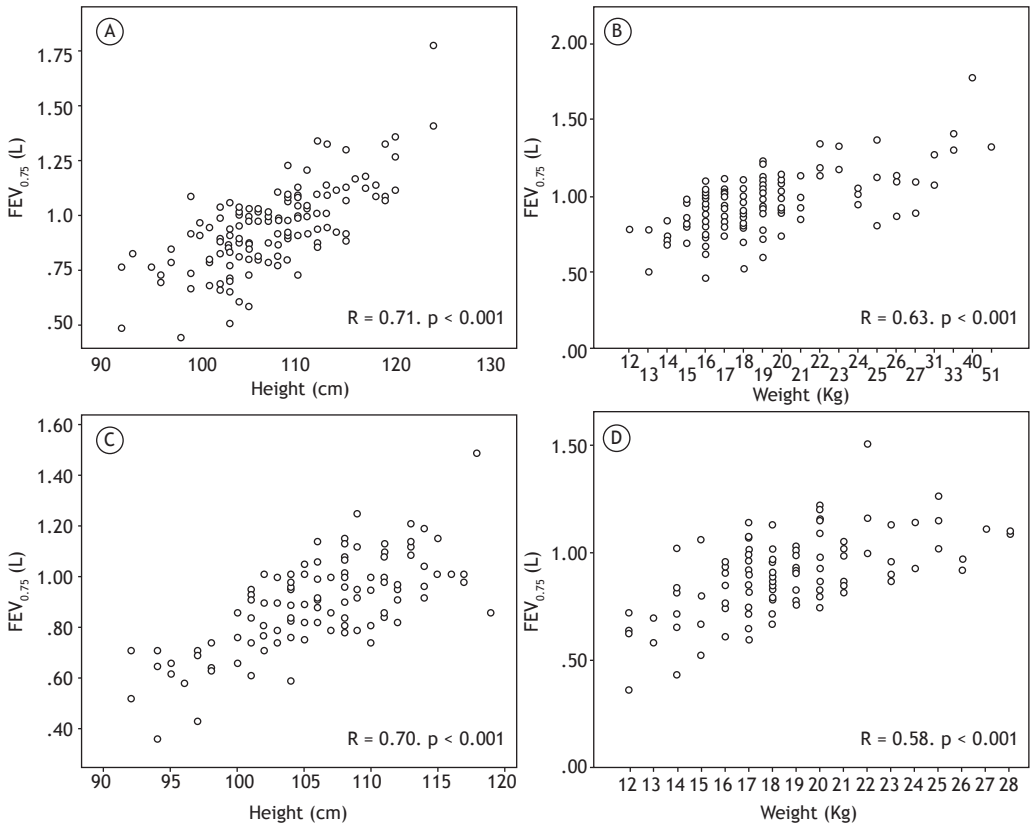

Figure 2. Scatter plots of FEV during the first 0.75 s of FVC ($FEV_{0.75}$) in relation to height and weight in male preschoolers (A and B) and in female preschoolers (C and D).

Table 3. Percentiles of the changes in FEV_1, $FEV_{0.5}$, $FEV_{0.75}$, and $FEF_{25-75\%}$ 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_1, L	% of predicted[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
$FEV_{0.5}$, L	% of predicted[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
$FEV_{0.75}$, L	% of predicted[b]	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
$FEF_{25-75\%}$, L/s	% of predicted[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

$FEV_{0.5}$: FEV during the first 0.5 s of FVC; and $FEV_{0.75}$: FEV during the first 0.75 s of FVC. [a]Values according to Piccioni et al.[13] [b]Values calculated on the basis of the data from the present study.

in the study by Borrego et al.[18] was a case-control sample. In addition, the high reproducibility and, consequently, low variability of $FEF_{25-75\%}$ 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_1, $FEV_{0.5}$, and $FEF_{25-75\%}$ were 4.5%, 6.8%, and 20.0%, respectively, whereas, in another study,[19] they were 8.9%, 2.9%, and 8.1%, respectively. The type of sample used in ours and in that study[19] (community-based and case-control samples, respectively), as well as the fact that dose of albuterol was lower in that study (200 µg),[19] might have contributed to those differences.

Table 4. Spearman's coefficients correlating the bronchodilator response indices with age, height, FEV during the first 0.5 s of FVC ($FEV_{0.5}$), and FEV during the first 0.75 s of FVC ($FEV_{0.75}$) in the study sample.

Variable	Absolute change from baseline $FEV_{0.5}$ after bronchodilator use, L	Percent change from baseline $FEV_{0.5}$ after bronchodilator use	Change in percent predicted $FEV_{0.5}$ after bronchodilator use
	SCC (p)	SCC (p)	SCC (p)
Age, months	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 $FEV_{0.5}$, L	−0.16 (0.47)	−3.27 (0.00)	−0.25 (0.02)
	Absolute change from baseline $FEV_{0.75}$ after bronchodilator use, L	**Percent change from baseline $FEV_{0.75}$ after bronchodilator use**	**Change in percent predicted $FEV_{0.5}$ after bronchodilator use**
	SCC (p)	SCC (p)	SCC (p)
Age, months	−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 $FEV_{0.75}$, L/s	−0.06 (0.60)	−0.18 (0.10)	−0.17 (0.11)

SCC: Spearman's correlation coefficient.

For FEV_1, 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%)[18] but different from that found by Linares et al. (10%, with a sensitivity of 12% and a specificity of 84%).[19] 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 FEV_1 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 $FEV_{0.5}$, 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%).[19] This low sensitivity suggests that 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 comparing patients and healthy controls, as was the case of the two aforementioned studies.[18,19] With regard to the change in the percentage of the predicted $FEV_{0.5}$ in response to bronchodilator use in the present study (16%), the fact that there have been no studies evaluating this parameter makes it impossible to make comparisons.

For baseline $FEV_{0.75}$, the bronchodilator response cut-off point found in the present study (18%) was higher than that found in another study (14%).[18] This difference might be due to the type of study (a case-control study)[18] and how the cut-off point was calculated (mean + 2 standard deviations after bronchodilator use in healthy participants).[18] With regard to the change in the percentage of the predicted $FEV_{0.75}$ 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 $FEF_{25-75\%}$ in the analysis of bronchodilator response,[1,19,20] $FEF_{25-75\%}$ is not given weight in studies evaluating bronchodilator response, because it varies widely.[6,20] For $FEF_{25-75\%}$, 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%) [18] and other authors (25%, with a sensitivity of 41% and a specificity of 80%).[1] Unlike the present study, the aforementioned studies were both case-control studies, and this might explain these discrepancies. The high ICC for $FEF_{25-75\%}$ in the present study indicates good reproducibility. With regard to the change in the percentage of the predicted $FEF_{25-75\%}$ in response to bronchodilator use in the present study (35.5%), 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 FEV_1.[6,25] However, for preschool children, the present study showed correlations of baseline $FEV_{0.5}$ with the percent change from baseline after bronchodilator use and the percent change in the predicted value after bronchodilator use. With regard to $FEV_{0.75}$, 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.

One of the strengths of the present study is that it was a community-based study, the results of which are more generalizable than are those of studies conducted in secondary or tertiary care settings. Another strength of the present study is that we used predicted values that had been derived from preschoolers in the same region as those in the present study, thus increasing the reliability of the results obtained. The high reproducibility of the spirometric measurements in the present study shows that they are reliable.

To our knowledge, this is the first study to determine, in preschool children, bronchodilator response cut-off points for FEV_1, $FEV_{0.75}$, $FEV_{0.5}$, and $FEF_{25-75\%}$, expressed as percentages of the predicted values. We derived reference values for $FEV_{0.75}$. Given that $FEV_{0.5}$ is reproducible and that $FEV_{0.5}$ measurements can be performed by a higher proportion of preschoolers, it is the most useful of all of the parameters studied here. $FEV_{0.75}$ is useful in children ≥ 4 years of age. . In community-based samples, spirometry is not useful in 3-year-olds due to the high rate of unacceptable tests.

For clinical practice, the recommended bronchodilator response cut-off points for percent predicted FEV_1, $FEV_{0.75}$, and $FEV_{0.5}$ are ≥ 12%, ≥ 8%, and ≥ 16%, respectively; for baseline FEV_1, $FEV_{0.75}$, and $FEV_{0.5}$, the recommended cut-off points are ≥ 13%, ≥ 18%, and ≥ 20%, respectively. For percent predicted and baseline $FEF_{25-75\%}$, the recommended cut-off points are ≥ 35% and ≥ 61%, respectively. Given that $FEF_{25-75\%}$ 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.

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