Lungen Kinder

"Der Lungenkinder Forschungsverein unterstützt die Entwicklung einer App für den 6-Minuten-Gehtest"

Projektbeschreibung

An der Universität Innsbruck forscht ein Team um Univ.-Prof. Ralf Geiger an einer Möglichkeit, die richtige Therapie für an Lungenhochdruck leidende Kinder leichter bestimmen zu können. Mit dem von der Forschergruppe entwickelten 6-Minuten-Gehtest für Kinder steht nun eine einfache und genaue Methode zur Messung der funktionellen Bewegungskapazität bei Kindern zur Verfügung, was gerade bei durch eine Erkrankung in der Mobilität behinderte Kinder zu einer besseren Überwachung der Auswirkungen einer Behandlung führen kann.

Der 6-Minuten-Gehtest ist eine einfache, effiziente, genaue und sichere Methode, um die funktionelle Trainingskapazität bei submaximalen Belastungswerten bei Erwachsenen zu messen; sie wird zur Vorhersage der Morbidität und Mortalität bei kardiopulmonalen Erkrankungen verwendet. Eine modifizierte Form des Tests hat sich nun als sicher, einfach durchzuführen und auch für Kinder sehr akzeptabel erwiesen. Er bietet ein einfaches und kostengünstiges Mittel zur Messung der funktionellen Bewegungskapazität bei Kindern, auch in jungen Jahren, und könnte bei der Durchführung vergleichbarer Studien von Nutzen sein.

In einer Folgearbeit kalkulierte das Forscherteam Z-Scores, die helfen, die Veränderung der Gehstrecke zum Wachstum zu korrelieren. Diese Referenzkurven erlauben eine genauere Einstufung der Mobilität und Bewegungsfähigkeit bei kranken Kindern oder Kindern mit Behinderung sowie eine bessere Überwachung der Auswirkungen der Intervention oder Behandlung.

Es soll nun eine App für den klinischen Gebrauch entwickelt werden, in die solche Referenzwerte eingetragen und Referenzkurven berechnet werden können. Sie könnte weltweit von jedem pädiatrischen, kardiologischen und pulmologischen Zentrum verwendet werden. Dafür stellt der Lungenkinder Forschungsverein der PH Austria – Initiative Lungenhochdruck eine Förderung von 5.000 Euro zur Verfügung.

Six-Minute Walk Test in Children and Adolescents

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Objective To evaluate the 6-minute walking distance (6MWD) for healthy Caucasian children and adolescents of a population-based sample from the age of 3 to 18 years.

Study design Two hundred and eighty boys and 248 girls completed a modified test, using a measuring wheel as incentive device.

Results Median 6MWD increased from the age of 3 to 11 years in boys and girls alike and increased further with increasing age in boys (from 667.3 m to 727.6 m), whereas it essentially plateaued in girls (655.8 m to 660.9 m). After adjusting for age, height ($P = .001$ in boys and $P < .001$ in girls) remained independently correlated with the 6MWD. In the best fitting and most efficient linear and quadratic regression models, the variables age and height explained about 49% of the variability of the 6MWD in boys and 50% in girls.

Conclusion This modified 6-minute walk test (6MWT) proved to be safe, easy to perform, and highly acceptable to children. It provides a simple and inexpensive means to measure functional exercise capacity in children, even of young age, and might be of value when conducting comparable studies. *(J Pediatr 2007;150:395-9)*

Currently, the self-paced 6-minute walk test (6MWT) is classified to represent the most suitable method to assess the submaximal level of functional exercise capacity in adults.[1] This test measures the distance that a patient or participant can quickly walk on a flat, hard surface in a period of 6 minutes. Recently, the American Thoracic Society (ATS) published guidelines for performing 6MWTs in adults in clinical settings.[2] Despite its usefulness in adults the 6MWT is not widely used in the pediatric population, mainly because of lack of standardized protocols, established reference values, and reference equations in healthy children for the 6-minute walking distance (6MWD). Previous studies using the 6MWT in children were either limited to patients with a given disease[3-7] or included only small numbers of participants.[8] Lack of motivation and understanding for the need of a 6MWT may affect performance more in children than in adults. The motivational aspects during the 6MWT have not been assessed and no qualifying criteria for a 6MWT in children have been defined.

We attempted to overcome those shortcomings in children by a modified 6MWT, providing a measuring wheel that displays the instantaneous walking distance. The aim of this study was to establish reference values for the 6MWD *in healthy children and adolescents* performing the modified 6MWT. Further, we determined the correlates of the total 6MWD in a population sample of children and adolescents.

METHOD

Subjects of this study were children of Caucasian ethnicity. The study was approved by the local university ethics committee and the institutional boards of the participating local schools and kindergartens. Informed consent was obtained from parents and subjects. The measuring wheels were commercially available (Nedo GmbH + Co. KG, Dornstetten, Germany). The handling bar of the measuring wheel was customized to three interchangeable different lengths (240 mm, 370 mm, 560 mm) to fit optimally to the children's height. The shortest handlebar (for the smallest children) came with a two-hand grip to ensure stability of the wheel during the test for those who could not manage or felt unsecure to steer the wheel one-handed (Figure 1; available at www.jpeds.com).

6MWD	6-minute walking distance	FEV_1	Forced expiratory volume in 1 second
6MWT	6-minute walking test	PEF	Peak expiratory flow
ATS	American Thoracic Society	SEE	Standard error of the estimate

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Each participant was required to choose a measuring wheel with the most appropriate length of the handlebar for convenient handling. Adequate size of the measuring wheel was assumed when the participant held the device tightly, arms slightly bent, the handlebar extending with minimal angulation from the forearm, when standing in upright position.

All children participated in the 6MWT voluntarily. The tests were conducted at school or kindergarten between 8:00 AM and 2:00 PM. Participants were told not to exercise vigorously 2 hours before the test. On the day of the test all children were given a general physical examination for their state of health. Children who were on medication, with chronic or acute disease, or with unsigned informed consent were excluded from testing and analysis. Before the start of the 6MWT the participants' weight and height, wearing light clothes but without shoes were determined using an electronic scale and a wall assembled stadiometer. Leg length was determined by measuring the distance from the upper edge of the symphisis to the ground in strict upright position.

Blood pressure was measured sphygmomanometrically by using either the Digital Blood Pressure Monitor ES-P2000 (Terumo Corporation, Tokyo, Japan) or the Colin Press-Mate (Colin Electronics Co., Ltd., Japan).

Transcutaneous oxygen saturation was measured and heart rate was recorded before and immediately after the 6MWT by using a finger pulse oximeter (Nonin Flight Stat, Aeromedix, Jackson Hole, Wyo). Forced expiratory volume in 1 second (FEV_1) of expiration and peak expiratory flow (PEF) were measured in standing position without noseclip using an electronic peak flow/FEV_1 meter (PiKo-1, Pulmonary Data Services, Inc., Louisville, Colo). Each participant performed three tests and the best of three satisfactory efforts was recorded. Values were compared with reference values matched for height and sex and expressed as percentage of predicted.[9]

For a subjective rating of intensity of perceived exertion by the child after exercising a visual analog scale was used. Immediately after the test children >5 years of age were asked to judge the degree of fatigue reached from the test by adjusting a scale bar on a open scale that corresponded to a 100-mm scale on the back. The bar positioned at the left end of the scale (0 mm) meant: "not exhausted/out of breath at all," and the bar at the right end (100 mm) meant "very exhausted/out of breath." The visual analog scale was not used in children 3 to 5 years of age because of the uncertainty of their cognitive abilities to rate perceived exertion.

The tests were performed on up to three separately located courses, depending on the facilities at the location, to avoid competition among the children. Two flagpoles were positioned on a straight course spaced at a distance of 20 m. Each child had a personal instructor during the test. Participants were instructed in a standardized way according to the recommendations of the ATS (with the exception of the role of the measuring wheel) as follows: "The object of this test is to *walk* as far as possible in 6 minutes, which means to *score as many meters on the scale as possible*. You will be walking back and forth around the poles. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able to. Are you ready to do that? Remember that the object is to score as many meters as possible in 6 minutes, but without jogging or running. Start now!" An exception was made in the children who were 3 to 4 years of age because in pilot tests we had noticed that many of those simply could not accomplish the task of strictly walking. Thus children of this particular age group were allowed to walk or run or jog as they liked to "score points." We did not extend this concession to the entire study population for safety reasons.

After each minute, participants were told in even tones the following standardized phrases: "You are doing well. You have 5 minutes to go." After the second minute: "Keep up the good work. You have 4 minutes to go." After three minutes: "You are doing well. You are halfway done." After four minutes: "Keep up the good work. You have only 2 minutes left." After five minutes: "You are doing well. You have only 1 minute to go." No other words of encouragement or body language were used to speed up the participant. The instructor did not walk with the participant but stood close to the course during the test period to keep control of the test person. At 6 minutes on the stopwatch the participant was told to stop. The distance on the scale was recorded, transcutaneous saturation as well as heart rate was measured by finger tip pulse oximetry and the degree of perceived exhaustion of the participant was acquired by visual analogue scale.

Continuous values normally distributed are presented as means ± SD. For skewed data medians with ranges are indicated. "Exact" 95% confidence intervals for the mean 6MWD according to sex and age group were calculated using the method of Clopper/Pearson.[10] Bivariate and partial correlation analyses were performed to evaluate outcomes in the 6MWD in relation to demographic and physical characteristics by means of nonparametric Spearman correlation. R^2 values for multiple linear and quadratic regression models were calculated according to forward and backward stepwise selection of possible independent predictors of the 6MWD simultaneously for boys and girls with the use of standard regression techniques. However, only the best and most efficient models are presented. Due to multiple testing Bonferroni correction was applied to reduce the risk of Type I error. Only two-sided *P* values equalling to .001 or less were considered to indicate statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences version 12.0 (SPSS Inc. Chicago, Ill).

RESULTS

Of the 640 intended participants, 280 boys and 248 girls completed the test (82.5%). The response rate varied from 39% in the group 3 to 5 years of age to 93% in 6 to 8 years, 99% in 9 to 11 years, 94% in 12 to 15 years, and 83% in ≥16 years of age. On the day of the test, three children had to be excluded after the physical examination because of acute

Table I. Characteristics of study groups at entry*

Sex	Age Category	n	Height (m)	Weight (kg)	BMI (kg/m²)	*P* median†	FEV1‡	PEF§
Male	3 to 5 y	22	1.14 (1.06, 1.22)	18.1 (16.0, 23.9)	14.2 (13.0, 17.0)	*P* 22	95 (60, 110)	75 (50, 110)
	6 to 8 y	66	1.30 (1.20, 1.41)	25.8 (20.9, 36.4)	15.3 (13.4, 20.9)	*P* 38	90 (70, 110)	81 (60, 110)
	9 to 11 y	57	1.47 (1.36, 1.57)	36.9 (27.3, 52.0)	17.3 (13.7, 23.4)	*P* 55	88 (60, 110)	88 (60, 110)
	12 to 15 y	80	1.66 (1.50, 1.88)	55.7 (39.6, 77.9)	19.2 (16.1, 26.9)	*P* 62	90 (70, 110)	92 (70, 130)
	16 y or older	55	1.82 (1.71, 1.93)	69.4 (50.6, 91.6)	20.7 (16.8, 26.2)	*P* 45	92 (70, 120)	97 (60, 130)
Female	3 to 5 y	25	1.13 (1.05, 1.30)	19.0 (16.3, 28.7)	14.8 (13.5, 18.9)	*P* 25	84 (60, 120)	66 (30, 120)
	6 to 8 y	46	1.28 (1.20, 1.39)	25.2 (20.0, 36.1)	15.1 (13.5, 20.1)	*P* 38	88 (60, 110)	76 (50, 100)
	9 to 11 y	62	1.45 (1.32, 1.61)	36.7 (26.2, 57.8)	16.9 (14.1, 23.4)	*P* 50	94 (60, 120)	83 (60, 130)
	12 to 15 y	71	1.64 (1.49, 1.77)	54.0 (38.9, 72.1)	20.5 (16.2, 25.5)	*P* 65	93 (70, 130)	85 (60, 120)
	16 y or older	44	1.70 (1.60, 1.79)	56.9 (46.5, 73.4)	19.6 (17.4, 28.2)	*P* 29	92 (60, 120)	84 (50, 110)

BMI, body mass index; *FEV1,* forced expiratory volume in1 second; *PEF,* peak expiratory flow.
*Values denote medians (95% reference range).
†Percentile of median BMI.
‡% FEV_1 of predicted.
§% PEF of predicted.

infection. In no case was it necessary to stop the test prematurely, and there were no unexpected events during the tests. Anthropometric characteristics and the spirometric data of the different age groups are shown in Table I. Data reflected normal values in healthy children and adolescents. Heart rate increased 50% to 60% from baseline in the participants, and most of the children perceived a mild degree of exertion (of around 30 mm on the viusal analogue scale) after performing the 6MWT (Table II; available at www.jpeds.com).

The 6MWDs are shown in Table III: 6MWD increased from 3 to 11 years of age in boys and girls alike, with the steepest increase between 6 and 11 years of age. After 11 years of age 6MWD increased further with increasing age in boys (from 667.3 m to 727.6 m), whereas it essentially plateaued in girls (655.8 m to 660.9 m) (Figure 2). Correlation analysis revealed the variables age, age group, height, weight, leg length, body mass index (BMI), blood pressure, heart rate, and percentage of predicted PEF were significantly related to 6MWD. After adjusting for age, height ($r = 0.20$, $P = .001$ in boys, and $r = 0.25$, $P < .001$ in girls) remained independently correlated with 6MWD (Table IV; available at www.jpeds.com). Children were categorized as "overweight," when their BMI exceeded the 95th percentile for children of the same age and sex.[11] Overweight children constituted 4.3% in the group of 3 to 5 years of age, 3.6% in the 6 to 8 years, 5.0% in the 9 to 11 years, 3.3% in the 12 to 15 years, and 2.0% in the group ≥16 years (Table I). When calculating best fitting and most efficient linear and quadratic regression models, the variables age (as quadratic term) and height explained 49% of the variability of the 6MWD in boys and 50% in girls (SEE = standard error of the estimate):

$$\text{Males 6MWD} = 196.72 + (39.81 \cdot \text{Age}) - (1.36 \cdot \text{Age}^2) + (132.28 \cdot \text{Height})$$

$$R^2 = 0.49,\ \text{SEE} = 66.72$$

$$\text{Females 6MWD} = 188.61 + (51.50 \cdot \text{Age}) - (1.86 \cdot \text{Age}^2) + (86.10 \cdot \text{Height})$$

$$R^2 = 0.50,\ \text{SEE} = 57.52$$

DISCUSSION

Weight correlates to the 6MWD in adults[1] but not in the children investigated. This might relate to the fact that the percentage of overweight children, according to age and sex-based BMI in our study sample was considerably lower (3.6%-5%) than the expected prevalence of 7% to 12%.[11-13] As this test was voluntary, obese children might thus have refused to participate. Because of this potential bias this study group might not represent a "true" population sample. We also have incomplete data on those children who did not show up on the day of the test although informed consent was given. In the group of the youngest children, where only 39% eventually completed the test, most of them were either sick or not sent to kindergarten by their parents on the day of the test for fear of contagion because of an endemic acute infection. In the group of the oldest children, candidates had changed their mind and refused to cooperate on the day of the test, explaining the second lowest response rate of 83% in this particular age group.

During a self-paced test, motivation of the individual child is of paramount importance. By implementing the measuring wheel we sought to give "a task" to the children that should serve as an intrinsic motivational factor, which could not be influenced by the instructor.[14] The study was not designed to measure the validity of this method. As expected, the measuring wheel proved very useful for focusing the concentration of the children on the test. The group of youngest children posed some methodical challenges. When allowed to run, most of the 3- to 4-year-old children switch between jogging and walking frequently during the 6 minutes. Within the test's concept of minimal external interference, these data are likely to reflect their capabilities more accu-

Table III. Six-minute walk distances in meters according to sex and age category in healthy children and adolescents

Sex	Age category	n	Median (range)	95% reference range	Mean ± SD	95% CI
Male	3 to 5 y	22	544.3 (318.0-680.6)	319.7-680.6	536.5 ± 95.6	494.1-578.9
	6 to 8 y	66	584.0 (455.0-692.0)	471.0-659.3	577.8 ± 56.1	564.0-591.6
	9 to 11 y	57	667.3 (540.2-828.0)	556.2-801.5	672.8 ± 61.6	656.5-689.2
	12 to 15 y	80	701.1 (276.1-861.0)	600.7-805.3	697.8 ± 74.7	681.2-714.4
	16 y or older	55	727.6 (569.0-865.3)	616.9-838.4	725.8 ± 61.2	709.3-742.4
Female	3 to 5 y	25	492.4 (352.0-713.3)	364.5-692.7	501.9 ± 90.2	464.7-539.1
	6 to 8 y	46	578.3 (406.0-707.2)	448.8-693.9	573.2 ± 69.2	552.7-593.8
	9 to 11 y	62	655.8 (548.0-818.0)	572.0-760.5	661.9 ± 56.7	647.4-676.3
	12 to 15 y	71	657.6 (485.5-785.0)	575.2-746.5	663.0 ± 50.8	651.0-675.0
	16 y or older	44	660.9 (557.0-774.3)	571.2-756.2	664.3 ± 49.5	649.3-679.3

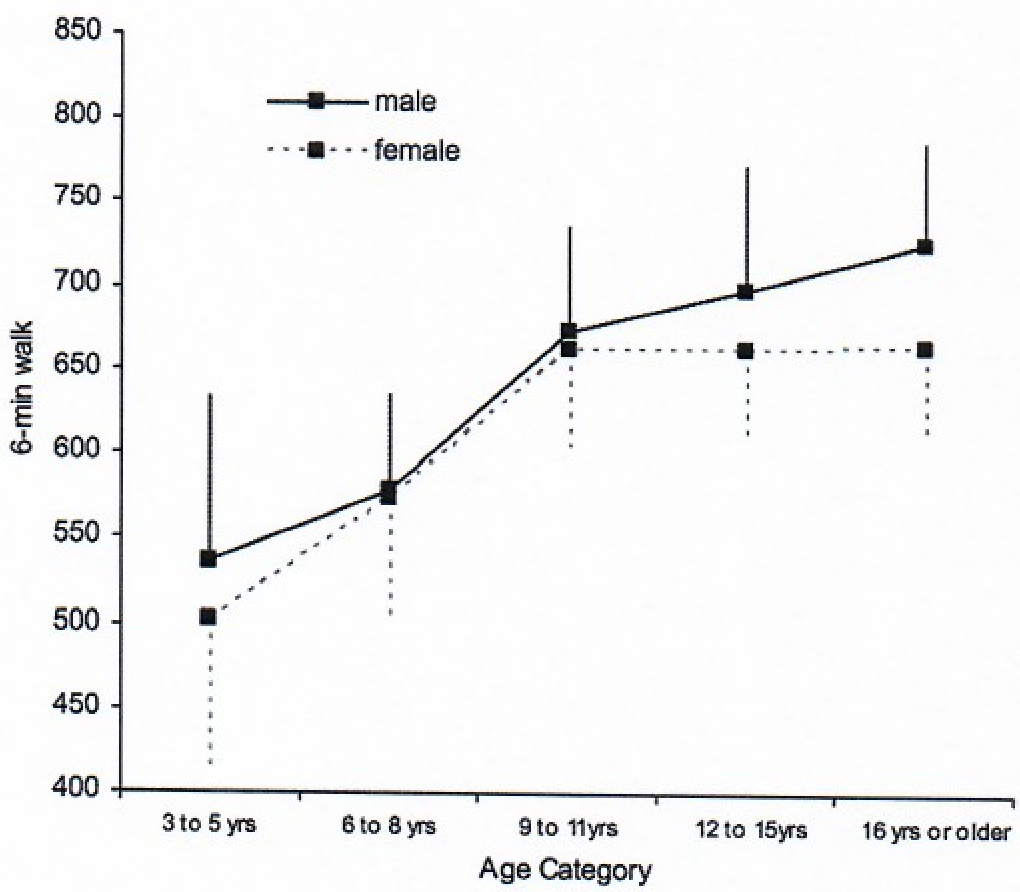

Figure 2. Mean ± SD 6-minute walk distance in healthy children and adolescents.

rately. In addition, running in the very young children did not seem to affect 6MWD to a great extend, given the lowest values of mean 6MWD in the youngest age group. As a self-paced test the 6MWT with measuring wheel reflects submaximal functional capacity of healthy children, which might represent more closely the patterns of their daily activities.[3]

It is most valuable for those who are moderately or severely impaired and whom a full cardiopulmonary exercise test would put at risk or would not be applicable. In those sick children where the 6MWT almost represents a maximal exercise test, it could help to grade their level of impairment. Repeated testing could aid to assess disease progression, the effects of medical intervention, or the need for additional or altered treatment. To allow for future direct comparisons among studies and to reduce the sources of variability caused by the test procedure itself, we used a standardized protocol that strictly followed the guidelines for the 6MWT in a clinical setting, prepared by the ATS, in all but one aspect. We found it particularly difficult to select a "straight, enclosed, longer then 30 m corridor with a plane hard surface that is seldom travelled" (as stated in the guidelines) in any of the buildings where the tests where performed. For practical reasons, therefore, we chose 20 m as the distance between the two poles. The theoretical drawback of reducing the 6MWD by requiring probands to take more time to reverse directions more often becomes irrelevant when using a measuring wheel because the distance of the turns is also recorded by the meter. Moreover, a recent multicenter study found no significant effect of the length of straight courses ranging from 50 to 164 ft.[2] Particularly in the very young children, the 20-m course seems to be advantageous as it allows the children to focus on the task more closely, and not "get lost" on the course.

We are not aware of any published reference values of the 6MWD in healthy children and adolescents with which we could compare our data. Thus, we cannot state whether the modified 6MWT would result in longer or shorter 6MWDs compared with those of a "normal 6MWT." 6MWDs were in the range of those from healthy adults and adolescents[1,2,8] and were positively correlated with age in children, which is opposite to that in adults, where 6MWD diminishes with growing age.[14]

By implementing age as a quadratic term, our regression models explain up to 50% of the variability of the 6MWD in healthy volunteers (R^2 values). Half of the variability of the 6MWD in children relates to other than anthropometric factors, such as physical fitness, coordination, and motor skills of the participants. Moreover, in children of all age groups we could observe some participants who were highly motivated and others in whom the degree of motivation could not easily be judged from their attitude toward the test. The results of our tests apply to the children's first 6-minute walk. A "learning curve" might have to be anticipated, especially in very young children, when performing subsequent tests. We did not intend to evaluate the magnitude of this assumed learning effect, but it is known from the literature in adults that it would range from 0 to17% of the 6MWD.[2,15] Excellent test-retest reliability of the 6MWT was recently reported in adolescents with a bias (mean difference between the two paired means) of 15 m (intraclass coefficient 0.94) at two separately held tests within 3 weeks.[8] It seems reasonable to dismiss the possibility of a practice or training effect when recruiting cross-sectional data, but it might be of relevance when analysing subsequent interventional or treatment effects on 6MWD.

REFERENCES

1. Enright PL. The six-minute walk test. Respir Care 2003;48:783-5.
2. American Thoracic Society. ATS Statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-17.
3. Nixon PA, Joswiak ML, Fricker FJ. A six-minute walk test for assessing exercise tolerance in severely ill children. J Pediatr 1996;129:362-6.
4. Gulmans VA, van Veldhoven NH, de Meer K, Helder PJ. The six-minute walking distance in children with cystic fibrosis: reliability and validity. Pediatr Pulmonol 1996;22:85-9.
5. Cunha MT, Rozov T, de Oliveira RC, Jardim JR. Six-minute walk test in children and adolescents with cystic fibrosis. Pediatr Pulmonol 2006;41:618-22.
6. Paap E, van der Net J, Helders PJ, Takken T. Physiologic response of the six-minute walk test in children with juvenile idiopathic arthritis. Arthritis Rheum 2005;53:351-6.
7. Moalla W, Gauthier R, Maingourd Y, Ahmaidi S. Six-minute walking test to assess exercise tolerance and cardiorespiratory responses during training program in children with congenital heart disease. Int J Sports Med 2005;26:756-62.
8. Li AM, Yin J, Yu CC, Tsang T, So HK, Wong E, et al. The six-minute walk test in healthy children: reliability and validity. Eur Respir J 2005;25:1057-60.
9. Neuberger M, Kundi M, Wiesenberger W, Frank W. Lungenfunktionsreferenzwerte für Schüler von 6 bis 16 Jahren. Pneumologie 48:175-81.
10. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.
11. Kromeyer-Hauschild K, Wabitsch M, Kunze D, Geler F, Geiss HC, Hesse V. Perzentile fuer den Bodymass-Index fuer das Kinder-und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. Monatsschr Kinderheilkd 2001;807-18.
12. Kalies H, Lenz J, von Kries R. Prevalence of overweight and obesity trends in body mass index in German pre-school children, 1982-1997. Int J Obes Relat Metab Disord 2002;26:1211-17.
13. Wabitsch M, Kunze D, Keller E, Kiess W, Kromeyer-Hauschild K. Ever more children and adolescents are overweight. How can the obesity epidemic be stopped? MMW Fortschr Med 2002;144:30-4.
14. Enright PL, McBurnie MA, Bittner V, Tracy RP, McNamara R, Arnold A, et al. The 6-min walk test: a quick measure of functional status in elderly adults. Chest 2003; 123:387-98.
15. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998;158:1384-7.

50 Years Ago in *The Journal of Pediatrics*

Agenesis of the Corpus Callosum: Report of Eight Cases in Infancy

Koch FP, Doyle PJ. J Pediatr 1957;50:345-51

Today it is not uncommon for a pediatrician to encounter at least one child with hypoplasia or agenesis of the corpus callosum found by using magnetic resonance imaging (MRI). However, 50 years ago, Koch and Doyle surveyed 8 infants with agenesis of the corpus callosum, diagnosed by means of autopsy or pneumoencephalography, and added to the only 100 cases that had been described since the first was described by Reil in 1812. Koch and Doyle "hoped that pediatricians may become alerted to the possibility of diagnosing agenesis of the corpus callosum" when faced with a child with macrocephaly, developmental delays, cerebral palsy, or other neurologic problems. Thanks to MRI, their wish has come true, but do we know much beyond their accurate report of the development and function of the corpus callosum?

As the "information superhighway" between the hemispheres, the corpus callosum is formed between the ninth and 20th weeks of gestation. An abnormality in this intrahemispheric connection is rarely found in isolation of other symptoms or signs and may provide a clue to the etiology of a child's underlying diagnosis. Agenesis of the corpus callosum can be associated with conditions as diverse as Dandy-Walker malformation, Chiari malformation, trisomies 13 and 18, holoprosencephaly, X-linked hydrocephalus, Aicardi syndrome, non-ketotic hyperglycinemia, methylmalonic acidemia, mitochondrial defects, and fetal alcohol syndrome. We know, as Koch and Doyle did, that there are some children with agenesis or hypoplasia who are clinically unaffected or whose agenesis or hypoplasia are detectable only with rigorous neuropsychological testing.

As prenatal ultrasound scanning and MRI and other not-yet-invented imaging technologies become standard for obstetrical and neurological care, the spectrum of cerebral anomalies and variants found will doubtlessly increase. Among these findings, agenesis or hypoplasia of the corpus callosum will become more of a finding than a diagnosis, and we should heed Koch and Doyle's advice. Like a simian crease or multiple café-au-lait spots, the pediatrician should use agenesis or hypoplasia as just one finding on the diagnostic journey for which he or she first obtained the MRI. Consideration of an ophthalmology evaluation is likely wise, and thought should be given to the possibility of an underlying genetic or metabolic disorder. In rare cases, the finding may just be incidental.

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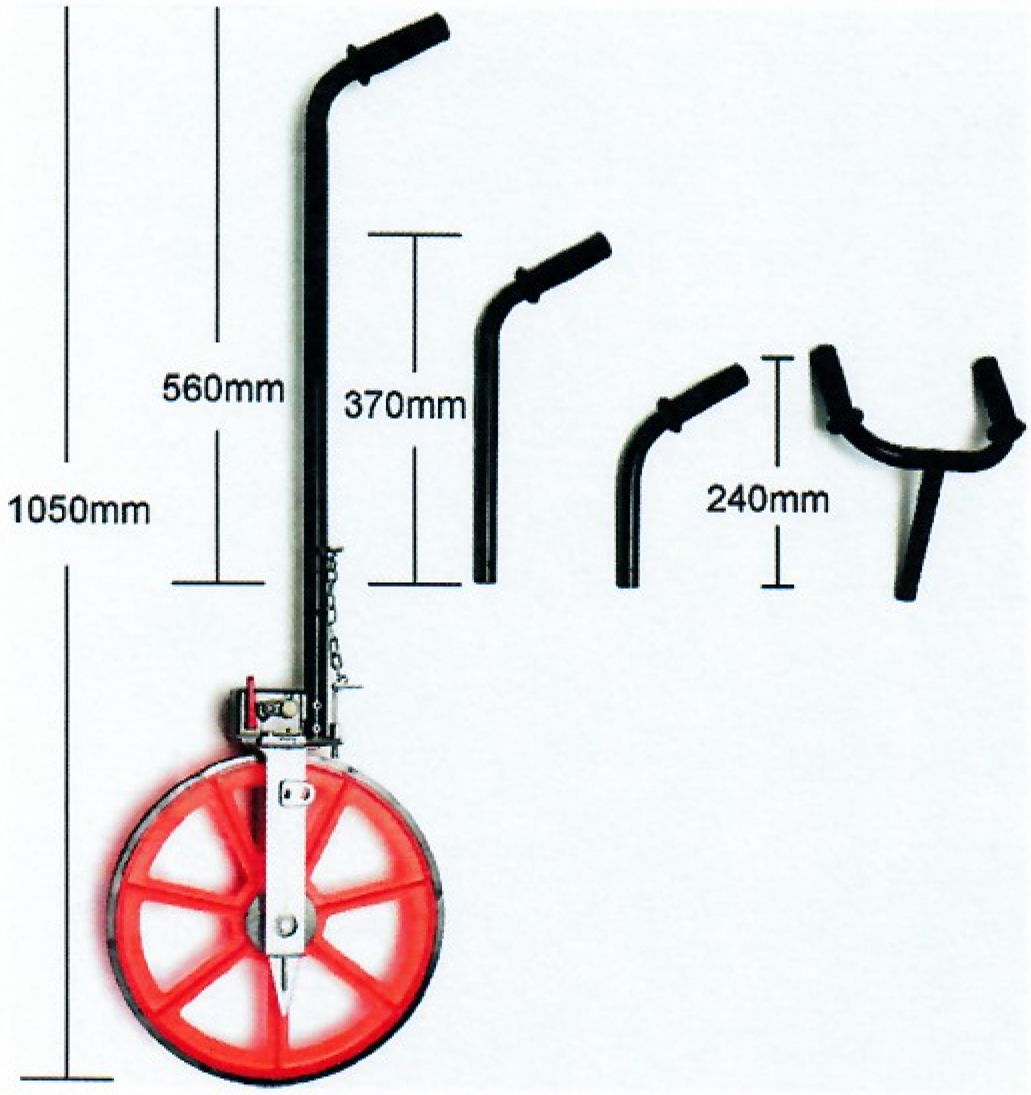

Figure 1. Measuring wheel with interchangeable size-adjusted handling bars.

Table II. Six-minute walk test in healthy children and adolescents, pre and post measures

Sex	Age category	n	Pre 6MWT		Post 6MWT		
			tcSAT*	HR†	tcSAT*	HR†	VAS†
Male	3 to 5 y	22	98 (97, 100)	96.6 ± 10.8	98 (95, 100)	146.9 ± 20.6	‡
	6 to 8 y	66	98 (96, 100)	88.1 ± 12.7	98 (95, 99)	133.0 ± 19.1	32.6 ± 24.9
	9 to 11 y	57	98 (96, 99)	86.8 ± 15.9	98 (94, 99)	135.5 ± 18.9	29.2 ± 21.1
	12 to 15 y	80	98 (97, 99)	85.3 ± 14.7	98 (95, 99)	138.9 ± 21.5	33.4 ± 18.6
	16 y or older	55	98 (96, 100)	76.6 ± 15.8	97 (94, 99)	130.4 ± 29.4	33.2 ± 19.6
Female	3 to 5 y	25	99 (97, 100)	97.1 ± 11.0	98 (91, 100)	150.0 ± 24.9	‡
	6 to 8 y	46	98 (96, 100)	96.0 ± 14.1	98 (94, 100)	146.1 ± 16.6	37.1 ± 28.3
	9 to 11 y	62	99 (97, 100)	84.6 ± 12.3	98 (96, 100)	144.1 ± 20.8	32.1 ± 21.9
	12 to 15 y	71	99 (98, 100)	88.0 ± 15.0	98 (95, 100)	149.4 ± 20.2	34.6 ± 18.9
	16 y or older	44	98 (96, 100)	89.0 ± 19.6	98 (95, 100)	141.9 ± 24.3	33.1 ± 14.5

6MWT, 6-minute walk test; *HR,* heart rate (beats/minute); *tcSAT,* transcutaneous oxygen saturation (%); *VAS,* visual analog scale (mm).
*Values presented as medians (95% reference range).
†Values presented as mean ± SD.
‡Not measured.

Table IV. Six-minute walk distance correlates in healthy children and adolescents, corrected for age*

	Height	Weight	BMI	tcSat	SBP	DBP	HR	PEF	FEV1
Male δ	0.20	−0.09	−0.15	0.02	−0.04	−0.09	−0.11	0.08	−0.00
P value (two-tailed)	.001	.17	.02	.81	.53	.14	.08	.23	.95
Female δ	0.25	0.00	−0.07	0.06	0.04	−0.02	−0.01	0.21	0.07
P value (two-tailed)	<.001	.96	.28	.40	.56	.81	.16	.02	.30

Due to multiple comparisons the level of significance is set at $P < .001$.
BMI, body mass index; *DBP,* diastolic blood pressure (pre-test); *FEV_1,* forced expiratory volume in 1 second; *HR,* heart rate (pre-test); *PEF,* peak expiratory flow; *SBP,* systolic blood pressure (pre-test); *tcSAT,* transcutaneous oxygen saturation (pre-test).
*Non-parametric Spearman correlation (male n = 280, female n = 248).

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SHORT COMMUNICATION

Sex-, age-, and height-specific reference curves for the 6-min walk test in healthy children and adolescents

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Abstract The 6-min walk test is a simple and accurate method to measure functional exercise capacity in children. We provide smooth reference curves for the modified 6-min walk test in 696 healthy children and adolescents aged 4–19 years, enabling calculation of sex-, age-, and height-specific Z-scores. *Conclusion*: These reference curves will allow more accurate grading of mobility and exercise capacity in sick or disabled children and monitoring the effects of intervention or treatment.

Keywords 6-min walk test · Mobility · Disability · Exercise capacity

Abbreviations

6MWD	6-min walk distance
6MWT	6-min walk test
SD	Standard deviation

Introduction

The 6-min walk test (6MWT) is a simple, efficient, accurate, and safe method to measure functional exercise capacity at submaximal levels of exertion in adults and is used to predict morbidity and mortality from cardiopulmonary disease [2].

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Recent studies have demonstrated its usefulness in the pediatric population [7] and established it as a simple, cost-effective, reliable, and valid test [8]. In children with cystic fibrosis and severe cardiopulmonary disease, the test is used to assess functional capacity, as a proxy measure of pulmonary function, nutrition, and treatment compliance [10]. The 6MWT has also been used to assess physical performance in children with sickle cell disease [6], disease progression in children with muscular dystrophy [9], response to training programs in children with cerebral palsy [5], as well as efficacy of enzyme therapy in mucopolysaccharidosis [3]. We [4], and others [7, 12], have previously reported reference values for the 6-min walking distance (6MWD) for several age categories of healthy children and adolescents. However, using age categories that cover a wide age range does not accurately represent growth, muscle function, and exercise capacity. A normally growing child with repeated 6MWT as part of clinical monitoring will suddenly switch from a higher 6MWD *Z*-score to a lower *Z*-score on the day he/she moves from a younger to an older age category. Growth in height and muscle function are continuous processes and do not occur in blocks. Therefore, the aim of the study was to provide smooth reference curves for the 6MWD in healthy children aged 4 to 19 years, to enable calculation of sex-, age-,and height-specific *Z*-scores for use in clinical practice.

Subjects and methods

The 6MWT measures the distance walked by the participant in 6 min. The modified 6MWT measures the 6MWD using a measuring wheel with interchangeable handlebars of three different lengths to suit the child's height. Healthy and injury-free Caucasian children and adolescents aged 4 to 19 years from kindergartens, elementary, and high schools in Dornbirn and Innsbruck, Austria, were recruited into two studies. Informed consent was obtained from the parents and the child/young person. Both studies were approved by the local ethics committee and used the same standardized methodology for the modified 6MWT. Participants were instructed to walk back and forth around two flagpoles, positioned 20 m apart on a straight course and the 6MWD recorded as displayed on the measuring wheel.

Children in the first study solely used a measuring wheel to record 6MWD (n=528 participants). Their characteristics have been described in detail previously [4]. Another 168 participants, randomized to using the measuring wheel, were recruited from a second study which compared 6MWD covered by children with (modified 6MWT) and without the use of a measuring wheel (conventional 6MWT). The reference data presented here serve as the reference data for the modified 6MWT only.

Children were discouraged from undertaking vigorous exercise for up to 2 h prior to the test, and all were physically examined to attest good physical health. Standardized instructions by a personal instructor were provided during the 6MWT, as previously described [4]. Children wore light clothes and sneakers and were refrained from jogging or running during the test.

To create smooth sex-specific 6MWD centile charts for age and height, we applied the Altman model [1], which uses the absolute residuals of the dependent variable to determine the standard deviation (SD) equation, since SD can vary naturally with age and height. First, the best fitting 6MWD mean curve (50th centile) was obtained by regression analysis. To determine the best fitting SD equation for either sex, the mean of absolute residuals was taken, as on this occasion, no specific equation fitted the absolute residuals. This was then multiplied by $\sqrt{(\pi/2)}$ to create the SD and subsequently regressed against age and height. Individual *Z*-scores (SD scores) can be calculated by inserting age or height in the equations for mean and then using the formula: $(x-\text{mean})/\text{SD}$.

Results

A total of 368 boys and 328 girls completed the test, while 122 children declined participation. No untoward events required the test to be aborted prematurely. The best fitting equations describing the smooth age- and height-related increment in 6MWD are given in Table 1. The sex-specific centile curves created from these equations, showing the 2nd, 50th, and 98th centiles for age and height, are shown in Fig. 1. As an example of the use of the formula in Table 1, a 10.4-year-old girl, with a height of 1.38 m covering 658 m in 6 min, would plot on the 50th centile for age-specific (0 SD) and between 50th and 75th centile on the height-specific centile chart (+0.39 SD).

In age-specific centile curves for girls, the 6MWD increased between 4 and 11 years of age, plateaued thereafter and dipped slightly in those aged 15 years and above. In boys, the 6MWD increased from 4 to 19 years of age with the steepest rise between 6 and 14 years of age (Fig. 1). In the height-specific curves, the 6MWD plateaued at a body height of approximately 1.60 m in girls and 1.85 m in boys. Overall and as expected, boys covered greater 6MWD than girls, both relative to age and height ($p<0.001$).

Discussion

This study presents smooth reference curves for the 6MWT in a large cohort of healthy Caucasian children aged 4 to 19 years for easy use in clinical practice and enables the calculation of sex-, age-, and height-specific *Z*-scores. These centile charts can be used to measure exercise capacity in both healthy and

Table 1 Sex-specific equations to calculate mean and SD score of the 6MWD (meters) for age (years) and height (meters)

	Centile/SD	Equations	R^2
Girls			
Age	50th	$320.7497+11.8821\times age+7.1593\times age^2-0.6661\times age^3+0.0161\times age^4$	0.48
	SD	60.374	
Height	50th	$-2554.9530+5112.4615\times height-2638.1319\times height^2+440.6610\times height^3$	0.44
	SD	61.450	
Boys			
Age	50th	$\exp(6.765497294541412-2.846474124886012/age)$	0.52
	SD	63.075	
Height	50th	$-574.2609+1378.1846\times height-362.3404\times height^2$	0.47
	SD	65.057	

Equations for the 50th centile (predicted mean) are given; 2nd and 98th centiles are created by predicted mean±2.05 SD. On this occasion, no specific equation fitted the absolute residuals; hence, the mean of the absolute residuals was taken and multiplied by $\sqrt{(\pi/2)}$ to create the SD. Sex-specific centile charts for age and height are available from the authors. To calculate an individual's *Z*-Score (SD Score), the patient's age or height first has to be entered in the sex-specific mean equations. Then the *Z*-score=(x−mean)/SD

chronically ill children, and assess response to intervention, in particular in children with physical disabilities and varying disease severity in whom performing a full cardiopulmonary exercise test could prove challenging. In addition, the curves may be used for the clinical monitoring of disease progression in children with musculoskeletal conditions such as muscular dystrophy [9] and for rehabilitation following fractures or illness. The availability of age- and height-specific *Z*-scores for 6MWD will also assist in measuring even more accurately the change in exercise capacity over time, during clinical monitoring, as a response to intervention [5], or in clinical research in children and young people.

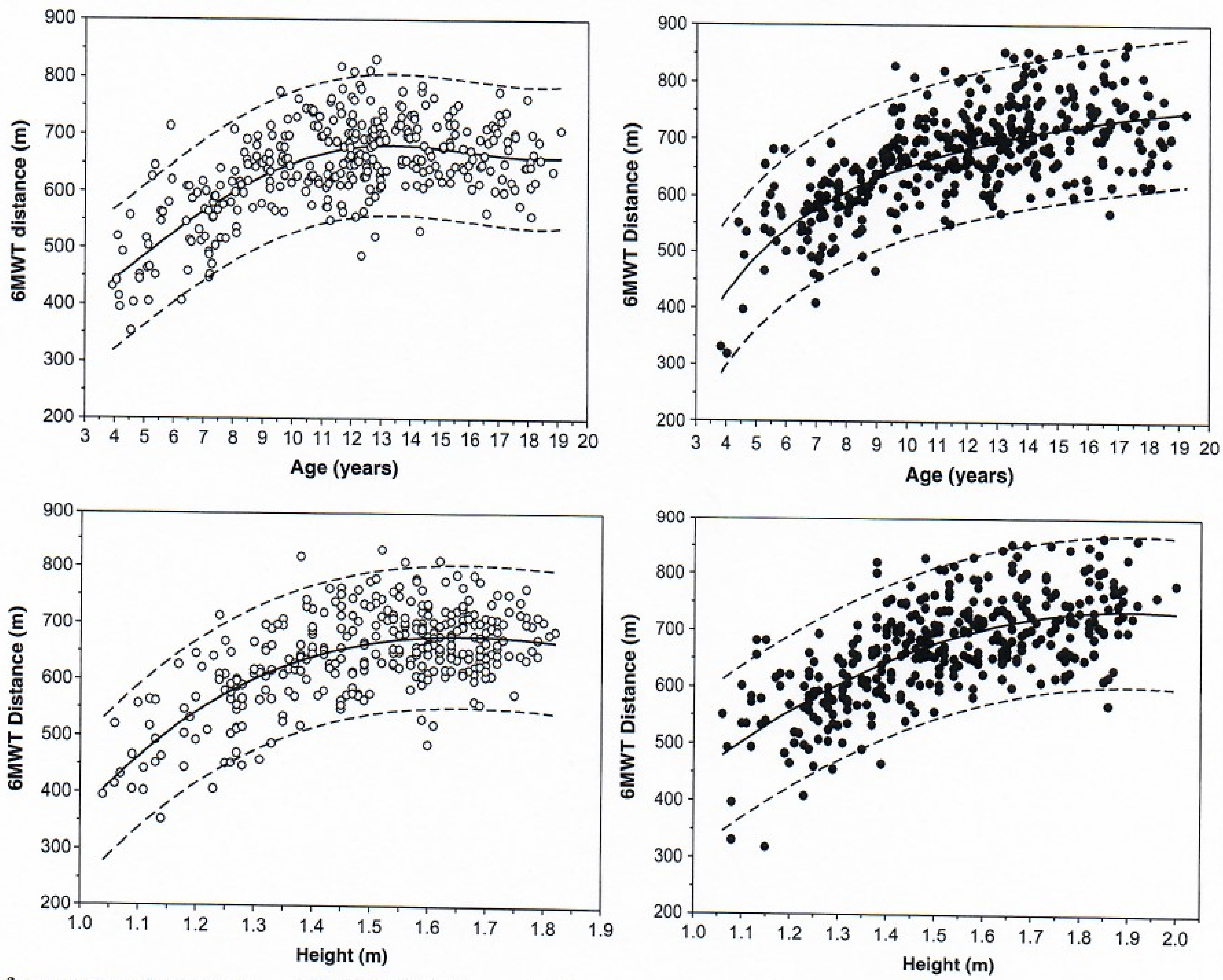

Fig. 1 Reference curves for the 6-min walk test (6MWT) distance in girls (*white circles*) and boys (*black circles*) for age (*top panels*) and height (*bottom panels*). Depicted curves represent the mean as well as 2nd and 98th centiles

Older and taller children are generally expected to cover a greater distance; however, we observed a slight decline in 6MWD in female teenagers, a phenomenon recently described [12]. While motivation may be a contributing factor, we speculate this decline is caused by estrogen-related increments in fat mass [11] thus contributing to the widening sex disparity in response to exercise in puberty.

A limitation of this study was that it included only Caucasian children. Although the 6MWT was performed only once in each participant, high test-retest reliability has been demonstrated in healthy children in a recent study, and hence, we do not consider this to have a significant impact on our results [8]. Although the validity of conventional 6MWT in measuring exercise tolerance and endurance in healthy children has been previously demonstrated [8], any new functional test needs to be validated for use in specific conditions.

In conclusion, we present smooth age- and height-specific reference curves for use in daily practice and provide equations that allow the calculation of *Z*-scores for the 6MWD in children from 4 to 19 years.

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Conflict of interest The authors declare no potential conflict of interest.

References

1. Altman DG (1993) Construction of age-related reference centiles using absolute residuals. Stat Med 12(10):917–924
2. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, Kronenberg M, Kostis JB, Kohn RM, Guillotte M (1993) Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. JAMA 270(14):1702–7
3. Clarke LA, Wraith JE, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, Berger KI, Sidman M, Kakkis E, Coxk G (2009) Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics 123(1):229–40
4. Geiger R, Strasak A, Treml B, Gasser K, Kleinsasser A, Fischer V, Geiger H, Loeckinger A, Stein JI (2007) Six-minute walk test in children and adolescents. J Pediatr 150(4):395–9
5. Grecco LAC, Zanon N, Sampaio LMM, Oliveira CS (2013) A comparison of treadmill training and overground walking in ambulant children with cerebral palsy: randomized controlled clinical trial. Clin Rehabil 27(8):686–696
6. Hostyn SV, de Carvalho WB, Johnston C, Braga JA (2013) Evaluation of functional capacity for exercise in children and adolescents with sickle-cell disease through the six-minute walk test. J Pediatr 89(6):588–594
7. Lammers AE, Hislop AA, Flynn Y, Haworth SG (2008) The 6-minute walk test: normal values for children of 4–11 years of age. Arch Dis Child 93(6):464–468
8. Li AM, Yin J, Yu CC, Tsang T, So HK, Wong E, Chan D, Hon EK, Sung R (2005) The six-minute walk test in healthy children: reliability and validity. Eur Respir J 25(6):1057–60
9. McDonald CM, Henricson EK, Han JJ, Abresch RT, Nicorici A, Elfring GL, Atkinson L, Reha A, Hirawat S, Miller LL (2010) The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve 41(4):500–10
10. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K (2000) Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 161(2):487–92
11. Schiessl H, Frost HM, Jee WS (1998) Estrogen and bone-muscle strength and mass relationships. Bone 22(1):1–6
12. Ulrich S, Hildenbrand FF, Treder U, Fischler M, Keusch S, Speich R, Fasnacht M (2013) Reference values for the 6-minute walk test in healthy children and adolescents in Switzerland. BMC Pulm Med 13(1):1–11