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Reference equation for maximal voluntary ventilation in children and adolescents

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Abstract

Objectives: To develop reference equations of maximal voluntary ventilation (MVV) in children and adolescents, and to test the validity and reproducibility of MVV.

Study Design: Cross-sectional study.

Patient-Subject selection: A total of 348 healthy volunteers (6-17 years)—248 for the development of reference equations and 100 to test the validity— were selected.

Methodology: Spirometry and MVV were performed. Volunteers were instructed to breathe quickly and strongly to estimate the MVV. Independent variables tested were age, sex, weight, height, and pulmonary function.

Results: All volunteers (50% boys) had a normal pulmonary function. Mean MVV was 66.3 (17.8) L/minute for children and 118.8 (20.0) L/minute for adolescents. The equation developed for children was MVV = 4.865 + (forced expiratory volume in the first second [FEV_{1}] × 16.257) + (peak expiratory flow [PEF] × 7.621); for adolescents was MVV = −25.450 + (FEV_1 × 11.591) + (PEF × 6.672) + (sex × 12.179) + (age × 3.613). No significant differences were observed between measured and predicted MVV in children (64.6 [10.3] vs 64.6 [8.5] L/minute; *P* = .34) or adolescents (111.8 [23.4] vs 113.1 [22.8] L/minute, *P* = .12). The intraclass correlation coefficient between measured and predicted MVV was 0.95 (0.91-0.97) for children and 0.90 (0.82-0.94) for adolescents. The mean bias of Bland-Altman analysis was −0.8 L/minute for children and −2.7 L/minute for adolescents.

Conclusions: Normative values for MVV were established for children and adolescents, additionally, these equations are reproducible and it can be used to determine the respiratory impairments in the pediatric population.

KEYWORDS

adolescents, children, maximal voluntary, reference equation, ventilation

1 | INTRODUCTION

The capacity to sustain high ventilatory demand has been evaluated based on maximal voluntary ventilation (MVV).[1,2] This measurement is used to determine the ventilatory reserves during cardiopulmonary exercise testing; it also estimates respiratory muscle endurance.[1]

Regression equations to estimate MVV have been described in the pediatric population.[3-6] This can be helpful because the measurement of MVV requires a maximal sustained effort, that can be difficult to evaluate in children. Additionally, it is necessary to determine the normative values to identify ventilatory impairment. According to Fulton et al,[3] MVV is estimated based on

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forced expiratory volume in the first second (FEV_1); however, that study only investigated African-American adolescents. Other studies on MMV in different pediatric populations have been conducted in India,[4] the United States,[5] and South Africa.[6] Budhiraja et al[4] evaluated urban and rural school children, ranging in age from 6 to 15, in the northern part of India. The authors described one reference equation for the entire dataset (children and adolescents) in which sex, height, and weight explained approximately equal to 30% of MVV. In the early 1970s, African-American children ranging in age between 6 and 14 were evaluated in Washington, DC in the US by Chehreh et al[5] based on that data, the authors described two equations, one for boys and another for girls, in which age and height explained approximately equal to 40% of MVV. More recently, Kroff et al[6] showed that the normative values of MVV for individuals over the age of 17 are higher than the previously published data because it was evaluated in athletic volunteers. In that study, sex, FEV_1, and peak expiratory flow (PEF) explained 78% of the MVV variation. The equations used in those previous studies have some limitations; children and adolescents are factored into the same equation as well as data from athletic volunteers. There is no data for individuals ranging in age between 15 and 17, and the previously-mentioned studies did not describe the validity or reproducibility of the data.

Ideally, the predicted pulmonary function values should be obtained from healthy individuals with anthropometric characteristics and ethnic characteristics that are similar to the patients being studied to avoid the underestimation or overestimation of the results.[7] As there are no MVV equations for the entire pediatric population, the present study aims to describe the normative values and to develop MVV reference equations in the pediatric population. It also aimed to test the validity and reproducibility of these equations.

2 | MATERIALS AND METHODS

A cross-sectional study was conducted with healthy children and adolescents. The volunteers were randomly selected to be included for the development of reference equations or validity equations. Children and adolescents were recruited from public and private schools in the city of São Paulo, Brazil. The research protocol was reviewed and approved by the institutional ethical review board (number 1.676.849).

Male and female individuals aged 6 to 17 years of age with no history of chronic or acute disease, with normal pulmonary function and participants and their legal guardians who had signed informed consent for the study were included. Volunteers who did not perform the tests in an acceptable manner, those with abnormal lung function (<80% of the predicted value based on reference values of Spirometry for Brazilians)[2] those as obese or excessively underweight, smokers, born prematurely (under 37 weeks of gestational age), and athletes (regular physical activity more than three times a week) were excluded from the study.

2.1 | Protocol

All the evaluations were performed on the same day by duly trained researchers. The data were collected at the physiology laboratory of University Nove de Julho or at the volunteer's schools. Data collection occurred between August 2016 and September 2017.

2.2 | Evaluations

The weight was measured with a precision of 0.1 kg and height was measured with a precision of 0.5 cm using a stadiometer (Welmy, São Paulo, Brazil). The body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Nutritional status was determined using the growth curve based on BMI for age recommended by the World Health Organization (2007).[8,9]

The ethnicity was declared by the parents (children group) or for the own volunteer (adolescent group) as Caucasian, Latin American (mixed), or Asiatic descendent.

2.3 | Pulmonary function

2.3.1 | Spirometry

Spirometry was performed using the KOKO Sx1000 device (nSpire Health, Longmont, CO) with a previously calibrated pneumotachograph. The technical procedures, as well as the acceptability and reproducibility criteria, were those recommended by the America Thoracic Association/European Respiratory Society.[1]

The following variables were recorded: forced vital capacity (FVC), FEV_1, FEV_1/FVC ratio, forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$) and PEF. Variables above 80% of the predicted Brazilian values[2] were considered as indicative of normal pulmonary function.

2.3.2 | Maximal voluntary ventilation

The MVV was determined with the volunteer in the sitting position. Each trial lasted 15 seconds and the volume achieved in this period was automatically extrapolated to 1 minute. The volunteers were instructed to breathe quickly and strongly during the test. All the volunteers received the same verbal encouraging by the physiotherapist during all the 15 seconds of the test. A minimum of three maneuvers was evaluated, with an interval of 60 seconds between trials.

The execution of MVV was considered acceptable when regular volume and respiratory rate were observed.[1] The reproducibility criterion was a difference of less than 10% between the two highest MVV values. If the highest value occurred during the last execution, a new evaluation was performed.[1] The highest recorded value of MVV was considered as the outcome.

2.4 | Statistical analysis

The sample size was calculated using the following equation: $N > 50 + (8 \times m)$, in which m = the number of independent variables in the analysis.[10] For $\alpha = .05$ and $\beta = .2$, a minimum sample of 122 participants would be needed. However, as other correlations were evaluated, at least 10 volunteers of each sex in each age group were included.

The Shapiro-Wilk test was used to determine the normality of the data. As parametric distribution was demonstrated, thus, the data are expressed as mean and standard deviation. Differences in MVV between boys and girls as well as between children (6-12 years old) and adolescents (13-17 years old) were analyzed using the unpaired *t* test. The age, weight, height, BMI, FVC, FEV_1, PEF, and $FEF_{25\%-75\%}$ were considered as independent variables in the stepwise multiple regression analysis. Pearson's correlation coefficients were used between the dependent and independent variables.

The paired *t* test was used for the comparison between measured and predicted MVV. The bland-altman analysis was performed[11] and the intraclass correlation coefficient (ICC) was calculated to determine agreement and variability between the measures. ICC values were interpreted as follows: 0.80 to 1.0 good reliability; 0.60 to 0.79 moderate reliability; and less than 0.60 low reliability.[12]

The probability of a Type I error was set to 5% ($P < .05$, two-sided) for all tests. The SPSS version 22 (Chicago, IL) was used for the statistical analyses.

3 | RESULTS

A total of 433 healthy volunteers were selected. However, 20 were physically active, 12 had spirometry under 80% of predicted value and/or did not perform MVV in an acceptable manner, 16 were classified as obese, two were classified as excessively underweight, two were smokers, 18 had been born prematurely, and the guardians of 15 volunteers did not sign the statement of informed consent. Thus, the final sample was composed of 348 volunteers, 248 of whom (50% males) were randomly selected for the development of the prediction equations and 100 of whom (59% males) were randomly selected to test the validity of these equations. The most part of the sample had declared as 57% Latin American people, 40% declared as Caucasian, 3% as Asiatic descendent people. Table 1 shows the anthropometric variables of the included volunteers.

The majority of volunteers (n = 291) achieved the highest MVV value in less than five trials: 63 on the first trial, 75 on the second trial, 62 on the third trial, 49 on the fourth trial, and 42 on the fifth trial. The last 57 volunteers had between 6 and 9 trials to achieve the highest MVV. Table 2 shows the lung function of children and adolescents' groups. The mean MVV in the overall sample was 87.8 [31.5] L/minute, and it was lower among the children (≤12 years old) compared to the adolescents (≥13 years old) (66.3 [17.8] vs 110.8 [20.0] L/minute, respectively; $P < .001$). No significant difference was found between boys and girls in the group of children (66.3 [17.8] vs 66.7 [18.3] L/minute, respectively; $P = .93$). Among the adolescents; however, MVV was lower in the girls (102.3 [18.5] L/minute) compared to the boys (119.2 [29.4] L/minute) ($P < .001$). Figure 1 shows a constant increase in MVV from 6 to 17 years old.

Positive correlations were observed between the highest MVV, anthropometric variables, and pulmonary function (FVC, FEV_1, PEF, $FEF_{25\%-75\%}$), Figure 2.

The stepwise multiple regression analysis revealed that FEV_1 and PEF explained 68% of the variance of MVV among the children ($P < .001$), whereas FEV_1, PEF, age, and sex explained 51% of the variance among the adolescents ($P < .001$, Table 3).

The MVV reference equations are:

TABLE 1 Characteristics of the volunteers, mean (SD)

	N = 348
Male, N (%)	164 (47)
Race	
Mixed, %	57
Caucasian, %	40
Japanese, %	3
Age, y old	11.2 [3.2]
Height, cm	148.0 [16.5]
Weight, kg	44.2 [15.8]
BMI, kg/m^2	19.5 [4.0]

Abbreviations: BMI, body mass index; SD, standard deviation.

TABLE 2 Anthropometric and lung function variables of children and adolescent groups, mean (SD)

	Children (N = 190)	Adolescents (N = 158)
Age, y old	8.6 [1.6]	14.1 [1.7]
Height, cm	136.4 [11.2]	161.9 [9.5]
Weight, kg	34.0 [10.5]	56.4 [12.0]
BMI, kg/m^2	17.9 [3.5]	21.3 [3.7]
FVC, L (% pred)	2.1 [0.5] (97.5 [12.1])	3.5 [0.7] (101.6 [12.8])
FEV_1, L (% pred)	1.8 [0.4] (93.5 [10.1])	3.1 [0.6] (96.6 [10.6])
FEV_1/FVC	88.8 [5.3]	89.3 [10.6]
PEF, L (% pred)	4.1 [0.9] (93.2. [18.8])	6.4 [1.1] (102.3 [20.1])
$FEF_{25\%-75\%}$, L (%pred)	2.3 [0.6] (985.5 [10.6])	3.7 [0.8] (91.9 [10.7])
MVV, L/min	66.3 [17.8]	110.8 [20.0]

Abbreviation: SD, standard deviation.

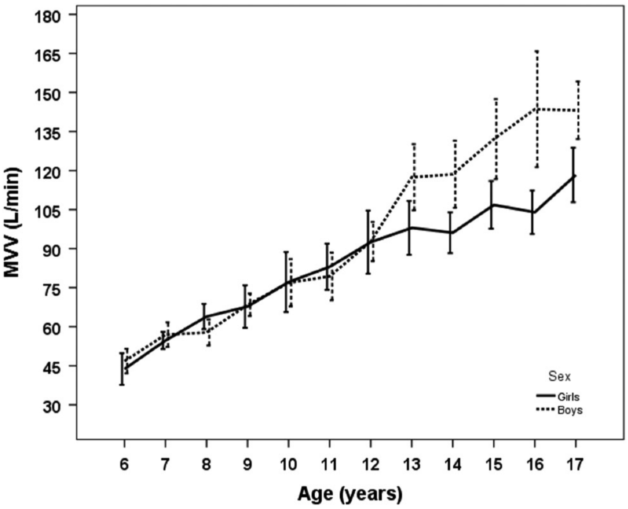

FIGURE 1 Maximal voluntary ventilation (MVV) in boys (dashed line) and girls (solid line)

MVV predicted for children = 4.865 + (FEV_1 × 16.257) + (PEF × 7.621),
FEV_1 and PEF in liters,
R^2 = 0.68.
MVV predicted adolescents = −25.450 + (FEV_1 × 11.591) + (PEF × 6.672) + (sex × 12.179) + (age × 3.613),
FEV_1 and PEF in liters,
Sex: 0 for female, 1 for male,
R^2 = 0.51.

The characteristics of the volunteers included in the equation validity were similar to those for the development of the reference equations (Table 4). No significant differences were found between the measured and predicted MVV for either children (64.6 [10.3] L/minute vs 64.6 [8.5] L/minute, respectively; P = .34) and adolescents (111.8 [23.4] L/minute vs 113.1 [22.8] L/minute, respectively; P = .12).

The ICC between measured and predicted MVV was excellent for both children (0.95 [0.91-0.97]; P < .001) and adolescents (0.90 [0.82-0.94]; P < .001). The Bland-Altman analysis revealed bias of −0.8 L/minute, with limits of agreement from 11 to −12 L/minute for children, and bias of −2.7 L/minute, with limits of agreement from 17 to −22 L/minute for adolescents (Figure 3).

4 | DISCUSSION

The present study described the MVV reference equations in children and adolescents. The predictor variables FEV_1 and PEF, explained 68% of the variance in MVV among children, whereas FEV_1, PEF, age, and sex explained 51% of the variance among adolescents. Excellent agreement was observed between the measured and predicted MVV for both groups.

In addition to age and sex, FEV_1 and PEF remained in the reference equations as variables that predict MVV. The FEV_1 has been described as being strongly related to MVV in studies involving adults[12-15] and children.[3] The use of FEV_1 as a predictor of MVV is not recent,[16] and the strength of the correlation between MVV and FEV_1 has been reported in studies that have established prediction equations for MVV in other populations (R^2 = 0.79-0.81).[14,15]

Additionally, to FEV_1, the present study's findings showed that PEF is also correlated with MVV. Pulmonary function variables are clearly related to MVV since the level of ventilation per minute depends on the velocity of air through the airways. Fulton et al[3] previously described PEF as a predictor of MVV for girls. PEF and FEV_1 represent different lung areas. The PEF indicates central and upper airway resistance and it is dependent on a patient's effort; whereas FEV_1 indicates expiratory volume in the small airways. Considering that the airway resistance is influenced by the bronchi diameter, and in the pediatric population it is reduced because it is not completely developed, the PEF influences the MVV values for this age. Unlike adults, who had completely lung developed and the bronchi diameter does not change much.

Anthropometric variables have also been found to impact the variation in MVV in the pediatric populations studied in India[4], the United States[5], and South Africa.[6] This finding is explained by the growth of the respiratory system. With the exception of the findings reported by Kroff et al[6], our equation showed better R^2, including lung function variables, age, and sex.

In the adult population, MVV increases with height, and it is higher in men.[14] The children and adolescents in the present study also demonstrated an increase in MVV with an increase in age; additionally, MVV was only higher in boys than girls after the age of 12. Faria et al[17] found the difference in MVV between boys and girls ranging in age from 10 to 17. During childhood, development is a relatively stable process and both sexes progress similarly until adolescence.[18,19] At the onset of puberty, development is more accentuated in boys, which explains the difference in MVV between the sexes. This is why an equation based on children cannot be applied to adolescents.

Considering the absolute values of MVV, on average, our results are similar to those reported by Fulton et al[3] (87 ± 31 L/minute and 86 ± 17 L/minute, respectively). However, Fulton et al[3] studied African-American adolescent girls; the present study did not investigate that population (the most part of volunteers was of Latin American ethnicity) and it also included both sexes. In the study by Budhiraja et al[4], the MVV values were lower (68 ± 26 L/minute); moreover, the subjects were from the northern part of India and ranged in age from 6 to 15. Emphasizing the difference between populations, the MVV measured in the present study differed by −4 ± 10 L/minute from the value predicted by Fulton et al[3], 5 ± 13 L/minute from the value predicted by Budhiraja et al[4], and 5 ± 16 L/minute from the value predicted by Chehreh et al[5].

In the present study, the validity of the developed MVV equations was tested. Validity refers to the capacity of a variable to reflect what is being measured without bias. In the present study, validity was demonstrated by the lack of significant differences between the measured and predicted MVV values for both children and adolescents. Additionally, excellent ICCs between the measured

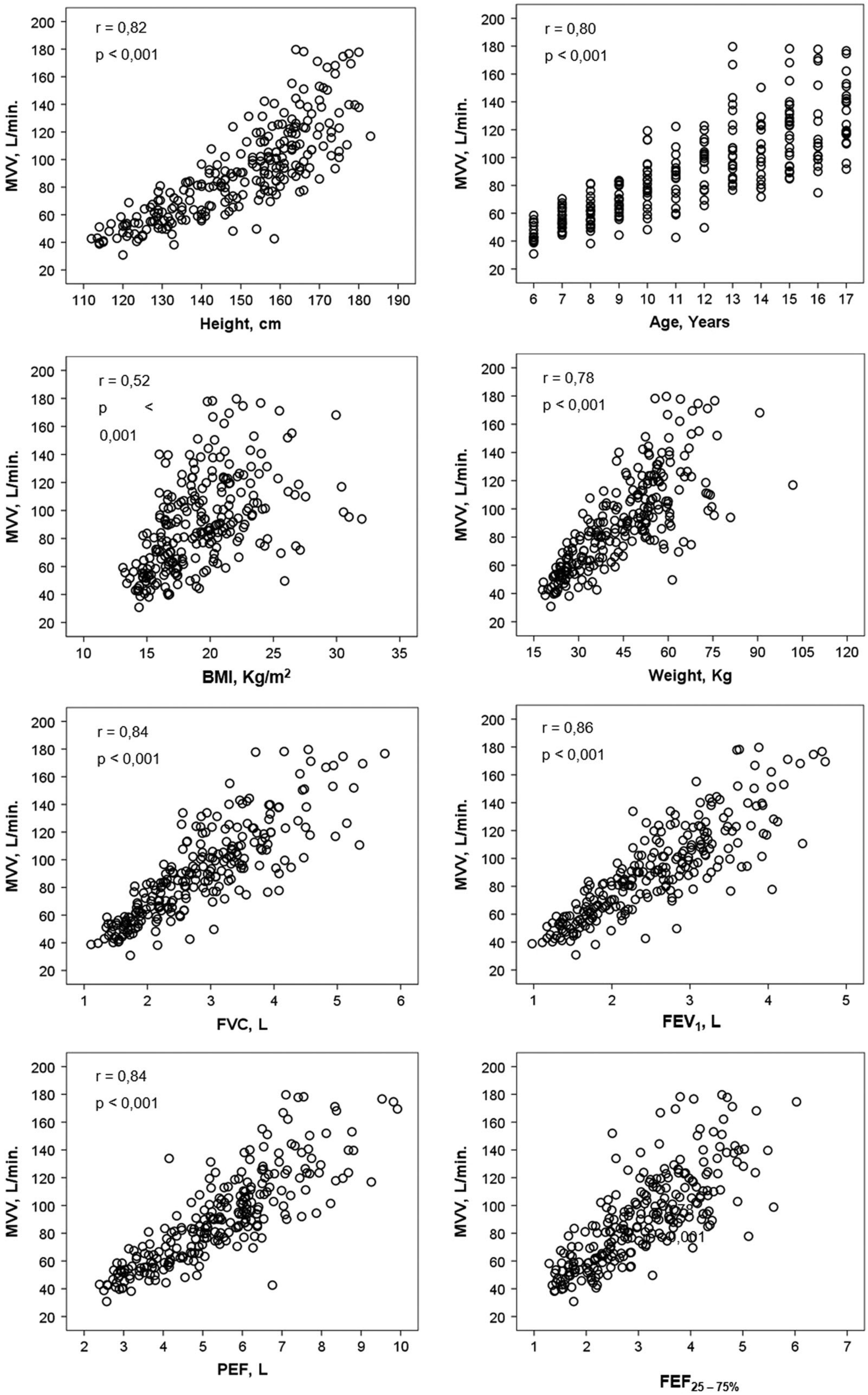

FIGURE 2 Correlation between maximal voluntary ventilation (MVV) and anthropometric and lung function. BMI, body mass index; FEF, forced expiratory flow; FEV_1, forced expiratory volume at the first second of FVC; FVC, forced vital capacity; PEF, peak expiratory flow

TABLE 3 Predictor variables for maximum voluntary ventilation obtained from multiple linear regression analysis

	Unstandardized coefficients (*B*)	SE	*P*
Children (≤12 y of age)			
Constant	4.865	4.133	.241
FEV_1, L	16.257	4.676	.001
PEF, L	7.621	2.128	<.001
Adolescents (≥13 y of age)			
Constant	−25.450	15.731	.108
FEV_1, L	11.591	4.729	<.016
PEF, L	6.672	2.340	.005
Sex	12.179	3.910	.002
Age, y old	3.613	1.173	.003

Note: Sex: 0 for female, 1 for male.
Abbreviations: FEV_1, forced expiratory volume at the first second of FVC; FVC, forced vital capacity; PEF, peak expiratory flow; SE, standard error.

TABLE 4 Characteristics of the volunteers to develop the reference equations and to test the validity of equations.

	Equation group n = 248	Validity group n = 100	*P*
Age, y old	11 [3]	11 [3]	.757
Height, cm	149.2 [17.4]	149.6 [16.8]	.948
Weight, kg	44.4 [16.7]	47.8 [18.4]	.115
BMI, kg/m^2	19.2 [3.6]	20.7 [4.8]	.004
FVC, L (% pred)	2.8 [0.7] (99 [13])	2.9 [1.0] (99 [12])	.822
FEV_1, L (% pred)	2.5 [0.8] (95 [11])	2.5 [0.8] (94 [10])	.733
FEV_1/FVC	89 [5]	87 [6]	.014
PEF, L (% pred)	5.4 [1.6] (90 [10])	5.2 [1.7] (88 [9])	.351
$FEF_{25\%-75\%}$, L (% pred)	3.0 [1.0] (99 [19])	2.9 [1.0] (94 [23])	.272
MVV, L/min	90.7 [33.1]	87.4 [29.7]	.348

Abbreviations: BMI, body mass index; FEF, forced expiratory flow; FEV_1, forced expiratory volume at the first second of FVC; FVC, forced vital capacity; MVV, maximum voluntary ventilation; PEF, peak expiratory flow.

and predicted MVV values were found for both groups. The Bland-Altman analysis showed small differences between the measured and predicted MVV values, with smaller limits of agreement for the group of children and larger limits for the group of adolescents.

Because MVV reference values can be influenced by ethnicity, the use of reference equations developed in other populations can overestimate or underestimate the results, leading to erroneous interpretations. Fulton et al[3] evaluated African-American adolescent girls, who were older and taller than the sample in our study; Budhiraja et al[4] studied children and adolescents from the northern part of India, and their sample was younger, weighed less, and had a smaller stature, than the sample in our study; Chehreh et al[5], investigated African-American children from the District of Columbia in the United States with different anthropometric variables than in the present study. Most of participants in our sample were of Latin American ethnicity. This reflects the significant ethnic diversity of the Brazilian population, therefore, it is crucial to establish our own MVV reference values. This either highlights the importance of using reference values from the population with similar anthropometric characteristics. Therefore, our reference equation for MVV is an easy and noninvasive way to identify ventilatory reserve during exercise, in a similar ethnicity population studied here.

The present study has some limitations. The sample was taken from a single city: São Paulo, Brazil. However, both public and private schools from different sections of that city were selected, which may ensure the external validity of the study. In terms of ethnicity, we decided to use the term Latin American considering individuals variability in the country. This decision was made to avoid bias, considering that the study relied on self-reported answers, additionally, this term was previously used for our population.[20] The data were collected in two different settings (at school and in a laboratory), which could be a potential bias. However, the same physiotherapist performed all the measurements according to international guidelines.

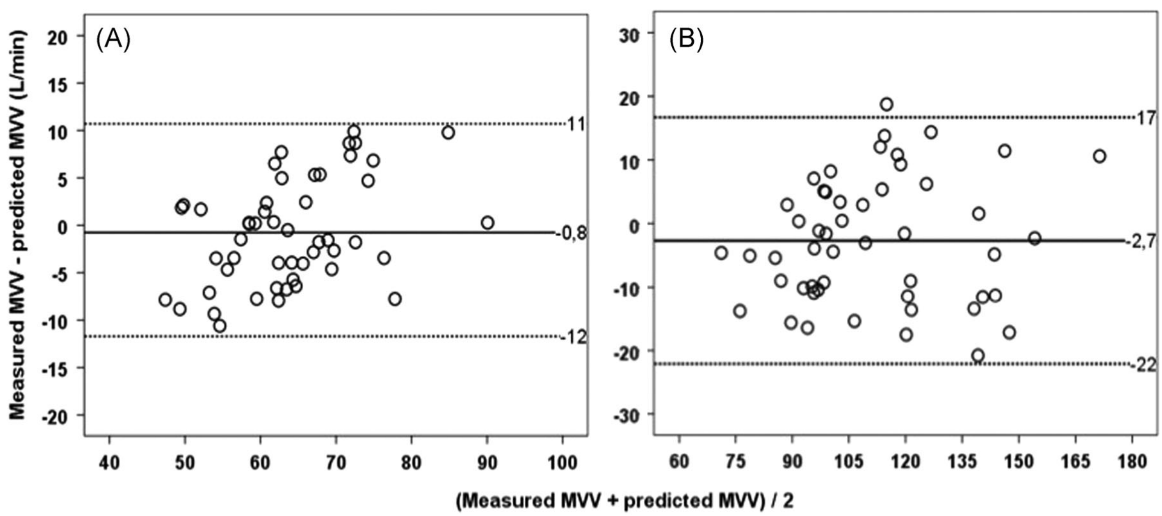

FIGURE 3 Bland-Altman analysis of measured and predicted maximal voluntary ventilation (MVV). Solid line indicates mean bias in reference and dashed lines indicate upper and lower limits of agreement. A, Children (≤12 years of age; n = 50). B, Adolescents (≥13 years of age; n = 50)

5 | CONCLUSIONS

The present study established the normative MVV values for children and adolescents in a Brazilian population in São Paulo. Additionally, we demonstrated the validity of these equations.

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AUTHOR CONTRIBUTIONS

FCL and SDC made substantial contributions to conception and design. JCS and IEC made substantial contributions to acquisition of data, and analysis, and interpretation of data. JCS and FCL drafted the submitted article and revised it critically for important intellectual content. SDC provided the final approval of the version to be published. All the authors are agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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