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Reference Values for the 6-min Walk Distance (6MWT) in Healthy Children Aged 7 to 12 Years in Brazil: Main Results of the TC6minBRASIL Multi-Center Study

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INTRODUCTION: Brazil is a country with great climatic, socioeconomic, and cultural differences that does not yet have a reference value for the 6-min walk test (6MWT) in healthy children. To avoid misinterpretation, the use of equations to predict the maximum walking distance should be established in each country. OBJECTIVES: We sought to establish reference values and to develop an equation to predict the 6-min walk distance (6MWT) for healthy children in Brazil. METHODS: This is a cross-sectional multi-center study that included 1,496 healthy children, aged 7 to 12 y, assessed across 11 research sites in all regions of Brazil, and recruited from public and private schools in their respective regions. Each child was assessed for weight and height. Walking distance was our main outcome. An open-source software environment for statistical computing was used for statistical analysis. RESULTS: We observed a higher average distance walked by boys (531.1 m) than by girls (506.2 m), with a difference of 24.9 m ($P < .001$). We established 6MWT reference values for boys with the following equation: Distance = (16.86 × age) + (1.89 × Δ heart rate) − (0.80 × weight) + (336.91 × R1) + (360.91 × R2). For girls the equation is as follows: Distance = (13.54 × age) + (1.62 × Δ heart rate) − (1.28 × weight) + (352.33 × R1) + (394.81 × R2). CONCLUSION: Reference values were established for the 6MWT in healthy children aged 7–12 y in Brazil. *Key words: exercise test; child; pediatrics; reference values.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

The 6-min walk test (6MWT) is a well-established tool for assessing submaximal exercise capacity in people with cardiopulmonary diseases worldwide.[1] In the 6MWT, patients are instructed to walk as far as they can for 6 min in a straight, flat, 30-m corridor.[2] This test is easy to perform,

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has low cost, and is well accepted in clinical practice and research.[1,2] The 6MWT is largely used for the assessment of exercise capacity before and after an intervention, such as an exercise training program, or for the prognostic stratification of selected patients, such as those with heart failure or COPD.[2-4]

Although the 6MWT has been widely performed in adults, its use in children has increased in the last 10 years.[5] The 6MWT is safe, well understood, and well tolerated in healthy children and in those with various diseases, such as cardiorespiratory[6,7,8] or neuromuscular disorders.[9,10]

Due to the high relevance of the 6MWT, some countries have already established reference values for the maximum walking distance for healthy children, such as China,[11] United Kingdom,[12] Thailand,[13] Turkey,[14] India,[15] and the United States of America.[16] Despite this, Brazil, a country with large climatic, socioeconomic, and cultural differences, does not have representative reference values for healthy children.[17] It is known that the use of formulas to predict the maximum walking distance in the 6MWT established in other countries may lead to significant interpretation error.

QUICK LOOK

Current knowledge

Several countries around the world have already established reference values for the 6-min walk test in healthy children. This concern about local reference values can minimize the test's interpretation errors. However, these Brazilian reference values were not available.

What this paper contributes to our knowledge

This study established reference values for the 6-min walk test in healthy children in Brazil at 7-12 y old. Now, researchers and clinicians have local reference values to make a more precise interpretation of the test. The work is relevant because it is a multi-center study that considered all regions of Brazil through a representative sample.

The aim of this study was to establish reference values and to elaborate an equation to predict the 6-min walk distance (6MWT) in healthy children in Brazil. In addition, our study aimed to test the equation in an independent sample.

Methods

Study Design and Population

This was a cross-sectional multi-center study that included healthy children between 7 and 12 y old from all Brazilian regions from August 2013 to December 2016. Children with some type of indisposition on the day of the test (eg, a cold or fever) or those did not understand the instructions or performed the 6MWT in disagreement with international standards[1] were excluded. The judgment of the efficiency of the test was at the discretion of each investigator. The eligibility criteria for the research sites (Brazilian physiotherapy schools) in the TC6minBrasil study were to have a physical structure and human resources according to the American Thoracic Society[1] (ATS) guideline for the 6MWT, such as a flat and straight corridor that is 30 m long, a pulse oximeter, a scale, a tape measure, a sphygmomanometer, a stethoscope, a stopwatch (or another means to track time, such as a watch or a mobile telephone). After this stage, the research steering committee sent a letter of invitation to the coordinator of research responsible for the research sites. After acceptance, the research sites were instructed how to perform the 6MWT accord-

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ing to the international recommendations.[1] The training was carried out through tutorial videos, conferences, telephone contacts, and printed material that covered all the phases of the research. The research sites had open communication channels with the TC6minBrasil study committee through videoconference, e-mail, or telephone.

All participants and legal guardians involved in the study were informed about the research aims and procedures. A legal representative signed the free and informed consent form approved by an ethics committee (CAAE 08827713.1.1001.0065) before participating in the study. This study was supported by Fapitec-SE (MS/CNPq/FAPITEC/SE/SES – PPSUS, No. 02/2013).

Sample Size Calculation

The sample size was calculated considering the construction of a 95% reference curve for the 6-min walk distance (6MWT) by healthy children in Brazil aged between 7 and 12 y, assuming the normal distribution for the distance covered. We considered in the sample size calculation the 12 sub-populations formed by the 6 age classes, that is, 7–12 y, and by sex. The estimated number of children in each sub-population of interest was 114 when we assumed an absolute error of 1.5% in relation to the percentiles of 2.5% and 97.5%. In the end, 1,496 children were selected from all Brazilian regions by stratified sampling by age and sex. The distribution of the sample in the different regions took into account the population density, seeking the representativeness according to IBGE data of 2010. In this distribution, the population of the North was 8.3%, the Northeast was 27.8%, the Southeast was 42.1%, the South was 14.4%, and the Center-West was 7.4%, totaling 100% of the Brazilian population.[18]

Considering the sample size calculation, it was proposed that 1 research site in the North would assess 118 children, 3 research sites in the Northeast would assess a total of 415 children (2 research sites with 138 and 2 research sites with 139), 1 research site in the Central-West region would assess 112 children, 4 research sites in the Southeast region would assess a total of 627 children (3 research sites with 157 and 1 research site with 156), and 2 research sites in the South region would assess a total of 224 children (112 per research site), totaling 1,496 children in Brazil. It was recommended that each research site distribute the number of participants equally, by sex, in the 6 age groups.

Training of Research Sites

After the formal acceptance of each eligible research site to participate in the TC6minBrasil study, a videoconference was held for a formal presentation. In this first conference, the study design was carefully explained. Moreover, standardized instructions were given regarding the organization of the physical space and application of the test according to the ATS guideline.[1] These instructions were given via tutorial videos, videoconference calls, and a checklist of the materials necessary to carry out the tests and data collection. After the assembly of the 6MWT circuit, the steering committee contacted the research sites by telephone to answer any queries.

After each research site completed the assessment of the first 10 children, there was another videoconference to check whether the test and data collection were being performed properly. Thenceforth telephone calls to the research site were made after the evaluation of every 50 children. A final videoconference was held at the end of the study to audit the data.

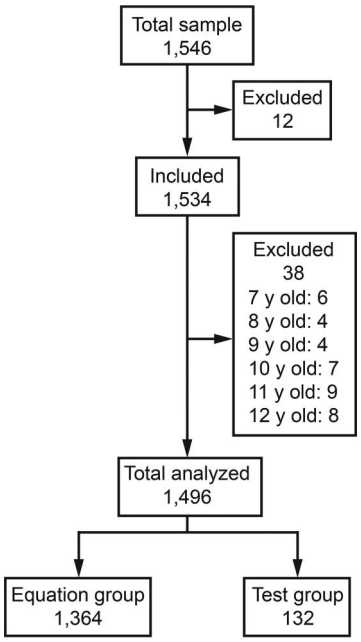

Fig. 1. Flowchart.

Screening of Participants by Research Sites

The research sites were responsible for recruiting the participants. To carry out the screening, a standardized form about the child's current health condition was sent to parents or any legal authority. An Internet address was also provided with an example of the 6MWT to allow parents or guardians to see the procedures of the test. After the consent was signed and the health screening form was completed, the researchers responsible for each site sched-

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Table 1. Sample Characteristics by Age and Sex

Age	Height, m	Weight, kg	Δ Heart Rate, beats/min	BMI, kg/m^2	Final Borg	Resting S_{pO_2}, %
Boys						
7, $n = 129$	1.26 (0.06)	26.55 (5.32)	20.21 (20.73)	16.52 (2.32)	2.0 (3.0)	97.20 (2.04)
8, $n = 117$	1.32 (0.07)	30.89 (6.95)	21.66 (20.96)	17.72 (3.08)	2.5 (3.0)	97.61 (1.52)
9, $n = 117$	1.36 (0.06)	32.66 (5.82)	20.66 (19.81)	17.48 (2.48)	2.0 (2.5)	97.03 (3.63)
10, $n = 114$	1.42 (0.07)	35.42 (9.09)	30.44 (24.96)	17.48 (3.15)	2.0 (3.5)	97.68 (1.86)
11, $n = 133$	1.48 (0.08)	40.89 (10.54)	26.51 (31.26)	18.54 (3.50)	2.0 (3.0)	97.56 (1.63)
12, $n = 121$	1.53 (0.09)	45.33 (10.38)	27.52 (26.10)	19.15 (3.42)	2.0 (3.75)	97.49 (2.51)
Total, $n = 731$	1.40 (0.12)	35.33 (10.43)	24.47 (24.65)	17.82 (3.14)	2.0 (3)	97.43 (2.30)
Girls						
7, $n = 118$	1.25 (0.06)	26.30 (6.74)	24.67 (24.58)	16.64 (3.00)	2.0 (2.5)	97.16 (2.68)
8, $n = 122$	1.30 (0.07)	29.88 (6.44)	20.49 (28.60)	17.57 (3.08)	2.0 (3)	97.34 (1.91)
9, $n = 130$	1.37 (0.08)	33.68 (9.44)	23.84 (21.45)	17.81 (3.49)	2.0 (3)	97.32 (3.01)
10, $n = 141$	1.43 (0.08)	37.43 (9.52)	29.55 (26.54)	18.16 (3.49)	2.0 (3)	97.80 (1.85)
11, $n = 126$	1.49 (0.08)	42.40 (10.15)	28.50 (28.89)	18.90 (3.35)	3.0 (3.5)	97.69 (1.91)
12, $n = 130$	1.53 (0.08)	45.65 (9.33)	32.42 (27.25)	19.44 (3.28)	3.0 (4)	97.63 (2.08)
Total, $n = 767$	1.40 (0.12)	36.09 (10.99)	26.71 (26.55)	18.11 (3.40)	2.0 (3.5)	97.50 (2.28)

Values expressed as mean and standard deviation in parentheses. The median and interquartile range were only used for the Final Borg variable. In this case, the median is the value outside the parentheses and the interquartile amplitude is what is in parentheses.
Δ Heart Rate = difference between the heart rate at the 6th minute and resting heart rate
BMI = body mass index
Resting S_{pO_2} (%) = oxygen saturation at rest

uled a date for each subject to come to the site for testing and data collection.

6MWT

The main outcome of the 6MWT was the maximum walking distance. The research sites recruited children in public and private schools in their respective regions. Data were collected and inserted into standardized forms. Each child was initially assessed to obtain the values of weight and height. After initial data collection, the child remained resting in a chair near the start line of the test for at least 10 min. During this time, the researchers recorded heart rate (beats/min), peripheral oxygen saturation (%), and blood pressure (mm Hg).

The researchers explained to the test subject that the goal was to walk as far as possible for 6 min without running or jogging. After the explanation, the investigator demonstrated the test by performing a complete turn. After receiving the instructions, the child was allowed to start the test when he or she chose. Standardized incentive phrases were used according to ATS guidelines.[1]

At the sixth minute of the test, the investigator instructed the participant to stop. The investigator went to the child with a chair to sit down. At this time researchers recorded a rating of perceived exertion (modified Borg Scale), peripheral oxygen saturation, final heart rate, and the heart rate at the 1 and 2 min of recovery. The maximum walking distance was measured.

Table 2. Maximum Walking Distance by Age and Sex

Age, y	Distance in Meters for Males, mean (SD)	Distance in Meters for Females, mean (SD)	*P*
7	474.4 (83.29)	469.1 (87.08)	.75
8	514.1 (77.13)	485.5 (91.30)	.007
9	525.0 (81.02)	505.5 (74.58)	.03
10	549.5 (87.24)	517.5 (89.61)	.008
11	557.3 (98.72)	530.3 (85.18)	.03
12	568.0 (99.74)	524.5 (102.50)	.002
Total	531.1 (93.83)	506.2 (91.04)	< .001

Tukey test was used for comparison of the overall average. $P < .05$ was considered statistically significant.

Statistical Analysis

The collected data were inserted in a standardized worksheet and sent to the steering committee by each research site. For data analysis, we used the statistical program R, v. 3.3.2. Initially, the correlation between all independent variables and also the dependent variable was verified with the Pearson coefficient (bivariate correlation). The hypothesis of equal means for the distance walked between different groups of qualitative variables such as sex and region were analyzed using the Tukey test. Then several models were adjusted by linear regression using sex, Brazilian region, age, height, body mass index (BMI), and change (Δ) in heart rate from the group of 1,364 subjects used to establish the equation. The equations were then

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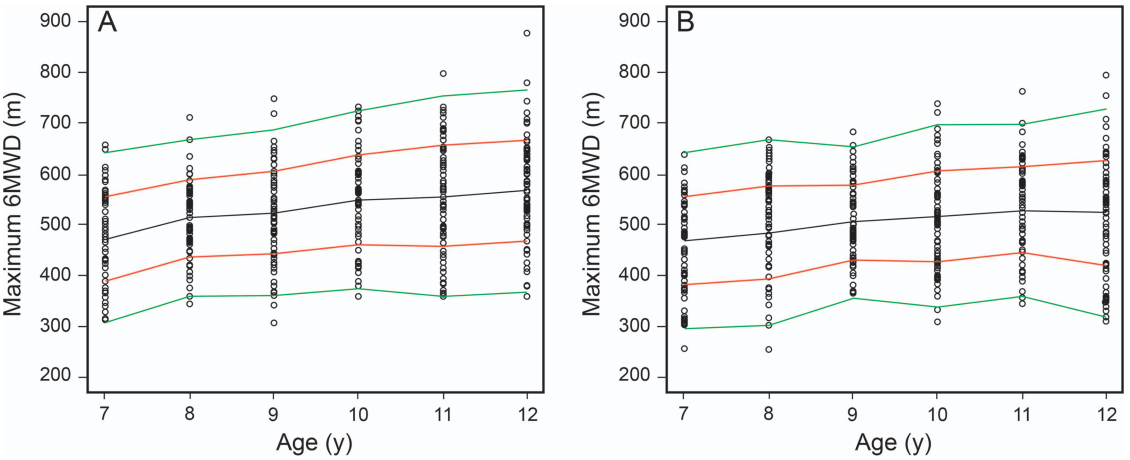

Fig. 2. Reference curve of maximum 6-min walk distance (6MWD) by age groups. Black lines represent the mean and red and green lines show ± 1 SD and ± 2 SD, respectively. Reference values are between the mean and −1 SD.

Table 3. Reference Values for the 6-min Walk Distance (6MWT)

Age, y	Mean Distance, m	−1 SD	−2 SD	−3 SD
Boys				
7	474.4	391.1	307.8	224.6
8	514.1	437.0	359.8	282.7
9	525.0	444.0	363.0	282.0
10	549.5	462.2	375.0	287.7
11	557.3	458.6	359.9	261.1
12	568.0	468.3	368.5	268.8
Girls				
7	469.1	382.1	295.0	207.9
8	485.5	394.2	302.8	211.5
9	505.5	430.9	356.3	281.8
10	517.5	427.9	338.3	248.7
11	530.3	445.2	360.0	274.8
12	524.5	422.0	319.5	217.0

6MWT = 6-min walk test
$-n$ SD = subtracting the average distance of n SD

Table 4. Regional Differences of the 6-min Walk Distance (6MWT)

Region	Difference	Lower Limit	Upper Limit	*P*
South and North	123.48	94.93	152.04	< .001
Center-West and North	92.25	59.09	125.41	< .001
Southeast and North	79.85	55.05	104.65	< .001
South and Northeast	64.24	43.01	85.46	< .001
Northeast and North	59.25	33.52	84.97	< .001
South and Southeast	43.63	23.54	63.73	< .001
Center-West and Northeast	33.00	5.90	60.10	.01
South and Midwest	31.23	1.43	61.03	.03
Southeast and Northeast	20.60	4.79	36.41	.001
Center-West and Southeast	12.40	−13.82	38.62	.70
Region 1 and Region 2	45.03	35.08	54.98	< .001

Mean values expressed in meters. Tukey test was used for comparison between regions.
P values was considered statistically significant.
6MWT = 6-min walk test
Region 1 = South, Southeast, and Midwest
Region 2 = North and Northeast

validated using the test group (132 independent healthy children). Then new models were adjusted for boys and girls. The best models were selected using the mean error, standard deviation of the errors of prediction, and Mean Squared Error (MSE), as well as by visual scatter plots.

Results

A total of 1,546 children were eligible for this study, and 1,496 were included in our final analysis; reasons for exclusion are shown in Figure 1. The sample was composed of children 7–12 y old and is characterized in Table 1. The results were similar between both boys and girls for all the independent variables, with height and weight increasing steadily, as expected, from approximately 1.25 m and 26 kg at 7 y to 1.53 m and 36 kg at 12 y, respectively. Researchers also observed higher BMI with age, but Δ heart rate, final Borg rating, and resting S_{pO_2} did not present any ascending or descending pattern associated with age. Regarding the main outcome of this study (6-min walk distance (6MWT)), there was a significant difference between boys and girls, with boys walking longer distances for all ages except 7 y, the only group whose difference was not statistically significant. When comparing the maximum walking distance between boys and girls, we identified a mean difference of 24.9 m ($P < .001$) in favor of boys (Table 2). The overall average was 518.4 ± 93.2 m. When comparing the maximum walking distance between the sexes, we identified a mean difference of

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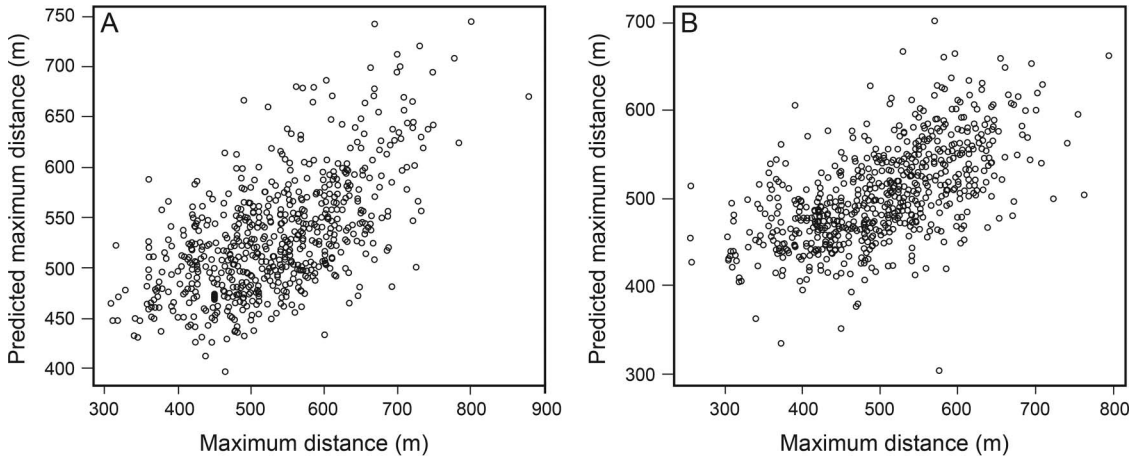

Fig. 3. Correlation between predicted and walked distance for the 1,364 children (equation group). Pearson correlation. A: R = 0.61 and $P < .001$ for boys. B: R = 0.60 and $P < .001$ for girls.

24.9 m ($P < .001$) in favor of boys. We also identified the variability in relation to age (Table 2).

The reference values for the maximum walking distance were obtained by subtracting the standard deviations of each age group from the corresponding mean walking distance for boys: 391–474 m for 7 y, 437–514 m for 8 y, 444–525 m for 9 y, 462–549 m for 10 y, 458–557 m for 11 y, and 468–568 m for 12 y; and then doing the same for girls: 382–469 m for 7 y, 394–485 m for 8 y, 430–505 m for 9 y, 427–517 m for 10 y, 445–530 m for 11 y, and 422–504 m for 12 y (Figure 2). After establishing the normal range, 2 reference curves (boys and girls) were created for the maximum walking distance by age group from 7 to 12 y (Table 3).

The maximum walking distance was compared among the 5 regions of Brazil (North, Northeast, South, Southeast, and Center-West), and a significant difference was found. Therefore, we decided to take into account the region of Brazil in establishing the formula to predict the maximum walking distance in the 6MWT. To avoid the use of a coefficient for each region, the research sites were grouped into 2 large regions: North/Northeast (R1) and South/Southeast/Center-West (R2) (Table 4).

After the investigation of the correlation matrix, the variables considered to be potentially associated with the 6-min walk distance (6MWT) were age (y), weight (kg), height (m), BMI (kg/m^2), sex, and Δ heart rate (beats/min). Considering the multicollinearity statistical phenomenon, our regression model was established with the variables of age, height, sex, and Δ heart rate. The equations were established considering the observation of 1,364 children (group equation). The criteria to choose the best regression model was based on the observation of mean error, error SD, and mean square error. The decision to establish 2 equations, one for boys and one for girls, was made so that it would be easier to interpret the effects of each independent variable for sex and to avoid the possibility of interaction effects for sex and other variables included in the model.

We established 6MWT reference values for boys with the following equation: Distance = (16.86 × age) + (1.89 × Δ heart rate) − (0.80 × weight) + (336.91 × R1) + (360.91 × R2). For girls the equation is as follows: Distance = (13.54 × age) + (1.62 × Δ heart rate) − (1.28 × weight) + (352.33 × R1) + (394.81 × R2). If the investigator chooses not to use the variable region of Brazil, just add the value of the 2 coefficients (R1 and R2) and divide by 2. R1 and R2 work as dummy variables.

The selected equations were evaluated through comparison of predicted and observed data. The correlation coefficient between the maximum walked distance of the 1,364 children with the distance predicted by the formula was R = 0.6 for boys and R = 0.6 for girls (Fig. 3).

The established equations were also tested on an independent sample of 132 healthy children 7–12 y old (group test). The equations produced an error of approximately 10 m for boys and for girls, which is acceptable in clinical practice. The correlation between the predicted and the walked distance showed good results, with R = 0.5 for boys and R = 0.5 for girls.

Discussion

This study established reference values for the maximum walking distance in the 6MWT for healthy children in Brazil. The variables that predicted the maximum walking distance were age, weight, Brazilian region, and heart rate variation during the test. In addition, the established equations (one for boys and one for girls) predicted the maximum walking distance when tested on an independent sample.

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A recently published systematic review[20] analyzed the reference values for the 6MWT in healthy children available worldwide through national studies and found that there could be a variation of up to 159 m from one country to the next. This difference means that if we use an equation to predict the maximum walking distance that was established in another country, we could be making a significant interpretation mistake. Our study reinforces the need to establish reference values through multi-center representative samples in countries with large territory and cultural diversity, such as the United States of America or Brazil.

This is of great clinical importance if we consider the minimally significant difference already established in several adult populations, such as 32 m for heart failure,[21] 25 m for coronary artery disease,[22] and 30 m for COPD.[23] However, no minimally significant difference is available for children.

Brazilian studies with children and the 6MWT are available in the literature, including one involving sickle-cell anemia[24] and another involving kidney disease.[25] These studies showed that the performance in the 6MWT was lower than predicted, but the authors used reference values from other countries.[23,24] In another Brazilian study involving children with cystic fibrosis,[26] the authors evaluated the relationship between maximum walking distance in the 6MWT with hospitalization time. The authors used the reference values for the 6MWT in healthy children in Porto Alegre, a city in southern Brazil. However, we cannot extrapolate these results to the rest of the country. Brazil is a country with great climatic, socioeconomic, and cultural differences.

When comparing the mean walking distance in the 6MWT found in our study with the study by Priesnitz et al[22] (579.4 m), we identified a discrepancy of 61 m. The difference in our study was the use of an additional variable, Brazilian region, to establish the equation to predict the maximum walking distance, in light of the variations in our country. The use of this variable makes the equations more precise in predicting the maximum walking distance. However, our equations can also be used without taking into account the Brazilian region. In this case, it is necessary to add the values of the variables R1 and R2 and divide by 2, but in doing so, the equation loses power to predict maximum walking distance.

Our study has some limitations. Our sample size calculation was based on Brazilian regions and not states. Even knowing that this is not the best scenario, our study represents the largest sample available in a Brazilian study. Moreover, our sample was not randomized, and the socioeconomic profiles of the subjects were not evaluated. In addition, the children were separated by chronological age rather than by biological maturity. Although there is some disagreement about the influence of biological maturity on exercise performance,[27] it is important to highlight this theme. A recent meta-analysis[28] showed that short-term resistance training was effective in improving strength in boys, and that this improvement was sensitive to level of biological maturity. This difference in strength was attributed to neurological and morphological adaptations mediated by the influence of growth hormones and androgens during puberty. No meta-analysis is available about biological maturation and peak aerobic capacity.

Regarding the number of tests, the recent guideline[19] suggests performing 2 tests with 1 h between them in a longitudinal follow-up. Although we understand that the learning effect is real in the 6MWT, we acknowledge the lack of 2 tests is a limitation of our study.[19]

Conclusion

This study established the reference values for the maximum walking distance in the 6MWT for healthy children in Brazil. In addition, the equations established in this study predicted the maximum walking distance with errors of approximately of 10 m when tested in an independent sample.

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