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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Three-minute walk test and timed function test in Belgian boys aged 2.5 - 6 years: reference values and comparison with Duchenne muscular dystrophy

Inge Appeltans

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij kinderen

PROMOTOR :

Prof. dr. Katrijn KLINGELS

BEGELEIDER :

Mevrouw Jasmine HOSKENS

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2018

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This thesis was written to obtain a master's degree in Rehabilitation Sciences and Physiotherapy within the faculty of medicine and life sciences at UHasselt. I would like to express my thanks to some people for their support and contribution. Without them, the writing of this thesis would not have been possible.

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Furthermore, I would like to thank Billiet Julie, Zabeau Anouk and Loos Rosanne for helping me with the collection of the data. My thanks also go to all the schools that participated, their teachers and all the children that volunteered as well as their parents for giving their permission.

Finally, I would like to thank my parents Appeltans Rik and Smits Heidi, my partner Espejo Guillaume, my family and my friends for their encouragements and support whenever I needed it.

Herk-de-Stad (BE), 5th June 2018 I.A.

Research context

This master's thesis is part of the educational program Master in Rehabilitation Sciences and Physiotherapy at UHasselt. The study fits in the research field of pediatric rehabilitation and is a collaboration between UHasselt (Prof. dr. K. Klingels & J. Hoskens), KU Leuven and UZ Leuven campus Gasthuisberg (Prof. dr. N. Goemans & M. van den Hauwe). It is a part of the starting PhD of J. Hoskens on early motor development in children with Duchenne muscular dystrophy (DMD).

Duchenne muscular dystrophy is an X-linked inherited progressive neuromuscular disorder caused by mutations to the dystrophin gene. Therefore, mainly boys are affected. Children with DMD already display motor problems due to progressive muscle weakness in very early stages of motor development. The first clearly noticeable signs appear around the age of 2.5 years and include muscle weakness, gross motor delay, problems with running, climbing and descending stairs (Ciafaloni et al., 2009; van Ruiten, Straub, Bushby, & Guglieri, 2014). The average diagnosis is usually only made above the age of four years and thus after the onset of motor delay. The timed function tests (TFTs) 10-meter run (10m run), the time to rise from the floor (TRF) and climbing and descending four stairs are often used in clinical research because of their sensitivity to detect changes in disease status (Beenakker, Maurits, Fock, Brouwer, & van der Hoeven, 2005; Brooke et al., 1981; Bushby et al., 2014; Mazzone et al., 2010; McDonald et al., 2013). Also timed walking tests like the six-minute walk test (6MWT) are found to be useful in the assessment of DMD children to measure the submaximal functional capacity (American Thoracic Society, 2002; McDonald et al., 2010). However, only few reference values are available in a very young population. To allow early screening and to limit the delay in motor development by early intervention, reference values with regard to these tests are needed.

The main goal of this study was to establish reference values per age and height categories in healthy Belgian boys between the age of 2.5 and 6 years for the three-minute walk test (3MWT), 10m run, TRF, climbing four stairs and descending four stairs. Correlations are calculated to examine the interactions between the different population characteristics (age and height) and the tests.

In addition, retrospective data of 19 DMD boys between 2.5 and 6 years old were compared to the new reference values to detect possible delays in early motor development.

The research protocol and ethical approval of this prospective non-interventional study was already established by the research team of KU Leuven and UZ Leuven campus Gasthuisberg. The data were already partially available from a first data collection of 114 healthy boys between August and December of 2013. During a second phase of data collection, another 67 healthy boys were recruited in different schools in Flanders and tested during January and February 2018 by I. Appeltans, supported by J. Hoskens and master's students in Rehabilitation Sciences and Physiotherapy. The data from the DMD boys were retrospectively collected from the patient files of the pediatric consultations for neuromuscular diseases at UZ Leuven campus Gasthuisberg. Afterwards, I. Appeltans selected an age-matched control group out of the typically developing healthy boys recruited during this study to make a first retrospective comparison with DMD data. Further data analysis and writing of this master's thesis was done by I. Appeltans. Prof. dr. K. Klingels and J. Hoskens guided this process and performed the proofreading.

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Abstract

Background: The six-minute walk test (6MWT) and timed function tests (TFTs) are often used as measures of functional capacity in children with Duchenne muscular dystrophy (DMD). However, in young children, a shorter three-minute protocol might be more suited.

Objectives: This study aimed to generate age- and height-specific reference values of the three-minute walk test (3MWT) and TFTs in typically developing (TD) Belgian boys aged 2.5 to 6 years. Secondly, the relation between these tests and anthropometric values was evaluated. Additionally, a retrospective comparison was made with DMD data.

Participants: In total, 179 boys with a mean age of 4.1 years (±1.0) were evaluated. Retrospective data were obtained of 19 DMD boys with an age ranging from 2.8 to 5.9 years (mean 4.9 years ±0.8).

Results: Three-minute walk distance (3MWD) increased and the time to complete the TFTs decreased with increasing age ($p \leq 0.652$) and height ($p \leq 0.015$). Mean 3MWD (±SD) for the total group was 191.2m (±30.4). Median values (interquartile ranges) for the TFTs were: 10-meter run: 4.06s (3.62-4.75), time to rise from the floor: 2.63s (2.12-3.47), climbing 4 stairs: 2.31s (1.89-3.46) and descending 4 stairs: 2.89s (2.15-4.62). The 3MWT and TFTs were moderately to strongly correlated with age and height ($|r|=0.54$-0.83). When compared to the reference values, DMD boys showed a similar performance on the 3MWT ($p=0.259$) while they performed significantly slower on all the TFTs ($p \leq 0.044$).

Conclusion: This study established age- and height-specific reference values for the 3MWT and four TFTs in Belgian TD boys between 2.5 and 6 years. Furthermore, these tests have shown to be clinically feasible and sensitive assessments of functional capacity in young ambulant DMD boys.

Introduction

Duchenne muscular dystrophy (DMD) is an inherited progressive neuromuscular, X-linked disorder. The estimated worldwide prevalence is 4.78 per 100 000 males with an incidence of approximately 1 in 3600 male births per year (Mah et al., 2014). DMD is caused by mutations to the dystrophin gene which results in progressive muscle weakness, cardiomyopathy, respiratory failure, delayed speech with articulation problems and cognitive delay (Birnkrant, Ararat, & Mhanna, 2015; Chung et al., 2015; Ciafaloni et al., 2009; Connolly et al., 2013).

The first clearly noticeable signs of DMD appear from a mean age of 2.5 years onward and are muscle weakness, gross motor delay, trouble walking or running and trouble climbing stairs. Even though these first signs show up early, the average diagnosis is usually made above the age of four years (Ciafaloni et al., 2009; van Ruiten, Straub, Bushby, & Guglieri, 2014). Hence, only limited literature is available regarding the clinical presentation and evaluation in very young children with DMD. In two studies, neurodevelopmental scales (Bayley and Griffiths Scale of Mental Development) were used to assess children under the age of four. They reported a delay in cognition, hearing, speech and motor function when compared to reference values. Overall, gross motor function was more affected than fine motor function (Connolly et al., 2013; Pane et al., 2013).

The timed function tests (TFTs) 10-meter run (10m run), the time to rise from the floor (TRF; starting position supine) and climbing and descending four stairs are sensitive to detect changes in disease status and are therefore often used in clinical research (Beenakker, Maurits, Fock, Brouwer, & van der Hoeven, 2005; Brooke et al., 1981; Bushby et al., 2014; Mazzone et al., 2010; McDonald et al., 2013). However, only few normative data are available. In 2015, Pereira, Ribeiro, and Araújo established reference values for the 10m run, 10-meter walk test and TRF in healthy children from 2 to 12 years old. However, TRF was assessed from a sitting starting position instead of supine. Therefore, reference values are only available for the 10m run, but not for the other three earlier mentioned TFTs. The 10m run and TRF are also incorporated in the North Star Ambulatory Assessment (NSAA). The NSAA is a clinical scale consisting of 17 items, ranging from standing to running and is used to assess gross motor ability in ambulatory boys with DMD (Mazzone et al., 2010; Scott et al., 2012).

Another frequently used motor test in children with DMD is the six-minute walk test (6MWT). This test measures the submaximal functional capacity by measuring the distance walked on a flat, hard surface over a time span of six minutes (American Thoracic Society, 2002; McDonald et al., 2010). Reference values of this test have been reported in several studies (Cacau et al., 2016; Goemans, Klingels, van den Hauwe, Boons, et al., 2013). Two studies even established reference values for children starting from the age of three years (Geiger et al., 2007; Mylius, Paap, & Takken, 2016). However, for very young children, especially with DMD, the assessment of the 6MWT might be too long as their attention span is shorter and the risk of falling increases with time (Vill, Ille, Schroeder, Blaschek, & Müller-Felber, 2015). Bohannon et al. (2014) studied if a two-minute walk test (2MWT) would be a reliable alternative. In this study, children and adults (3-85 years) had to walk during six minutes and the distance after two minutes was recorded. Twelve percent of the children under the age of six already stopped walking before the six minutes had elapsed, confirming the consideration that this test might be too long for very young children. Both in a population of community dwelling children and adults (3-85 year) as in boys with DMD (5-11 years) a high correlation was found between the distance covered in two versus six minutes, suggesting that a 2MWT would be a reliable alternative for the 6MWT to evaluate functional endurance (Bohannon et al., 2014; Vill et al., 2015). Bohannon, Wang, Bubela, and Gershon (2017) established reference values for the 2MWT in typically developing children and adolescents (3-17 years) according to age, gender, height and weight. However, in children with DMD between 5 and 11 years, Vill et al. (2015) reported a higher walking speed during the first minute compared to the other five minutes of the 6MWT, during which the walking speed remained stable. Furthermore, an increase in test-retest reliability with prolonged time of walking was found both in healthy children and in children with DMD between the ages of 5 and 12 years (Goemans, Klingels, van den Hauwe, Van Orshoven, et al., 2013; Vill et al., 2015). In healthy boys between five and six years old, a moderate to good reliability was only established from three minutes onwards (Goemans, Klingels, van den Hauwe, Van Orshoven, et al., 2013). In order to minimize the effect of the increased walking speed in DMD boys during the first minute and in order to establish a higher test-retest reliability, a three-minute walk protocol was chosen for this study.

Both Goemans et al. (2016) and Mazzone et al. (2010) reported a moderate to high correlation between the distance covered during the 6MWT and the performance on the 10m run, TRF and climbing four stairs in ambulant DMD boys between 4 and 17 years old. Furthermore, these three particular TFTs are shown to have an important prognostic value in order to predict the change in six-minute walk distance (6MWD) after one year in this population and thus provide valuable extra information (Goemans et al., 2016).

The primary aim of this study was to collect age- and height-specific reference values in typically developing young boys between 2.5 and 6 years old for the three-minute walk test (3MWT) and four TFTs (10m run, TRF, climbing and descending 4 stairs). Additionally, retrospective data of DMD boys between 2.5 and 6 years old were compared to the new reference values to detect possible delays in early motor development.

Methods

Participants

A group of typically developing (TD) boys between 2.5 and 6 years old were recruited from nine randomly selected Flemish primary schools. A first data collection took place between August and December 2013 (N=114). Afterwards, extra data were collected in January and February 2018 (N=67) to enlarge the number of subjects in each group. The children were divided into four groups according to age (2.5-<3y; 3-<4y; 4-<5y; 5-<6y) and three height groups (<100cm; 100-<110cm; ≥110cm). A short medical questionnaire was filled out by the parents in order to exclude children with chronic cardiac, respiratory or motor disorders (Appendix A).

Additionally, retrospective data on the 3MWT and the TFTs of boys between 2.5 and 6 years old with DMD were collected from the patient files of the pediatric consultations for neuromuscular diseases at the UZ Leuven campus Gasthuisberg. To allow comparison, an age-matched control group was selected from the group of TD boys participating in this study.

Ethics statement

This study was approved by the institutional committee of the University Hospitals Leuven (S60777; 10 November 2017). The institutional board of the participating schools were asked for permission to perform the test procedure at their school (Appendix B). A written informed consent was obtained from all children's parents (Appendix C).

Test procedure

Prior to testing, weight and height of the children were determined using standardized anthropometric methods (without shoes). Subsequently, the three-minute walk test (3MWT) and four different timed function tests (TFTs) were conducted by three physiotherapists experienced with the test procedure, assisted by master's students in Rehabilitation Sciences and Physiotherapy. The total test procedure took about 15 minutes per child. Children had to wear comfortable clothes and shoes.

The 3MWT is a submaximal functional capacity test measuring the distance walked in a time span of three minutes. The test was performed in a large, flat hallway or open space. The setup consisted of two cones with a 25-meter-long measuring tape in between. Markers were placed at a 45-centimeter distance around the cones to determine the turning circle. The boys were

asked to walk counter-clockwise around the cones at their preferred pace without jogging or running. They were followed by a safety chaser giving limited standardized encouragements during the test. Both the distance per minute and the time per length were registered. Overall velocity during the 3MWT (m/min), the velocity during each minute and their percentage to the overall velocity as well as the percentage of the total distance covered after one and two minutes were calculated.

For the four timed function tests (10m run, TRF, climb four stairs and descend four stairs), a chronometer with an accuracy of 0.01 seconds was used to measure the time to complete each test separately.

For the 10-meter run, the children were asked to run as fast as possible from one cone to another over a distance of 10 meters while continuous encouragements were given. The timer was started at the 'GO'-signal and stopped when the second foot passed the second cone. Time to rise from the floor (TRF) was performed without shoes or socks. The starting position was supine on a mat or on the floor (without a pillow) with their arms by their side and legs together. Instructions were given to get up as fast as possible and stand up straight with their arms by their side.

The last two tests were climbing four stairs and descending four stairs. To start, the children were standing up straight at the bottom of the stairs with their arms by their side. They were instructed to climb four stairs as quickly as possible after a 'GO'-signal was given and to stand still at the top with their arms by their side after completion. Afterwards, they were asked to do the same task in the opposite direction (descending). If needed, the handrail could be used.

Data-analysis

Descriptive statistics were calculated for the participant characteristics (age, height and weight) and results of the 3MWT and the four TFTs for the total sample and for each age and height group separately. Normality and homoscedasticity were checked by the Shapiro-Wilk and Levene's test respectively. Since the data of both the participant characteristics and the 3MWT were normally distributed over all the sub-groups according to age and height, as well as the total group, means and standard deviations (SD) were described. Medians and interquartile ranges (IQR) were reported for the results of the TFTs.

To compare the three-minute walk distance (3MWD) among the four age groups as well as among the three height groups, a one-way analysis of variance (ANOVA) with Bonferroni post hoc test was used. To compare the TFTs among age and height groups, the Kruskall-Wallis test with post hoc pairwise comparison using Dunn's test corrected by the Bonferroni method was used. Pearson correlation coefficients (r) were calculated to analyze correlations between age, height, 3MWD and the four TFTs. Correlation coefficients were interpreted according to Hinkle: $r>0.90$ very high correlation; $r=0.70$-0.90 high or strong correlation, $r=0.50$-0.70 moderate correlation, $r=0.30$-0.50 low or weak correlation and $r<0.30$ little or no correlation.

Each DMD boy individually was compared to the reference values established in this study. The boys were classified as normal (within 1 SD around the mean or between percentile (P) 16-84), at risk (between 1-2 SD below the mean or between P2.3-16) or deviant (more than 2 SD below the mean or below P2.3). To make the comparison between the DMD boys and the age-matched control group, a Mann-Whitney U test was used to determine if there was a difference in both 3MWD and in time for each of the four TFTs.

All statistical analysis were performed using IBM SPSS25 with an alpha level of 0.05.

Results

Participant characteristics

Parents of 308 boys between 2.5 and 6 years old were invited to participate in this study. In total 192 written informed consents and medical questionnaires were returned. Thirteen children were excluded. One boy was excluded because of a clubfoot, ten boys were absent or refused to cooperate and two boys were excluded because of deviating values due to running or exhaustion during the 3MWT. Finally, 179 boys completed the full test procedure. Mean age, height and weight of the total group were 4.1 years (±1.0), 103.8cm (±8.6) and 17.4kg (±3.0) respectively. Means and standard deviations per age and height group are reported in Table 1.

3MWT and velocity

Descriptive data of the 3MWT, distances per minute and velocity are displayed in Table 1. The overall mean 3MWD was 191.2m (±30.4). An increase in mean 3MWD was seen from 168.4m (±18.8) at the age of 2.5 years to 214.5m (±26.1) at 5 years. The largest increase in distance between two subsequent age groups was seen between 3 and 4 years and was 23.5m. Overall, the velocity remained fairly constant throughout the three minutes of walking as can be seen by the percentages of the total distance that was covered after one and two minutes (total mean percentages of 33.8% (±1.9) and 66.8% (±1.7) respectively; Table 1). The total velocity increased with age from 56.1m/min (±6.3) at 2.5 years to 71.5m/min (±8.7) at 5 years. The mean distance according to height increased, from 172.6m (±21.8) for children <100cm to 212.7m (±26.2) in children ≥110cm. In parallel, an increase in velocity was seen from the shortest group (57.5m/min (±7.3)) to the tallest group (70.9m/min (±8.7)). Figure 1 shows the mean 3MWD and standard deviation per age (Figure 1A) and per height group (Figure 1B).

Table 1. Descriptive data of the participant characteristics, three-minute walk distance, distance after one and two minutes, percentage of total distance after one and two minutes, velocity (mean values ± standard deviation) and the timed function tests (median – interquartile range).

		N	Age (y)	Height (cm)	Weight (kg)	3MWD (m)	1MWD (m)	%3MWD after 1 min	2MWD (m)	%3MWD after 2 min	Velocity (m/min)	10m run (s)	TRF (s)	4 stairs up (s)	4 stairs down (s)
Age	2.5 years	44	2.8 (±0.1)	93.9 (±3.33)	14.6 (±1.8)	168.4 (±18.8)	56.9 (±6.3)	33.9 (±2.5)	112.2 (±12.6)	66.7 (±1.8)	56.1 (±6.3)	5.05 (4.53-5.81)	3.71 (3.22-4.93)	3.71 (2.97-5.02)	6.11 (5.02-7.13)
	3 years	44	3.5 (±0.3)	99.9 (±4.92)	16.0 (±1.8)	178.6 (±23.8)	60.3 (±9.5)	33.7 (±1.8)	118.8 (±17.1)	66.4 (±1.7)	59.5 (±7.9)	4.53 (4.00-4.94)	3.03 (2.61-3.58)	2.78 (2.29-3.59)	3.71 (2.97-4.35)
	4 years	46	4.5 (±0.3)	107.8 (±4.39)	18.6 (±1.8)	202.1 (±27.8)	68.4 (±10.3)	33.8 (±1.6)	135.2 (±19.1)	66.9 (±1.4)	67.4 (±9.3)	3.81 (3.53-4.05)	2.41 (2.13-2.75)	2.11 (1.87-2.42)	2.41 (2.09-2.79)
	5 years	45	5.4 (±0.2)	113.3 (±4.60)	20.4 (±2.3)	214.5 (±26.1)	72.4 (±10.3)	33.7 (±1.6)	144.1 (±18.9)	67.1 (±1.7)	71.5 (±8.7)	3.51 (3.32-3.94)	1.96 (1.79-2.28)	1.80 (1.60-1.95)	1.97 (1.72-2.42)
Height	<100 cm	69	3.0 (±0.4)	94.8 (±3.26)	14.7 (±1.6)	172.6 (±21.8)	58.1 (±8.2)	33.7 (±2.3)	114.8 (±15.3)	66.5 (±1.8)	57.5 (±7.3)	4.85 (4.29-5.56)	3.54 (2.89-4.68)	3.47 (2.66-4.61)	4.96 (3.80-6.64)
	100-<110 cm	56	4.2 (±0.6)	105.2 (±2.95)	17.6 (±1.3)	193.2 (±29.1)	65.5 (±10.4)	33.9 (±1.6)	129.1 (±19.6)	66.8 (±1.3)	64.4 (±9.7)	3.93 (3.57-4.39)	2.57 (2.10-3.03)	2.16 (1.84-2.84)	2.59 (2.12-3.28)
	≥110 cm	54	5.2 (±0.4)	114.0 (±3.47)	20.7 (±2.0)	212.7 (±26.2)	71.9 (±10.3)	33.7 (±1.6)	142.9 (±19.0)	67.1 (±1.8)	70.9 (±8.7)	3.62 (3.31-3.98)	2.15 (1.86-2.48)	1.89 (1.64-2.12)	2.12 (1.79-2.48)
TOTAL		179	4.1 (±1.0)	103.8 (±8.60)	17.4 (±3.0)	191.2 (±30.4)	64.6 (±11.1)	33.8 (±1.9)	127.8 (±21.2)	66.8 (±1.7)	63.7 (±10.1)	4.06 (3.62-4.75)	2.63 (2.12-3.47)	2.31 (1.89-3.46)	2.89 (2.15-4.62)

(N= number of subjects; y= years; 3MWD= three-minute walk distance; 1MWD= distance after one minute; 2MWD= distance after two minutes; TRF= time to rise from floor; 4 stairs up= climbing 4 stairs; 4 stairs down= descending 4 stairs)

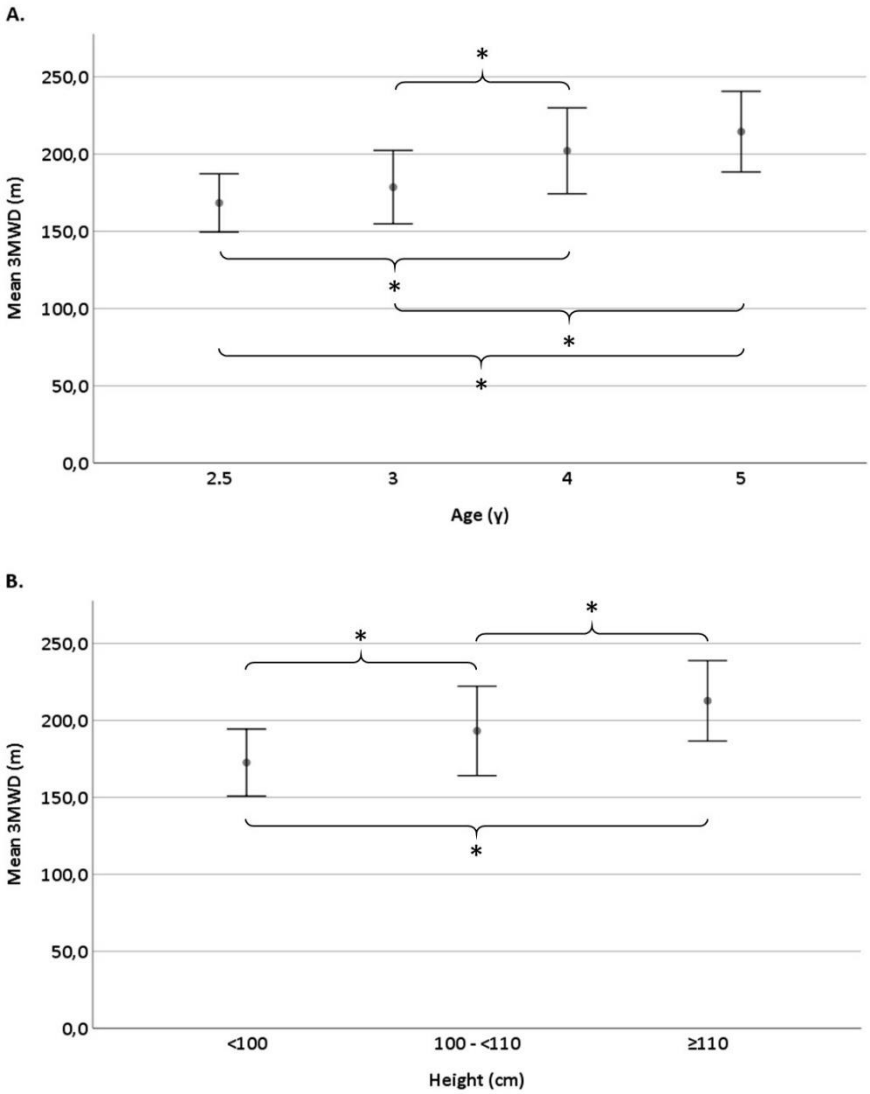


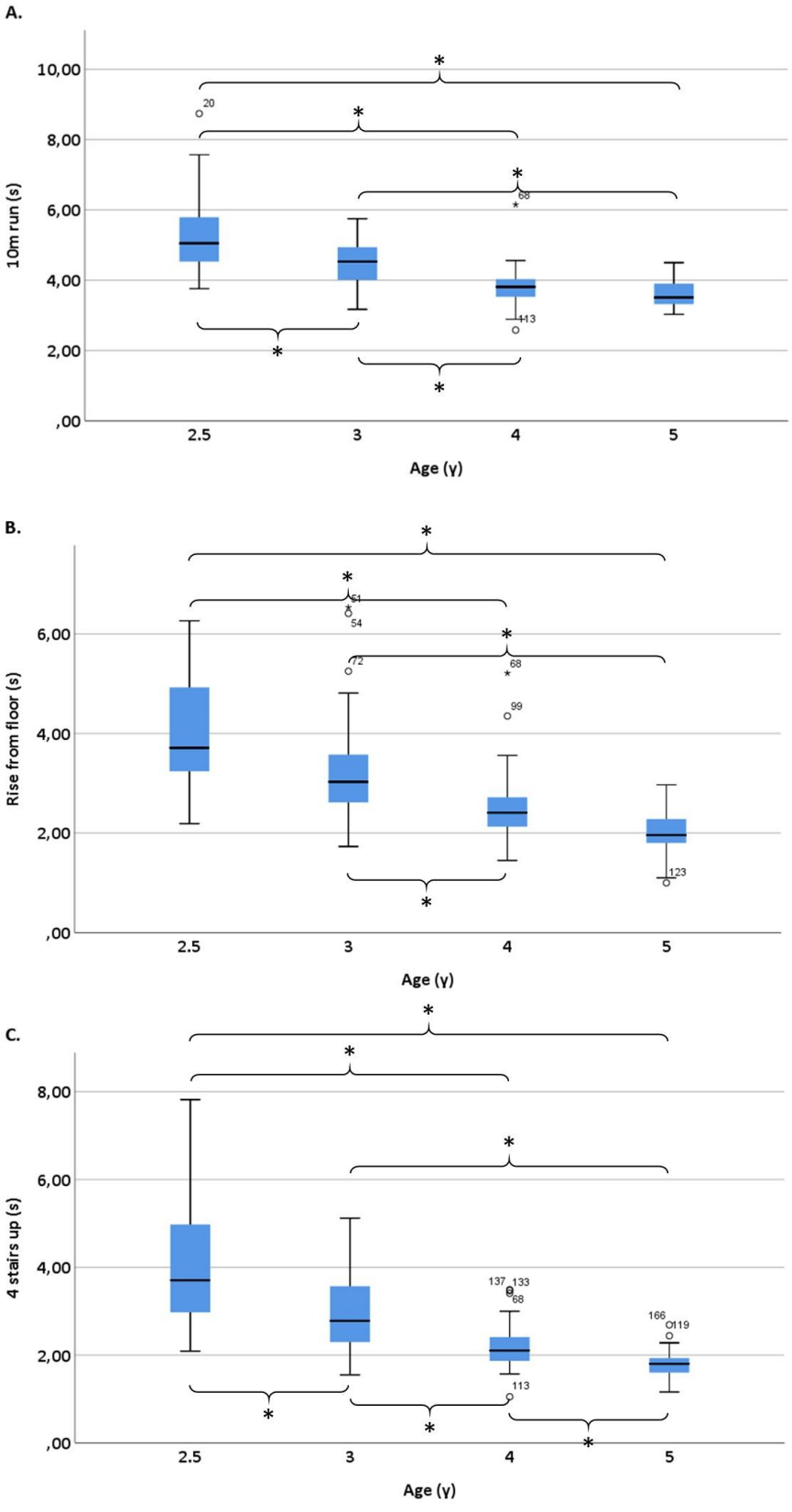
Figure 1. Mean 3MWD values (±SD) according to age (A) and height group (B). *groups are significantly different (p=0.000) (3MWD= three-minute walk distance; SD= standard deviation; y= years)

Significant differences in 3MWD between the four age groups were found (F(3,175)=33.431, p<0.001). Post hoc analyses showed significant differences between 2.5 and 4 years (p<0.001), 2.5 and 5 years (p<0.001), 3 and 4 years (p<0.001) and 3 and 5 years (p<0.001). No significant difference was found between the 2.5 and 3 (p=0.313) and the 4 and 5 year age group (p=0.098). According to height, a significant difference was found between all groups (F(2,176)=37.556, p<0.001) (p<0.001 for all groups; Figure 1).

Timed Function Tests (TFTs)

The overall median time to perform the four TFTs was 4.06s for the 10m run, 2.63s to rise from the floor, 2.31s to climb four stairs and 2.89s to descend four stairs. An overall decrease in median time for all four TFTs was seen with age and height (Table 1).

Figures 2 A, B, C and D show boxplots for each TFT, according to age group. The same graphs according to height can be found in appendix D.



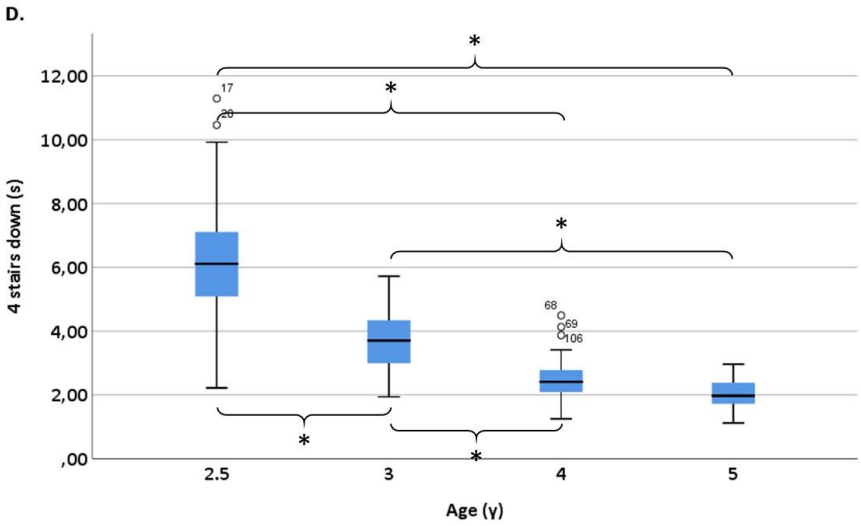


Figure 2. Boxplots of the time to run 10 meter (A), to rise from the floor (B), to climb four stairs (C) and to descend four stairs (D) according to age group. Medians are represented as solid horizontal lines with their interquartile range represented as a shaded box. *groups are significantly different ($p<0.05$) (y= years; Rise from floor= time to rise from the floor; 4 stairs up= climbing 4 stairs; 4 stairs down= descending 4 stairs)

Significant differences in the four TFTs between age groups were found. Post hoc tests showed that age groups 2.5 and 4 years, 2.5 and 5 years, 3 and 4 years and 3 and 5 years differed significantly for each of the four TFTs (10m run, TRF, climbing four stairs and descending four stairs; $p\leq0.004$; Figure 2 A,B,C and D). Between age groups 2.5 and 3 years, significant differences were found for 3 TFTs (10m run: $p=0.04$, climbing four stairs: $p=0.04$ and descending four stairs: $p=0.001$). Between age group 4 and 5 years, only the time to rise from the floor and to climb four stairs showed to be significantly different ($p=0.01$ for both). According to height, all three groups differed statistically significant for all TFTs ($p\leq0.028$, individual p-values of the post hoc tests can be found in Appendix E).

Correlations between age, height, 3MWD and the four TFTs

Correlations between age, height, 3MWD and the four TFTs are shown in Table 2. The 3MWD was moderately correlated with age and height ($r=0.61$ and $r=0.57$, respectively) as with all four TFTs ($r=-0.54$ to -0.59). Ten-meter run, rise from the floor and climbing four stairs correlated all moderately with age and height ($r=-0.61$ to -0.69). In addition, descending four stairs correlated strongly with age and height ($r=-0.77$ and $r=-0.73$, respectively). All TFTs, except for 10m run and climbing four stairs ($r=0.68$) were highly intercorrelated ($r=0.70$-0.83).

Table 2. Pearson correlations (r) between age, height, three-minute walk distance, 10-meter run, rise from the floor, climbing four stairs and descending four stairs.

	3MWD (m)	10m run (s)	TRF (s)	4 stairs up (s)	4 stairs down (s)
Age (y)	0.61*	-0.67*	-0.67*	-0.69*	-0.77*
Height (cm)	0.57*	-0.65*	-0.61*	-0.66*	-0.73*
3MWD (m)	/	-0.54*	-0.59*	-0.57*	-0.54*
10m run (s)	/	/	0.70*	0.68*	0.74*
TRF (s)	/	/	/	0.72*	0.70*
4 stairs up (s)	/	/	/	/	0.83*
4 stairs down (s)	/	/	/	/	/

*Correlation is significant at the 0.01 level (2-tailed). (3MWD= three-minute walk distance, TRF= time to rise from the floor; 4 stairs up= climbing 4 stairs; 4 stairs down= descending 4 stairs; y= years)

Comparison between DMD and TD children

Retrospective data from 19 boys with DMD were collected and compared to the reference values established in this study, as well as to an age-matched control group. Three-minute walk distances were available from seven boys between 3.3 and 5.8 years of age with a mean of 4.9 years (±0.8) and compared to an age-matched control group. Secondly, TFT values were available in 18 boys with DMD. Both the 18 boys with DMD and their age-matched control group had an age ranging from 2.8 to 5.9 years with a mean of 4,8 years (±0.9).

When compared with a TD age-matched control group, the boys with DMD performed significantly slower for all TFTs (10 m run: $U(18)=95.5$, $Z=-2.105$, $p=0.034$; rise from the floor: $U(18)=55.5$, $Z=-3.37$, $p<.001$; climbing four stairs: $U(18)=83$, $Z=-2.5$, $p=0.012$; descending four stairs: $U(18)=98$, $Z=-2.025$, $p=0.044$). No significant difference was found in 3MWD ($U(7)=15$, $Z=-1.215$, $p=0.259$). Medians with interquartile range and mean ranks can be found in Table 3. Boxplots were made to display the distribution graphically (Figure 3).

Table 3. Medians with interquartile range and mean ranks of the 3MWD, 10m run, TRF, climbing four stairs and descending four stairs for both the typically developing group and the Duchenne muscular dystrophy group.

	TD			DMD			
	Median	IQR	MR	Median	IQR	MR	p-value
3MWD (m)	211.4	(157-222)	8.86	201	(163-207)	6.14	0.259
10m run (s)	3.78	(3.30-4.21)	14.81	4.245	(3.80-6.55)	22.19	0.034*
TRF (s)	2.41	(1.93-2.64)	12.58	3.88	(3.08-4.80)	24.42	<.001*
4 stairs up (s)	2.035	(1.88-2.80)	14.11	3.145	(2.19-4.30)	22.89	0.012*
4 stairs down (s)	2.465	(2.01-3.07)	14.94	3.055	(2.30-3.06)	22.06	0.044*

* groups are significantly different ($p<0.05$) (TD= typically developing group; DMD= Duchenne muscular dystrophy group; 3MWD= three-minute walk distance; TRF= time to rise from the floor; 4 stairs up= climbing 4 stairs; 4 stairs down= descending 4 stairs; IQR= interquartile range; MR= mean rank)

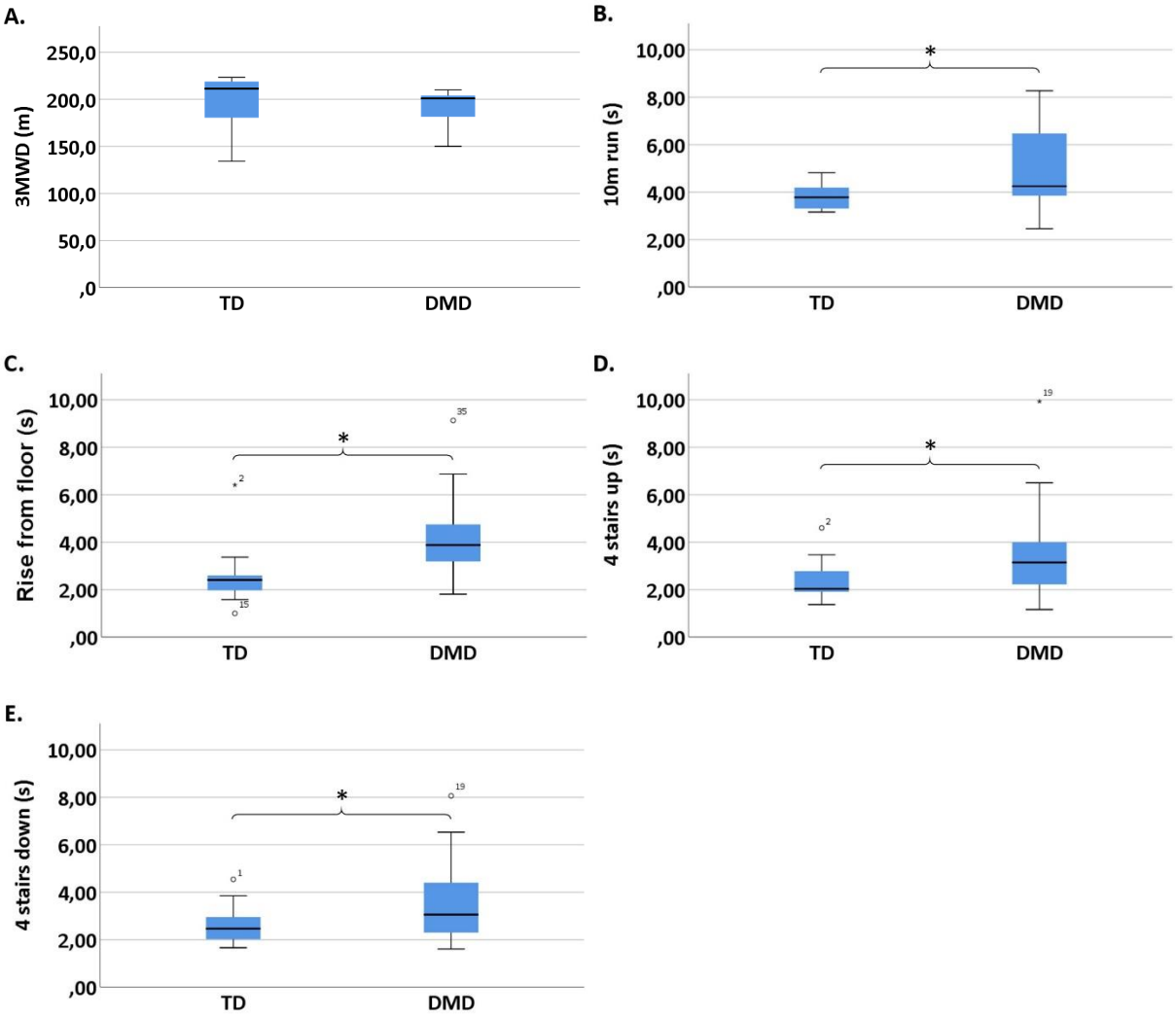


Figure 3. Boxplots of the 3MWD in meter (A) and of the time in seconds to run 10 meter (B), to rise from the floor (C), to climb four stairs (D) and to descend four stairs (E) of the typically developing boys (TD) versus the boys with Duchenne muscular dystrophy (DMD). Medians are represented as solid horizontal lines with their interquartile range represented as a shaded box. *groups are significantly different ($p<0.05$) (3MWD= three-minute walk distance; Rise from floor= time to rise from the floor; 4 stairs up= climbing 4 stairs; 4 stairs down= descending 4 stairs)

When individually compared to the reference values, five boys walked a distance within the normal range for their age. Of these five boys, one three-year-old boy scored normal on all the TFTs, three boys had at least one TFT 'at risk' or 'deviant' and one boy was 'at risk' or 'deviant' for all TFTs. One boy of four years old was considered as being 'at risk' for 3MWD, TRF and descending four stairs and 'deviant' on the 10m run and climbing four stairs. Finally, one five-year-old boy walked a distance that was more than two SD lower than the mean and was classified as 'deviant', but no values of the TFTs were available.

For 12 boys, only values of the TFTs were available. Five of these boys, were considered as being ‘at risk’ or ‘deviant’ on all four TFTs. The other boys were classified as being ‘at risk’ or ‘deviant’ on one (N=2), two (N=3) or three (N=2) TFTs (Table 4).

Table 4. Comparison of 19 boys with Duchenne muscular dystrophy with the reference values established in this study.

N	age	age group	3MWD	Reference mean (±SD)		10m run	Reference P2.3-P16		TRF	Reference P2.3-P16		4 stairs up	Reference P2.3-P16		4 stairs down	Reference P2.3-P16	
1	3y 3m	3y	201	178.6 (±23.8)	normal	3.64	5.75-5.20	normal	2.32	6.53-4.19	normal	2.10	5.11-3.86	normal	1.61	5.71-4.72	normal
2	4y 10m	4y	163	202.1 (±27.8)	**at risk**	7.56	6.02-4.25	**deviant**	4.31	5.14-3.02	**at risk**	3.52	3.49-2.60	**deviant**	3.52	4.46-3.03	**at risk**
3	4y 10m	4y	207	202.1 (±27.8)	normal	6.47	6.02-4.25	**deviant**	6.87	5.14-3.02	**deviant**	3.55	3.49-2.60	**deviant**	3.87	4.46-3.03	**at risk**
4	5y	5y	210	214.5 (±26.1)	normal	3.85	4.49-4.12	normal	3.50	2.96-2.43	**deviant**	2.78	2.68-2.04	**deviant**	2.30	2.95-2.54	normal
5	5y 2m	5y	201	214.5 (±26.1)	normal	4.20	4.49-4.12	**at risk**	1.81	2.96-2.43	normal	1.85	2.68-2.04	normal	2.30	2.95-2.54	normal
6	5y 2m	5y	150	214.5 (±26.1)	**deviant**	/	/	/	/	/	/	/	/	/	/	/	/
7	5y 9m	5y	200	214.5 (±26.1)	normal	2.46	4.49-4.12	normal	4.18	2.96-2.43	**deviant**	1.93	2.68-2.04	normal	2.24	2.95-2.54	normal
8	2y 10m	2.5y	/	/	/	8.15	8.70-6.08	**at risk**	4.75	6.26-5.33	normal	9.93	7.81-5.44	**deviant**	8.06	11.26-8.12	normal
9	3y 5m	3y	/	/	/	2.70	5.75-5.20	normal	3.88	6.53-4.19	normal	5.20	5.11-3.86	**deviant**	4.40	5.71-4.72	normal
10	4y	4y	/	/	/	6.80	6.02-4.25	**deviant**	5.10	5.14-3.02	**at risk**	4.00	3.49-2.60	**deviant**	4.20	4.46-3.03	**at risk**
11	4y 4m	4y	/	/	/	4.46	6.02-4.25	**at risk**	4.12	5.14-3.02	**at risk**	3.35	3.49-2.60	**at risk**	2.56	4.46-3.03	normal
12	4y 6m	4y	/	/	/	4.40	6.02-4.25	**at risk**	3.66	5.14-3.02	**at risk**	2.96	3.49-2.60	**at risk**	4.85	4.46-3.03	**deviant**
13	4y 7m	4y	/	/	/	3.41	6.02-4.25	normal	3.21	5.14-3.02	**at risk**	3.25	3.49-2.60	**at risk**	2.50	4.46-3.03	normal
14	4y 11m	4y	/	/	/	6.44	6.02-4.25	**deviant**	4.93	5.14-3.02	**at risk**	6.50	3.49-2.60	**deviant**	6.13	4.46-3.03	**deviant**
15	5y 2m	5y	/	/	/	4.10	4.49-4.12	normal	3.19	2.96-2.43	**deviant**	2.22	2.68-2.04	**at risk**	2.52	2.95-2.54	normal
16	5y 6m	5y	/	/	/	4.29	4.49-4.12	**at risk**	1.90	2.96-2.43	normal	1.16	2.68-2.04	normal	2.27	2.95-2.54	normal
17	5y 7m	5y	/	/	/	4.13	4.49-4.12	**at risk**	2.76	2.96-2.43	**at risk**	2.27	2.68-2.04	**at risk**	2.74	2.95-2.54	**at risk**
18	5y 9m	5y	/	/	/	8.27	4.49-4.12	**deviant**	9.13	2.96-2.43	**deviant**	5.92	2.68-2.04	**deviant**	6.53	2.95-2.54	**deviant**
19	5y 10m	5y	/	/	/	3.97	4.49-4.12	normal	3.88	2.96-2.43	**deviant**	3.04	2.68-2.04	**deviant**	3.37	2.95-2.54	**deviant**

(N= subject number; y= years; m=months; 3MWD= three-minute walk distance; SD= standard deviation; P= percentile; TRF= time to rise from the floor; 4 stairs up= climbing 4 stairs; 4 stairs down= descending 4 stairs; at risk= between 1 and 2 SD below mean or between percentile 2.3 and 16; deviant= more than 2 SD below mean or below percentile 2.3; /= no data available)

Discussion

This study established age- and height-specific reference values for the 3MWT and the TFTs in 179 typically developing Belgian boys aged 2.5 to 6 years old. As expected, an improvement in performance on the 3MWT and all four TFTs was seen with increasing age and height. Correlations between all the tests interchangeably, and of each test with age and height were calculated. In addition, comparison showed that DMD boys needed more time to complete each of the four TFTs when compared to an age-matched TD control group.

In general, the 3MWD increased with increasing age. However, this increase was not linear across the age categories. The largest and only significant increase in distance between two subsequent ages was seen between the 3 and 4 year age group (23.5m). This could be due to a sudden gain in strength or postural control, which are two important factors in the development of a mature walking pattern. The level of postural control can be seen by the anteroposterior, mediolateral and vertical movement of the center of mass (COM). With maturation, the step width (mediolateral movement) decreases while the step-length (anteroposterior movement) increases, resulting in a higher walking speed. By the age of 4 to 5 years, children establish the possibility to create a controlled forward propulsive force by pushing on the leg that supports their body weight rather than falling from one leg into the other. This results in a positive vertical acceleration of the COM (Adolph, Vereijken, & Shrout, 2003; Bril, & Brenière, 1993; Kubo, & Ulrich, 2006; Sutherland, Olshen, Cooper, & Woo, 1980). This sudden gain in control might explain the bigger increase in walking distance between the 3 and 4 year age group. According to height, a more steady increase in 3MWD was seen with significant differences between each subsequent height group. This might be explained by the fact that total body height has a strong positive correlation with both age and leg-length.

With regard to the TFTs, a better performance was seen by a decline in the time needed to complete each task with increasing age and height. The 10-meter run showed significant decreases in time with increasing age until the age of four. Between the ages of four and five years, a smaller, non-significant decrease in time was seen (-0.3s). The time to rise from the floor showed a stagnation between the ages of 2.5 and 3 years, after which the time decreased significantly till the age of 5 years. The study of Pereira et al. (2015), showed similar patterns for these two TFTs, but with one year delay, which probably reflects the variability within normal development. When compared per age group, the values of the 10m run were

consistently two to three seconds faster in our study while our TRF values were consistently slower. The slower execution times on the TRF can be explained by a difference in protocol. The starting position in the study of Pereira et al. (2015), was being seated on the floor while we started from a supine position, which takes more time to get up from. Furthermore, we established median values with IQR due to lack of a normal distribution, while they used means and SD, which hampers comparison.

According to age, only the time to climb four stairs showed a significant difference between each consecutive group. The time to descend four stairs decreased significantly with increasing age from the 2.5 to 3 year age group and from the 3 to 4 year age group (-2.4s and -1.3s respectively). Between the age groups of four and five years, a smaller, non-significant decline in time was seen (-0.44s). Accordingly, Noller, and Ingrisano (1983) reported a fallback in the percentage of children being able to descend stairs from 80 to 70 percent around that same age (57 to 63 months). An explanation for this smaller decline in time and fallback in ability to descend stairs might be a transition in movement pattern. Around the age of four to five years old, children will pass from descending the stairs with two feet per step while holding the handrail to using an alternating pattern with one foot per step (Dosman, Andrews, & Goulden, 2012; Gerber, Wilks, & Erdie-Lolena, 2010; Kakkebeeke, Caflisch, Locatelli, Rousson, & Jenni, 2012). In this study, the boys were free to choose if they wanted to descend the stairs with one or two feet per step and whether they wanted to hold the handrail or not. The only instruction given was to descend the stairs as quickly as possible.

In this study, moderate to strong correlations were found between the 3MWD and all TFTs, all TFTs mutually, as well as all these tests with age and height. Mazzone et al. (2010) reported comparable correlations between the 6MWD and both the 10m run (r=-0.60) and TRF (r=-0.54) in healthy children between four and 17 years old. Moderate to strong correlations with age and height were also found in other studies with healthy children between three and 17 years which included a walking protocol (6MWT, 2MWT) or a timed function test (9m run, 10m run, TRF) (Beenakker et al.,2005; Bohannon et al., 2017; Goemans, Klingels, van den Hauwe, Boons, et al., 2013; Lammers, Hislop, Flynn, & Haworth, 2008). Additionally, Goemans et al. (2016) reported correlations between the 6MWD, 10m run, TRF and four stairs climb in children with DMD between 4 and 16 years old. The strongest correlation was found between climbing four stairs and the time to rise from the floor (r=0.79). This is in accordance with the

findings in our study. Even though the 3MWT and all the TFTs correlate strongly to one another, each of them requires different movement patterns and provides different information. For example, TRF is more linked to pelvic stability and pelvic motor strength (Pereira et al., 2015) while descending four stairs requires eccentric muscle contraction and control and climbing four stairs demands more muscle strength to move against gravity (Fernandes et al., 2014).

A small sample of retrospective data of DMD boys was used to allow comparison with the TD boys. Overall, 3MWD seemed to be normal in most of the DMD boys, while a clear decrease in performance was seen on all four TFTs. The fact that these results were not only found in the general comparison of the entire groups, but also in the individual comparison according to age (means ±SD and P2.6-16), shows the clinical relevance of these reference values. Several studies confirm these findings by stating that timed function tests are more sensitive to assess disease progression than muscle testing or gait assessment (Beenakker et al., 2005; Bendixen, Lott, Senesac, Mathur, & Vandenborne, 2014; Fernandes, Caromano, Hukuda, Escorcio, & Carvalho, 2010; Martini et al., 2018). Five studies involving DMD boys between 3 and 17 years old, showed an increase in time to completion or a stagnation in movement strategy with increasing age for the TFTs (Beenakker et al.,2005; Bendixen et al., 2014; De Sanctis et al., 2015; Fernandes et al., 2014; Mazzone et al., 2010). The ability to rise from the floor is one of the first clinically-based tasks that is lost with age in boys with DMD (Beenakker et al.,2005). De Sanctis et al. (2015) and Pane et al. (2013) even reported that rising from the floor without using the hands, could not be performed by the age of four, while typically developing children are capable of doing this at that age.

Only two TD boys had problems with the execution of the 3MWT. One due to fatigue and the other one because he was running too much. For the TFT's, all TD boys were able to follow the protocol. However, especially in the youngest age group, multiple trials and instructions were needed. This suggests that both the TFT's and the 3MWT are feasible in young TD children from the age of 2.5 years.

Limitations

This study has some limitations. First, some sort of self-selection bias might be present. The parents of the boys had to give their child the permission to participate in this study. As a consequence the boys that did not get permission of their parents could differ in an unknown

way of those who did. However, by recruiting children in nine different schools from different regions in Flanders, we assume to have a representative sample. Secondly, the assessment of the boys was conducted by different assessors. The difference in verbal encouragements, enthusiasm and instructions could have influenced the performance of the boys. Nonetheless, to limit the inter-rater variability, one or more of the three physiotherapists, experienced by the test procedure always took part in the assessments and a standard protocol was followed. In order to limit fatigue in the youngest age category, boys under the age of three years were always tested before noon. Thirdly, height, weight and medication status were not taken into account when comparing the DMD boys to the TD ones. However, no difference in performance was seen depending on medication status for the four stair climb between 5 and 7 years according to McDonald et al. (2013).

Future research

The 3MWD registered during a 6MWT is already found to have a good test-retest reliability in order to assess the functional capacity of typically developing Caucasian boys between 5 and 12 years old (Goemans, Klingels, van den Hauwe, Van Orshoven, et al., 2013). However, reliability studies should also be established with a 3MWT protocol and in a younger population from 2.5 years on. Since we only focused on young Belgian boys, generalization to other countries and ethnic groups has to be done with caution. According to gender, Beenakker et al. (2005), and Pereira et al. (2015) reported no differences between boys and girls for the 6MWT and the TFTs before the age of puberty, which implies that our reference values could also be used for young Belgian girls. However, to be sure, additional reference values for girls could be collected. In this study, the reference values were reported as means and medians with SD and IQR respectively. Percentiles 2.3 and 16 were calculated for each of the four TFTs per age category in order to make an individual comparison possible. In addition, percentile curves according to age and height could be established to facilitate the use in early screening and assessment. For the comparison between the DMD boys and the control group, we used retrospective data comparison. Prospective research should be done to compare the 3MWD and the TFTs in a larger group of DMD boys with a control group according to age, height and weight.

Conclusion

This study was the first to establish age- and height-specific reference values for the 3MWT and four TFTs (10m run, time to rise from the floor, climbing 4 stairs and descending 4 stairs) in young Belgian boys between 2.5 and 6 years of age. Age and height correlated significantly with each of the tests and a better performance was seen with increasing age and height group. A first retrospective comparison of the data of DMD boys to our reference values showed a similar performance on the 3MWT but a worse performance on the TFTs, suggesting a delay in early motor development. These tests have shown to be clinically feasible and sensitive assessments of functional capacity in young ambulant DMD boys.

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APPENDIX A

MEDISCHE VRAGENLIJST

Dit formulier bevat vragen in verband met de medische gegevens van uw kind. Wij willen vragen deze zo eerlijk en compleet mogelijk te beantwoorden.

Naam + voornaam kind: ……

Geboortedatum kind: ……

Heeft uw kind een chronische hartaandoening?

- Ja
- Neen

Indien ja, welke? ……

Heeft uw kind een chronische longziekte?

- Ja
- Neen

Indien ja, welke? ……

Heeft uw kind een motorische stoornis?

- Ja
- Neen

Indien ja, welke? ……

Wordt uw kind momenteel opgevolgd door een kinesitherapeut?

- Ja
- Neen

Indien ja, reden van verwijzing? ……

Neemt uw kind op regelmatige basis medicatie?

- Ja
- Neen

Indien ja, welke? ……

Datum:…… Naam en Handtekening: ……

De bovenstaande gegevens hebben w ij nodig om inclusiecriteria van dit onderzoek te kunnen controleren. De persoonlijke gegevens van uw kind w orden uitsluitend gebruikt voor dit onderzoek en onder geen beding aan derden verstrekt.

Indien u nog vragen of opmerkingen heeft, kan U steeds contact met ons opnemen op het telefoonnummer +32 16 32 91 75 of via e-mail: jasmine.hoskens@faber.kuleuven.be

APPENDIX B

Referentiewaarden voor de drie minuten wandeltest (3MWT), North Star Ambulatory Assessment (NSAA) en tijdstesten voor typische ontwikkelende Caucasische jongens tussen 2, 5 en 5 jaar oud

Beste directie,

Het Departement Revalidatiewetenschappen (KU Leuven, Prof. Dr. K. Klingels en J Hoskens) voert samen met het Neuromusculair Referentiecentrum (UZ Leuven, Dr. N. Goemans en M. Van den Hauwe) onderzoek uit naar de behandeling bij de ziekte van Duchenne. Dit is een aangeboren en erfelijke ziekte die de spieren aantast en bijna uitsluitend bij jongens voorkomt. In het kader van een studie zijn we op zoek naar gezonde jongens tussen 2,5 en 6 jaar oud. Het doel van deze studie is het verzamelen van referentiewaarden voor enkele eenvoudige testjes die functionaliteit en uithouding nagaan. Er is tot op heden weinig of niets gekend over deze testjes bij jonge, gezonde kinderen, en de resultaten van dit project zullen belangrijk zijn om kinderen met de spierziekte van Duchenne beter te kunnen opvolgen en behandelen.

Voor dit onderzoek zullen drie evaluaties uitgevoerd worden: 1. de drie minuten wandeltest (3MWT), 2. De North Star Ambulatory Assessment (NSAA) en 3. 4 tijdstesten. De 3MWT meet op een gestandaardiseerde manier de afstand die een kind in drie minuten kan stappen. Vervolgens is er de NSAA, een testbatterij die 17 kleine proefjes omvat zoals rechtstaan, op één been staan, een trapje op- en afstappen, op de hielen staan, springen, en springen op één been. Tenslotte zullen vier tijdstesten afgenomen worden (de tijd nodig om recht te staan vanuit liggende positie, om tien meter te lopen, en om vier trapjes op- en af te stappen). Verder zullen we de lichaamslengte en het lichaamsgewicht van de jongens meten. Geen van bovengenoemde evaluaties zal ongemakken veroorzaken voor de kinderen, aan deelname aan dit project zijn geen risico's verbonden. Elk kind heeft tevens het recht op elk ogenblik vragen te stellen over de testjes en de testafname kan op elk moment gestopt of onderbroken worden.

We zoeken een aantal Vlaamse scholen om deel te nemen aan deze studie. Deze evaluatiest zullen per kind ongeveer 20 minuten in beslag nemen. Indien mogelijk zullen de evaluaties bij u op school doorgaan tijdens de schooluren. Als u beslist tot deelname over te gaan, wordt een overlegmoment met U en/ of de betrokken leerkrachten gepland om de praktische afspraken te maken. De evaluaties worden afgenomen door ervaren kinesitherapeuten (Prof. Dr. K Klingels en J Hoskens, Master revalidatiewetenschappen en kinesitherapie), al dan niet in aanwezigheid van een masterstudent revalidatiewetenschappen en kinesitherapie ter hulp en ondersteuning.

Wij verzekeren u dat de gegevens van de kinderen, in het kader van dit onderzoek, volledig anoniem zullen worden verwerkt, zodat de privacy van de kinderen ten allen tijde wordt gerespecteerd en gegarandeerd. Bijgevoegd kan u ook het informatie- en toestemmingsformulier voor de ouders vinden.

Graag hadden we bovenstaande onderzoeken op uw school uitgevoerd. Indien u bereid bent hieraan mee te werken, gelieve dan bijgevoegd toestemmingsformulier in te vullen a.u.b.

Dank bij voorbaat voor uw bereidwillige medewerking.

Met vriendelijke groeten,

Prof. Dr. N Goemans (hoofdonderzoeker)
Prof. Dr. K Klingels
Marleen Van den Hauwe
Jasmine Hoskens

Referentiewaarden voor de drie minuten wandeltest (3MWT), North Star Ambulatory Assessment (NSAA) en tijdstesten voor typische ontwikkelende Caucasische jongens tussen 2, 5 en 5 jaar oud

Bijkomende informatie:

Indien u meer informatie omtrent deze studie wil of als u vragen heeft, kan u steeds terecht bij mevr. J Hoskens, 016 32.91.75 of jasmine.hoskens@kuleuven.be

School (naam + adres): _____

_____

_____

Contactpersoon voor praktische afspraken (naam, telefoonnummer, emailadres):

_____

_____

_____

De directie, hier vertegenwoordigd door _____ **geeft toestemming aan de de onderzoekers om kinderen van de school te laten deelnemen aan deze studie, mits voorafgaande schriftelijke toestemming van de ouders.**

Datum en handtekening directie **Datum en handtekening KU Leuven**

INFORMATIE- EN TOESTEMMINGSFORMULIER

TITEL: Referentiewaarden voor de drie minuten wandeltest (3MWT), North Star Ambulatory Assessment (NSAA) en tijdstesten voor typische ontwikkelende Caucasische jongens tussen 2, 5 en 6 jaar oud

Beste ouders,

Het departement Revalidatiewetenschappen (KU Leuven, Prof. Dr. K Klingels en J Hoskens) voert samen met het Neuromusculair Referentiecentrum (UZ Leuven, Prof. Dr. N Goemans en M Van den Hauwe) onderzoek uit naar de behandeling bij de ziekte van Duchenne. Dit is een aangeboren en erfelijke ziekte die de spieren aantast en bijna uitsluitend bij jongens voorkomt. In het kader van deze studie zijn we op zoek naar gezonde jongens tussen 2,5 en 6 jaar. Het doel van deze studie is het verzamelen van referentiewaarden bij gezonde jongens voor enkele eenvoudige testjes die de functionaliteit en uithouding nagaan. Er is tot op heden weinig of niets gekend over deze testjes bij jonge, gezonde kinderen, en de resultaten van dit onderzoek zullen belangrijk zijn om kinderen met de spierziekte van Duchenne in de toekomst beter te kunnen opvolgen en behandelen.
Graag willen wij uw medewerking voor deze studie vragen door uw zoon te laten deelnemen.
Alvorens te beslissen willen wij u goed informeren over de studie. We raden u dan ook ten zeerste aan om deze formulieren grondig te lezen.

Beschrijving van de studie

Wij zijn op zoek naar een 120-tal typisch ontwikkelende jongens tussen 2,5 en 6 jaar oud. We zullen bij deze jongens 3 evaluaties uitvoeren, namelijk de 3 minuten wandeltest (3MWT), North Star Ambulatory Assessment (NSAA) en tijdstesten. Tijdens de 3MWT wordt uw zoon gevraagd om 3 minuten over een afstand van 25 meter heen en weer rond kegels te stappen. Vervolgens zal de NSAA afgenomen worden. Deze test bestaat uit 17 korte testitems zoals recht staan, wandelen, een trapje op- en af stappen, op de hielen staan, springen,… Ten slotte zullen 4 tijdstesten geëvalueerd worden. De tijd van volgende taken wordt geregistreerd: recht staan vanuit liggende positie, tien meter lopen, vier trappen op en vier trappen af. Verder zullen ook de lichaamslengte en het lichaamsgewicht van uw kind gemeten worden.
Kinderen met chronische cardiale, respiratoire en/of motorische problemen zullen niet geïncludeerd worden in deze studie. We voeren dit onderzoek uit in een aantal Vlaamse scholen die erin toegestemd hebben om deel te nemen. De metingen kunnen gewoon doorgaan tijdens de schooluren op de school van uw zoon. De totale duur van een evaluatie bedraagt ongeveer 20 minuten. De evaluaties worden afgenomen door ervaren kinesitherapeuten (Prof. Dr. K Klingels en J Hoskens), met de hulp van een masterstudent revalidatiewetenschappen en kinesitherapie.

Implicaties deelname

Met dit schrijven wordt uw zoon gevraagd om deel te nemen aan de studie. Als u hierin toestemt, zullen wij verder contact opnemen met de school om de evaluatie van uw zoon in te plannen.

Geen van bovengenoemde evaluaties zal ongemakken veroorzaken voor de kinderen, aan deelname aan dit project zijn geen risico's verbonden. Elk kind heeft tevens het recht op elk ogenblik vragen te stellen over de testjes en de testafname kan op elk moment gestopt of onderbroken worden.

In overeenstemming met de Belgische wet van 7 mei 2004 over experimenten op de menselijke persoon is de opdrachtgever, ook indien er geen sprake is van fout, aansprakelijk voor schade die uw kind rechtstreeks of onrechtstreeks ten gevolge van zijn deelname aan het onderzoeksproject ervaart. De opdrachtgever van deze studie (KU Leuven) heeft een verzekering afgesloten die deze aansprakelijkheid dekt.

Conform de Belgische wet van 8 december 1992 en 22 augustus 2002 zal uw persoonlijke levenssfeer en deze van uw kind gerespecteerd worden. Wij kunnen u garanderen dat de gegevens van uw kind anoniem en vertrouwelijk zullen behandeld worden. De studiegegevens worden van een code voorzien vooraleer ze aan derden worden overgemaakt. De code (link tussen de deelnemer en zijn/haar gegevens) wordt door de onderzoekers bewaard. De onderzoeker is bijgevolg de enige persoon die een verband kan leggen tussen code en deelnemer. Indien gewenst kan u de testgegevens van uw kind bij de onderzoekers opvragen. De resultaten van dit onderzoek worden minstens tot 5 jaar na publicatie bewaard zodat andere onderzoekers juistheid van de gegevens en verwerking kunnen controleren.

Deelname aan deze studie is geheel vrijblijvend en op vrijwillige basis. Ook heeft u het recht om de deelname op elk moment stop te zetten. Hiervoor is geen geldige reden noodzakelijk en dit zal nooit in het nadeel van uw kind spelen. Tenslotte is deelname aan dit onderzoek volledig kosteloos.

Deze studie werd tevens goedgekeurd door de Ethische Commissie Onderzoek UZ/KU Leuven.

Indien u akkoord gaat met het gebruik van gegevens van uw zoon ten gunste van wetenschappelijk onderzoek, volstaat het om bijgevoegd toestemmingsformulier ondertekend terug te bezorgen.

De deelname van uw kind aan deze studie levert een waardevolle bijdrage tot wetenschappelijk onderzoek. Dit kan leiden tot nieuwe onderzoeks- en behandelmethoden, welke kinderen in de toekomst kunnen helpen.

Contact

Indien u meer informatie wenst of nog vragen heeft omtrent deze studie, mag u steeds contact opnemen met :

Jasmine Hoskens
Tel: 016 32 91 75
E-mail: jasmine.hoskens@kuleuven.be

Prof. Dr. Katrijn Klingels
Tel: 016 32 91 17
E-mail: katrijn.klingels@kuleuven.be

Dank bij voorbaat voor uw bereidwillige medewerking.

Toestemmingsformulier voor het deelnemen aan wetenschappelijk onderzoek

Titel onderzoek:

'Referentiewaarden voor de drie minuten wandeltest (3MWT), North Star Ambulatory Assessment (NSAA) en tijdstesten voor typische ontwikkelende Caucasische jongens tussen 2, 5 en 6 jaar oud'

Ik, ondergetekende, moeder/ vader/ voogd/ wettelijke vertegenwoordiger (*schrap wat niet past*)

_____(*voornaam, naam*), van

_____(*voornaam, naam kind*)

_____(*geboortedatum kind*)

verklaar hierbij in de mogelijkheid gesteld te zijn de informatie in dit formulier te lezen en vrij te kiezen om mijn kind wel of niet te laten deelnemen aan dit onderzoek. Ik heb van deze informatie ook een eigen kopij ontvangen en ga akkoord met de inhoud hiervan.
Ik ben geïnformeerd dat ik vrij ben om mijn medewerking aan het project in te trekken op gelijk welk ogenblik.
Ik begrijp dat alle gegevens strikt en vertrouwelijk behandeld zullen worden. De gecodeerde gegevens kunnen deel uitmaken van wetenschappelijk publicaties of voorstellingen zonder evenwel de identiteit van mijn kind kenbaar te maken.

Gelieve ook uw persoonlijke contactgegevens hieronder aan te vullen, zodat wij u ten allen tijden kunnen contacteren.

Tel: _____

E-mail: _____

Datum en handtekening ouder(s)/ voogd/ wettelijke vertegenwoordiger:

Datum en handtekening onderzoeker:

Ik, ondergetekende .....(naam onderzoeker), bevestig dat ik de nodige informatie in verband met deze studie heb verschaft aan de verschillende partijden. Zij kregen een tevens persoonlijk een kopij van het informatieformulier en het toestemmingsformulier werd ondertekend door de verschillende partijen.
Ik ben steeds bereid om zo nodig aanvullende informatie te geven en/ of vragen te beantwoorden. Er zal geen druk op het kind uitgeoefend worden om aan de studie deel te nemen. Ik verklaar dat ik werk volgends de ethische principes beschreven in de verklaring van Helsinki en de Belgische wet van 7/5/2004 over proeven op mensen.

KOPIJ OUDERS

Toestemmingsformulier voor het deelnemen aan wetenschappelijk onderzoek

Titel onderzoek:

'Referentiewaarden voor de drie minuten wandeltest (3MWT), North Star Ambulatory Assessment (NSAA) en tijdstesten voor typische ontwikkelende Caucasische jongens tussen 2, 5 en 6 jaar oud'

Ik, ondergetekende, moeder/ vader/ voogd/ wettelijke vertegenwoordiger (*schrap wat niet past*)

_____(*voornaam, naam*), van

_____(*voornaam, naam kind*)

_____(*geboortedatum kind*)

verklaar hierbij in de mogelijkheid gesteld te zijn de informatie in dit formulier te lezen en vrij te kiezen om mijn kind wel of niet te laten deelnemen aan dit onderzoek. Ik heb van deze informatie ook een eigen kopij ontvangen en ga akkoord met de inhoud hiervan.
Ik ben geïnformeerd dat ik vrij ben om mijn medewerking aan het project in te trekken op gelijk welk ogenblik.
Ik begrijp dat alle gegevens strikt en vertrouwelijk behandeld zullen worden. De gecodeerde gegevens kunnen deel uitmaken van wetenschappelijk publicaties of voorstellingen zonder evenwel de identiteit van mijn kind kenbaar te maken.

Gelieve ook uw persoonlijke contactgegevens hieronder aan te vullen, zodat wij u ten allen tijden kunnen contacteren.

Tel: _____

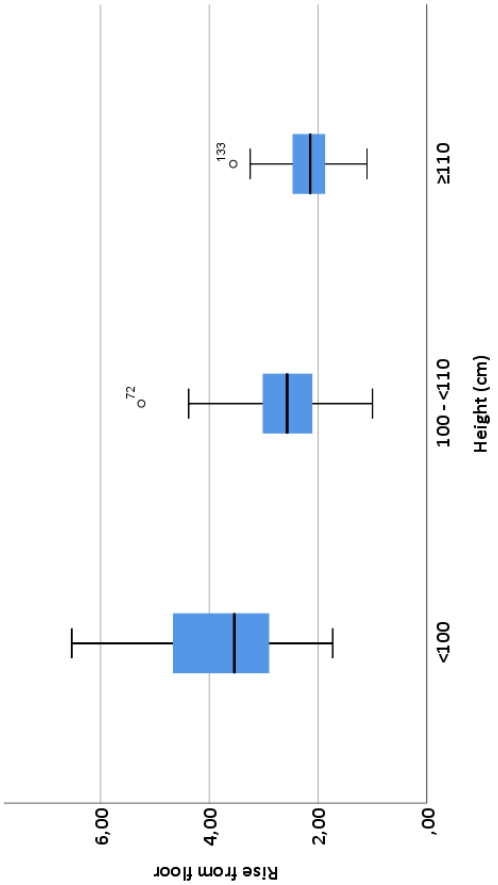
E-mail: _____

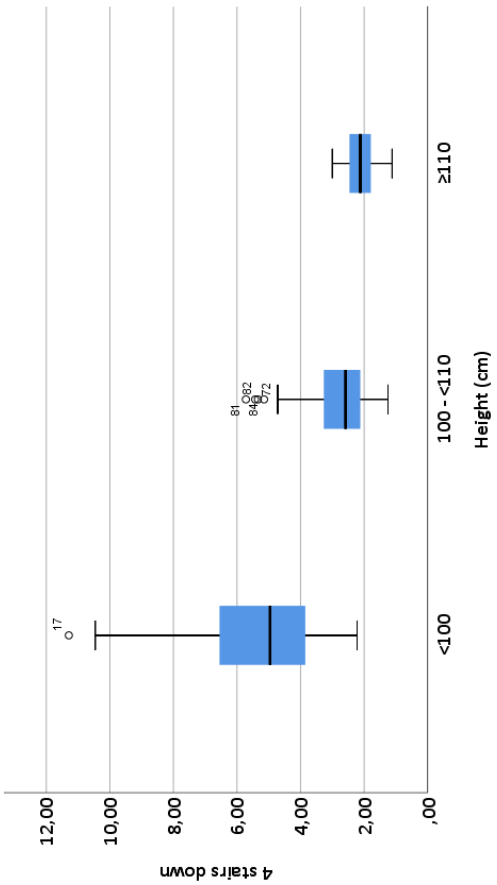
Datum en handtekening ouder(s)/ voogd/ wettelijke vertegenwoordiger:

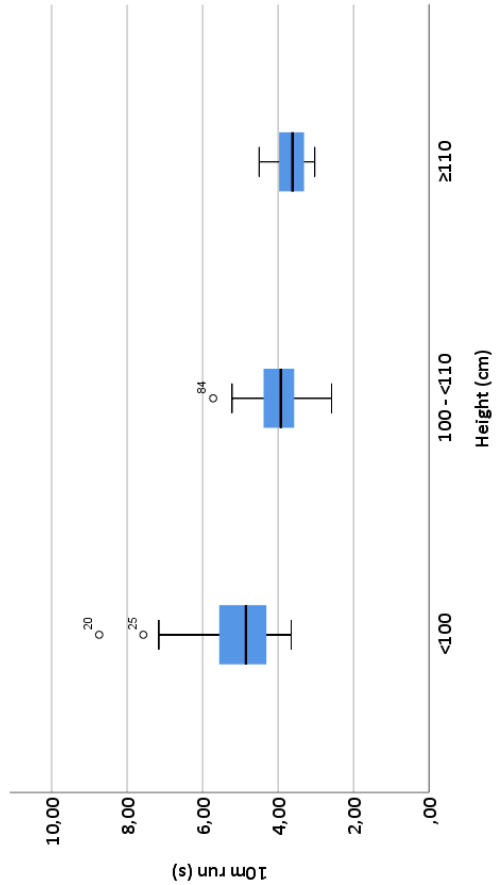
Datum en handtekening onderzoeker:

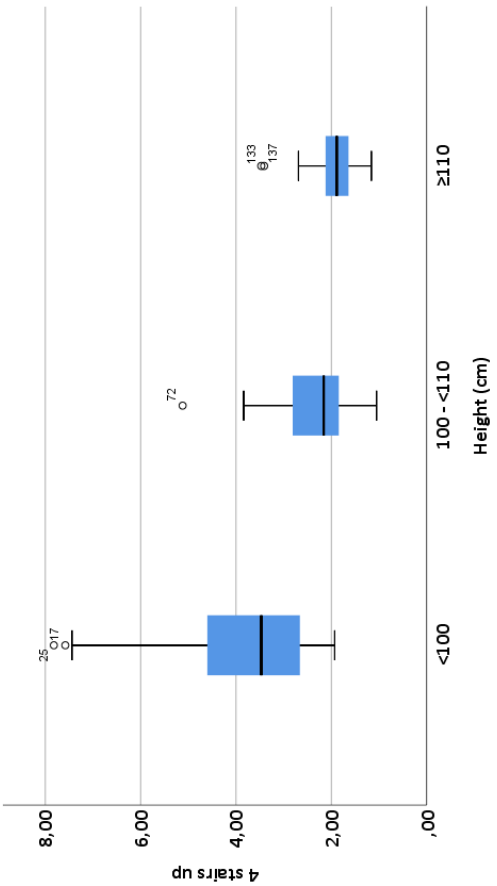
Ik, ondergetekende .....(naam onderzoeker), bevestig dat ik de nodige informatie in verband met deze studie heb verschaft aan de verschillende partijden. Zij kregen een tevens persoonlijk een kopij van het informatieformulier en het toestemmingsformulier werd ondertekend door de verschillende partijen.
Ik ben steeds bereid om zo nodig aanvullende informatie te geven en/ of vragen te beantwoorden. Er zal geen druk op het kind uitgeoefend worden om aan de studie deel te nemen. Ik verklaar dat ik werk volgends de ethische principes beschreven in de verklaring van Helsinki en de Belgische wet van 7/5/2004 over proeven op mensen.

APPENDIX D


Rise from floor
6,00
4,00
2,00
,00
<100
100 - <110
≥110
Height (cm)
72
133


4 stairs down
12,00
10,00
8,00
6,00
4,00
2,00
,00
<100
100 - <110
≥110
Height (cm)
17
81
82
72


10m run (s)
10,00
8,00
6,00
4,00
2,00
,00
<100
100 - <110
≥110
Height (cm)
20
25
84


4 stairs up
8,00
6,00
4,00
2,00
,00
<100
100 - <110
≥110
Height (cm)
25
17
72
133
137

APPENDIX E

Post hoc results for the three-minute walk distance, 10 m run, time to rise from the floor, climbing four stairs and descending four stairs.

		3MWD	10m run	TRF	4 stairs up	4 stairs down
Age groups	2.5y / 3y	.313	.042*	.062	.040*	.001*
	3y / 4y	<.0001*	<.0001*	.004*	<.0001*	<.0001*
	4y / 5y	.098	.652	.009*	.014*	.085
	2.5y / 4y	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*
	2.5y / 5y	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*
	3y / 5y	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*
Height groups	<100 cm / 100 - <110 cm	<.0001*	<.0001*	.0001*	<.0001*	<.0001*
	<110 cm / ≥110 cm	<.0001*	.015*	.001*	<.005*	.006*
	<100 cm / ≥110 cm	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*

* groups are significantly different (p<.05) (3MWD= three-minute walk distance; y=years; TRF= time to rise from the floor; 4 stairs up= climbing 4 stairs; 4 stairs down= descending 4 stairs)

APPENDIX F

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UHASSELT
KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
03/10/2017	Overleg met begeleider Jasmine Hoskens: Voorstellen onderwerp/topic + bespreking inhoud introductie en methoden + opstellen globale planning met betrekking tot vervroegd afstuderen.	Promotor: Copromotor: Student(e): Student(e):
09/11/2017	Bespreking topic met promotor Prof. dr. Katrijn Klingels. Overleg met begeleider Jasmine Hoskens: Bekijken van de reeds beschikbare ruwe data + opzoeken data DMD kinderen in de database van UZ Leuven Gasthuisberg.	Promotor: Copromotor: Student(e): Student(e):
07/12/2017	Overleg met begeleider Jasmine Hoskens: Bespreking en feedback op het schrijfwerk van de inleiding en methoden + statistiek bespreken.	Promotor: Copromotor: Student(e): Student(e):
12/12/2017	Overleg met promotor Prof. dr. Katrijn Klingels: Bespreking inhoud situering + resultaten + algemene progressie schrijfwerk. Beslissing om niet vervroegd in te dienen in Januari.	Promotor: Copromotor: Student(e): Student(e):
08/01/2018 09/01/2018 15/01/2018	Afnames 3MWT en TFT's in SBS Kuringen samen met begeleider Jasmine Hoskens.	Promotor: Copromotor: Student(e): Student(e):
23/01/2018	Overleg met begeleider Jasmine Hoskens: Administratief in orde brengen van informatie- en toestemmingsformulieren ouders en medische vragenlijsten.	Promotor: Copromotor: Student(e): Student(e):
29/01/2018 05/02/2018	Afnames 3MWT en TFT's in kleuterschool de Kleurdoos in Zonhoven samen met begeleider Jasmine Hoskens.	Promotor: Copromotor: Student(e): Student(e):
23/02/2018	Overleg met promotor Prof. dr. Katrijn Klingels: Administratief in orde brengen van de resterende informatie- en toestemmingsformulieren ouders en medische vragenlijsten + planning en deadlines opstellen in verband met verder schrijfwerk.	Promotor: Copromotor: Student(e): Student(e):
22/03/2018	Skype-overleg met begeleider Jasmine Hoskens: Bespreking en feedback op de eerste volledige versie van de resultaten + bespreking opbouw en inhoud van de discussie.	Promotor: Copromotor: Student(e): Student(e):
03/05/2018	Overleg met promotor Prof. dr. Katrijn Klingels en Jasmine Hoskens (skype): Feedback eerste draft + opstellen titel + ondertekenen inschrijvingsformulier met toestemming om in te dienen.	Promotor: Copromotor: Student(e): Student(e):

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Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij kinderen**
Jaar: **2018**

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Datum: **15/06/2018**