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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Early upper limb involvement in boys with Duchenne Muscular Dystrophy aged under 6.5 years: A cross sectional study

Pieter Caeyers
Marthe Van Hoof

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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2021

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Acknowledgement

This master's thesis would not have been possible without the support of our promotor Prof. dr. Klingels K. and co-promotor Dra. Hoskens J.

We would like to express a special thank you to the research group of the ongoing project "Evaluation of early development in infants and young children with Duchenne Muscular Dystrophy", our educational institution (Faculty of Rehabilitation Sciences, Hasselt University), the Neuromuscular Reference Centre UH Leuven and last but not least our promotor Prof. dr. Klingels K. and co-promotor Dra. Hoskens J. We hope that this master's thesis can contribute to the ongoing research regarding upper limb function in young boys with Duchenne Muscular Dystrophy.

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Research context

This research is carried out as a dual master's thesis for the Faculty of Rehabilitation Sciences at Hasselt University. It can be situated in the domain of pediatric rehabilitation, more specifically, upper limb (UL) involvement in young boys with Duchenne Muscular Dystrophy (DMD). This research is part of the overarching project "Evaluation of early development in infants and young children with DMD" which is a collaboration between Hasselt University, KU Leuven and the Neuromuscular Reference Centre (NMRC) UH Leuven.

A lot is known regarding boys with DMD. Nevertheless, most research focuses on lower limb function, corticosteroid therapy and loss of ambulation. Evidence concerning UL involvement is rather scarce, especially in boys with DMD under the age of seven.

When the disease progresses, contractures in the upper limbs become more present (Case et al., 2018)[1]. This could lead to difficulties with performing UL activities, which could result in a decrease of participation in daily activities, and thus lower quality of life. For example, due to reduced arm strength, boys with DMD would not be able to propel a manual wheelchair, which in turn could lead to restrictions in social participation. For these reasons, preservation of UL function is important. Therefore this study focuses on the early involvement of UL function and fine motor skills in young boys with DMD.

This research was conducted under supervision of Prof. dr. Klingels K. and Dra. Hoskens J. The cross sectional study design was selected in consultation with our supervisors, with the aim that our study could contribute to the overarching project.

Due to the Covid-19 pandemic, in combination with the chronic disease of the boys, recruitment of participants and data collection could not be carried out by the students. Dra. Hoskens J. collected data from February 2018 to April 2021. Raw data was handed over to the students. In exchange, the students recruited and assessed typically developing (TD) boys who could serve as a control group in future studies within this research project.

Further elaboration of this research (data processing, statistical analysis, interpretation of the results and the writing process) was carried out independently by the students.

Both students made an equal contribution to this master's thesis.

[1] Case, L. E., Apkon, S. D., Eagle, M., Gulyas, A., Juel, L., Matthews, D., . . . Posselt, H. F. (2018). Rehabilitation Management of the Patient With Duchenne Muscular Dystrophy. Pediatrics, 142(Suppl 2), S17-s33. doi:10.1542/peds.2018-0333D

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Early upper limb involvement in boys with Duchenne Muscular Dystrophy aged under 6.5 years: a cross sectional study

1 Abstract

Background: Duchenne Muscular Dystrophy (DMD) is a neuromuscular disease which affects 1:5000 live newborn boys. It is characterized by a progressive loss of muscle function due to a deficit in the dystrophin protein. This leads to loss of ambulation around the age of 12 - 13 years. In the non-ambulant stage, upper limb (UL) function becomes more important. Evidence concerning UL function and fine motor skills is still scarce, especially in young children (< 5 years old).

Objectives: This study investigated a possible difference in UL function and fine motor skills between typically developing (TD) boys and boys with DMD aged 0 – 6.5y.

Participants: Eighteen boys with DMD were recruited from the Neuromuscular Reference Centre (NMRC) UH Leuven. The control group was recruited from Flemish kindergartens and day-care centers (n=35).

Measurements: The Bayley-III fine motor skills, PUL 2.0 and subdomains grasping, object manipulation and visual-motor integration of PDMS-II were conducted by a skilled assessor in both groups.

Results: Significant differences were found between the DMD and TD groups on Bayley-III ($p<0.001$), PDMS-II (grasping $p=0.002$, object manipulation $p<0.001$, visual-motor integration $p<0.001$) and PUL 2.0 ($p=0.001$).

Conclusion: At a very young age (< 6.5y) boys with DMD have significantly lower UL function and fine motor skills compared to TD boys. Boys with DMD mainly experienced problems with more complex fine motor skills like pen and paper tasks. To execute these skills not only motor skills are important, but also cognitive abilities and trunk control could play an important role.

Keywords: Duchenne Muscular Dystrophy, neuromuscular disease, pediatrics, upper limb, fine motor skills

2 Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disease which affects 1:5000 live newborn males (Mendell et al., 2012). It is characterized by a deficit in the dystrophin protein, which leads to a progressive loss of muscle function (Hoffman, Brown, & Kunkel, 1987). This loss of muscle function, that proceeds from proximal to distal direction, leads to loss of ambulation and consequently to wheelchair dependency at age 12 – 13 (Brooke et al., 1989). The lack of dystrophin can also have an impact on the brain. It can lead to an abnormal organization of various brain structures (i.e. hippocampus and cerebral cortex) which could have a negative impact on cognitive development (Muntoni, Torelli, & Ferlini, 2003).

Currently, there is no curative treatment (Arora, 2019). However, due to the rise of novel therapies and management strategies (e.g. corticosteroids), life expectancy of boys with DMD has evolved from 14 years in the 1960s to over 40 years nowadays (Eagle et al., 2002; Landfeldt et al., 2020).

To delay function loss and disease progression, an anticipatory and preventive approach is recommended for musculoskeletal, respiratory, bone health and cardiac problems. Interventions focusing on upper limb (UL) function are often postponed until loss of ambulation (Birnkrant et al., 2018; Case et al., 2018). At this point, the degree of independence relies strongly on the upper limbs. For this reason, preservation of UL functionality becomes more important. However, current literature reports that UL function is already affected before loss of ambulation. Boys with DMD show an increase of UL strength until the age of 10, followed by a decrease in the second decade of life (Lerario et al., 2012; Mattar & Sobreira, 2008; McDonald et al., 1995; Ricotti et al., 2019). Nevertheless, studies have shown that before the age of 10, UL strength in boys with DMD is lower compared to typically developing (TD) children (M. Janssen, Harlaar, Koopman, & de Groot, 2017; Mattar & Sobreira, 2008; McDonald et al., 1995; Pizzato et al., 2014). Not only strength is affected before loss of ambulation. Boys with DMD also experience difficulties performing basic and complex UL activities, like getting dressed and reaching for objects (M. M. Janssen, Bergsma, Geurts, & de Groot, 2014).

In the last couple of years, there is a growing awareness of the importance of UL involvement in DMD. Nevertheless, most studies include boys older than five years of age and focus on the development of strength. There is still a lack of evidence concerning UL function and fine motor skills, especially in young boys with DMD. Therefore, this study aims to focus on UL function and fine motor skills in young DMD-patients between 0 and 6.5 years old.

Due to the proximal to distal progression of the disease, we hypothesize that the early proximal involvement could influence the more distal hand function and fine motor skills. To gain more and better insight in UL function and fine motor skills in infants and young boys with DMD, we investigated whether there is a difference in UL function and fine motor skills between boys with DMD and TD boys under the age of 6.5 years. These new insights could lead to early recognition of UL problems in boys with DMD, which in turn could lead to increased attention for UL function within the early disease management.

3 Methods

3.1 Participants

The sample of boys with DMD was recruited via the Neuromuscular Reference Centre (NMRC) of the University Hospital (UH) Leuven. Boys aged under 6.5 years, who were diagnosed with DMD by a (pediatric) neurologist were included in the DMD group. During their semi-annual consultation at the NMRC, information about the project was communicated to the parents. When interested, further information was given through an informed consent. A total of 18 boys were recruited between February 2018 and April 2021.

For each boy with DMD, two age matched TD boys were recruited from Flemish kindergartens and day-care centers. An informed consent was handed over to parents of eligible children. Boys with any neurological, cardiorespiratory, neuromuscular or musculoskeletal disorder were excluded from the control group. This resulted in a control group consisting of 35 TD boys. Data was collected from April 2019 to October 2020.

This study was approved by the ethical committee of UH/KU Leuven (reference number S59068 and S63340).

3.2 Procedure

Based on the age of the participants different assessments were administered. For the younger boys (0 - 3.5y) the Bayley-III was used. In the older boys (3.5y-6.5y) the PUL 2.0 was administered. For all participants (total group) the PDMS-II was administered.

The assessments of the DMD group were carried out by two experienced physical therapists. Assessments took place at the NMRC, UH Leuven or if necessary at the boys' home, day-care center or kindergarten. The TD group was assessed in kindergartens and day-care centers by five different assessors: four trained master's students under supervision of an experienced physical therapist.

The assessments lasted one to two hours depending on the age of the child and if necessary were divided over two different testing moments.

The Bayley Scales of Infant and Toddler Development, third edition (Bayley-III)

This scale measures the development of infants and toddlers aged 15 days to 42 months of age in five developmental domains: cognition, language (expressive and receptive communication), motor (fine and gross motor), social-emotional and adaptive behavior. This study focuses on the UL and fine motor skills. Therefore, only the scores on subdomain *"fine motor skills"* were used. This subdomain consists of 66 items, regarding visual tracking, reaching, object manipulation, grasping, quality of movement, functional hand skills and sensory integration. This scale is found reliable and valid (Bayley, 2006; Deroma et al., 2013).

Peabody Developmental Motor Scales, second edition (PDMS-II)

This scale measures the gross and fine motor skills of children aged zero to six years old. It consists of six subdomains: reflexes, stationary, locomotion, object manipulation, grasping and visual-motor integration of which the latter three were included in this study. The subdomain object manipulation consists of 24 items, regarding different ball skills. The subdomains grasping and visual-motor integration are part of the fine motor scales. Grasping consists of 26 items, regarding grasping, manipulating and holding different objects. Visual-motor integration consists of 72 items, such as building figures, cutting and folding paper. The PDMS-II is found reliable and valid (Folio et al., 2000).

Performance of Upper Limb Measure for DMD 2.0 (PUL 2.0)

The PUL 2.0 is specifically designed for the assessment of UL function of patients with DMD. It contains 23 items focusing on three different levels: high level, middle level and distal level. The high level assesses different movements of the shoulder, like shoulder abduction and flexion. The middle level contains items regarding movements of the elbow, like moving hands from their lap to a table and moving a weight on a table. The distal level includes movements of the wrist and hand, like picking up coins and tearing a sheet of paper. The scale is found reliable for ambulant and non-ambulant children with DMD (Mayhew et al., 2020).

3.3 Statistical analysis

Data analysis was carried out by two assessors using IBM SPSS Statistics (version 26) (de Vocht, 2016). For all analyses, a p-value of less than 0.05 was needed to reject the null hypothesis. If the data was normally distributed, checked by the Shapiro-Wilk test, the independent samples t-test was executed. If normality was not met, the Mann-Whitney U test was used.

For the total group and both the younger and older group, the ages of the DMD and TD boys were compared using an independent samples t-test.

For the Bayley-III and the PDMS-II, scaled and standard scores were analyzed. These scores were used as they have been adjusted and converted to a standardized scale taking the age of the boys into account.

Scaled scores of the Bayley-III fine motor skills were compared between younger DMD and TD boys (0 – 3.5y). The standard scores of the PDMS-II grasping, object manipulation and visual-motor integration subdomains were compared between DMD and TD boys for the total group and both the younger and older group (0 - 6y ; 0 – 3.5y ; 3.5y – 6.5y). As the PUL 2.0 is a disease specific assessment tool, only raw scores were available. The sub scores (high, middle and distal level) and the total score were analyzed for the older boys (3.5y – 6.5y).

When a statistical difference was found during analysis, individual score forms of the DMD boys were screened and compared in order to analyze whether there were mutual test items where the majority of boys had difficulties with.

4 Results

4.1 Participant characteristics

Table 1 shows the age of the DMD and TD boys for the total, younger and older group. The mean age of the total DMD group was 3.78y (SD ±1.63) and the mean age of the total TD group was 3.58y (SD ±1.57). There was no significant difference in age between the DMD and TD boys for the total, younger and older group (p=0.655, p=0.748, p=0.938).

Table 1

Participants age for total, younger and older group

	DMD			TD			p-value
	n	Mean *(SD)*	Range	n	Mean *(SD)*	Range	
Total group	18	3.78 *(±1.63)*	*0.97 – 6.46*	35	3.58 *(±1.57)*	*0.95 – 6.02*	0.655
Younger group	8	2.23 *(±0.63)*	*0.97 – 3.22*	19	2.33 *(±0.77)*	*0.95 – 3.38*	0.748
Older group	10	5.03 *(±0.92)*	*3.88 – 6.46*	16	5.06 *(±0.76)*	*3.97 – 6.02*	0.938

*p<0.05 ; n = number of participants ; SD = Standard deviation

4.2 Total group

For the PDMS-II grasping subdomain, the median standard score of the DMD group (8.00) was significantly lower compared to the median standard score of the TD group (10.00, p=0.002). A visualization of these results can be found in Fig. 1a.

For the PDMS-II object manipulation subdomain, the DMD group scored a mean standard score of 5.63, compared with a mean score of 9.97 in the TD group (p<0.001).

The mean standard score of the visual-motor integration subdomain of the PDMS-II in the DMD group was significantly lower than those of the TD group (p<0.001). More details can be found in Table 2. Fig. 1b shows the mean standard scores and standard deviations of PDMS-II object manipulation and visual-motor integration subdomains for the total DMD and total TD group.

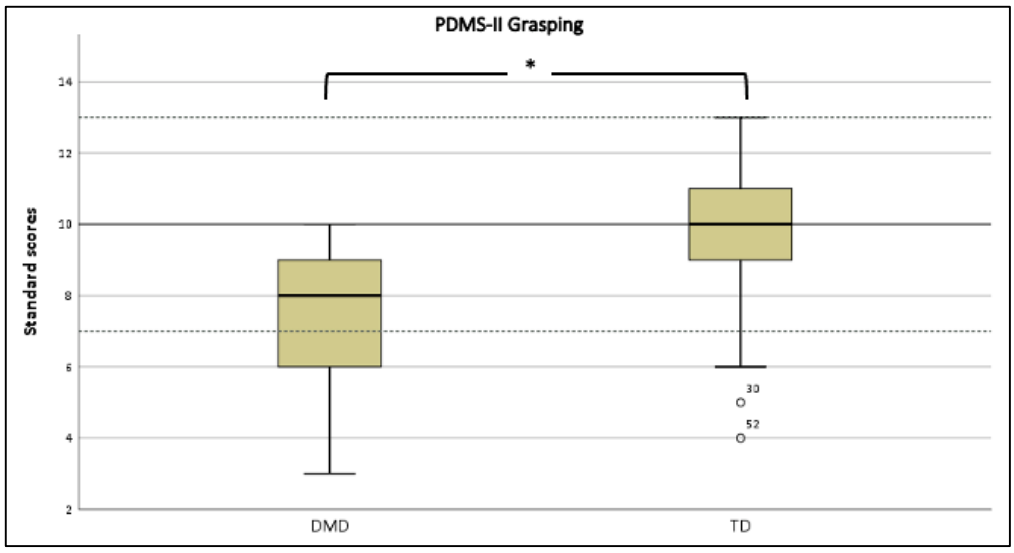

Fig. 1a. Box plots of median Standard Scores and Interquartile Range (IQR) of the PDMS-II Grasping from total DMD and TD groups *(*significant difference in median scores, dotted line = mean ±1 SD, bold line = mean)*

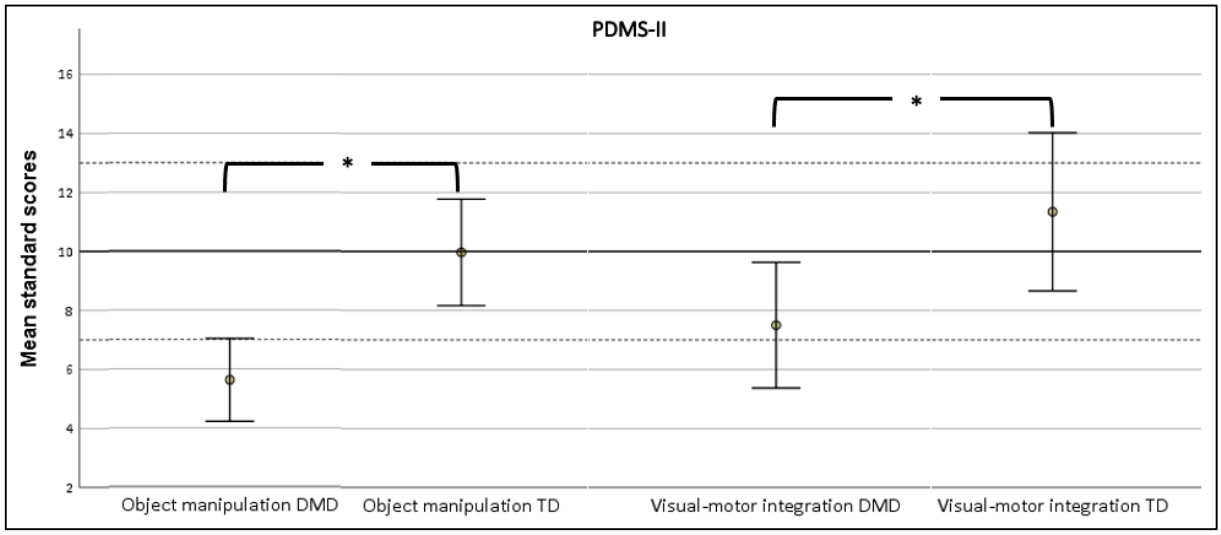

Fig. 1b. Mean Standard Scores and Standard Deviations of PDMS-II Object Manipulation and Visual-Motor Integration for total DMD and total TD group (**significant difference in mean scores, dotted line = mean ±1 SD, bold line = mean)*

Table 2
Results Total Group

Group	n (% of total)	Median SS *(IQR)*	Range	p-value	
PDMS-II Grasping[b]					
DMD	17/18 (94.4%)	8.00 *(4)*	3 – 10	0.002*	
TD	35/35 (100%)	10.00 *(2)*	4 – 13		
Group	**n (% of total)**	**Mean SS *(SD)***	**Range**	**p-value**	**95%CI**
PDMS-II Object Manipulation[a]					
DMD	16/18 (88.9%)	5.63 *(±1.41)*	2 - 8	<0.001*	[3.305 – 5.383]
TD	32/35 (91.4%)	9.97 *(±1.81)*	6 – 13		
PDMS-II Visual-Motor Integration[a]					
DMD	16/18 (88.9%)	7.50 *(±2.13)*	4 - 13	<0.001*	[2.313 – 5.373]
TD	35/35 (100%)	11.34 *(±2.68)*	7 - 17		

n = number of participants ; SS = Standard Scores ; CI = Confidence Interval
[a]parametric independent two sample t-test; [b]Non-parametric Mann-Whitney U test; *p<0.05

4.3 Younger group

The mean scaled score from the DMD group on Bayley-III fine motor skills was 4.75. This was significantly lower compared to a mean of 10.53 of the TD group (p<0.001). The boys with DMD showed problems on items concerning pencil grasp and drawing (e.g. drawing a horizontal/vertical line, square, …). They also experienced difficulties with building a tower with blocks.

For the subdomain grasping of the PDMS-II, no significant difference in standard scores was found between the young DMD (mean 8.63) and young TD boys (mean 9.32) (p=0.323). Both the object manipulation and the visual-motor integration subdomains showed a significant difference in standard scores between both groups (p<0.001, p=0.001). Boys with DMD had problems with items like throwing a tennis ball underhand (3ft) and catching a ball on the subdomain object manipulation. On subdomain visual-motor integration, they showed difficulties with items regarding cutting paper, building a tower of eight blocks and copying a vertical line. Details of the results can be found in Table 3.

Fig. 2 visualizes the mean standard scores and standard deviations of Bayley-III fine motor skills, PDMS-II grasping, object manipulation and visual-motor integration subdomains for the DMD and TD group aged 0 – 3.5y.

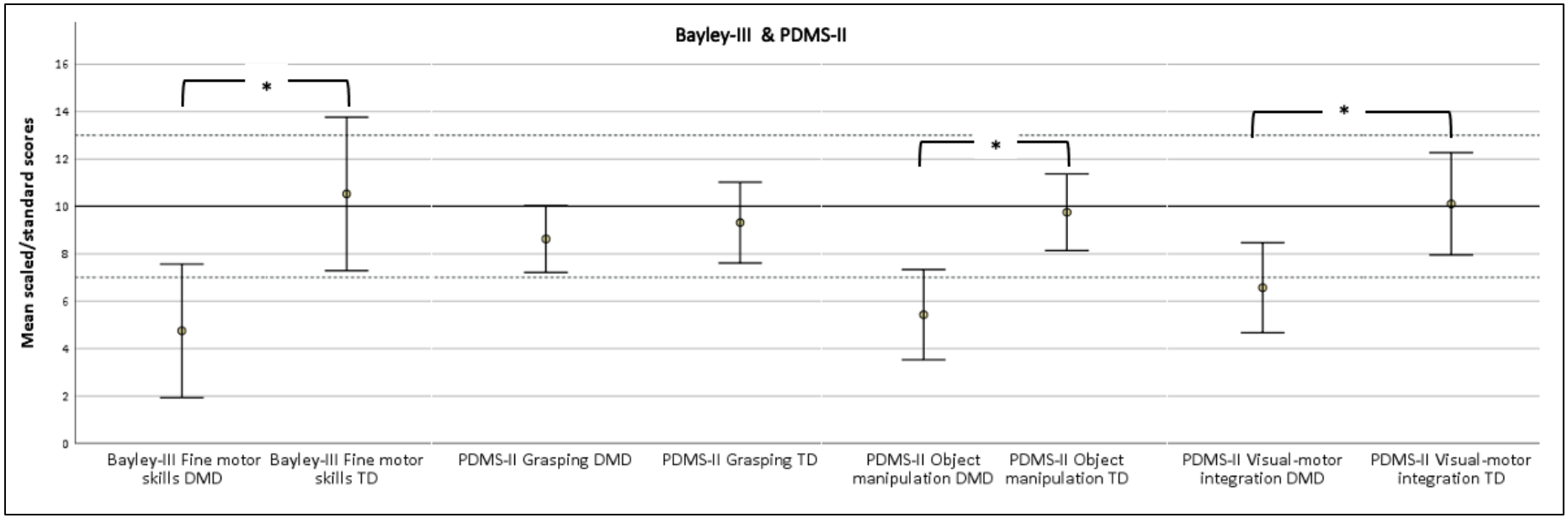

Fig. 2. Mean Standard Scores and Standard Deviations of Bayley-III Fine Motor Skills, PDMS-II Grasping, Object Manipulation and Visual-Motor Integration for DMD and TD group aged 0 – 3.5y (**significant difference in mean scores, dotted line = mean ±1 SD, bold line = mean*

Table 3
Results Younger Group

Group	n (% of total)	Mean SS *(SD)*	Range	p-value	95%CI
Bayley-III Fine Motor Skills[a]					
DMD	8/8 (100%)	4.75 *(±2.82)*	1 – 9	<0.001*	[-8.489 – -3.063]
TD	19/19 (100%)	10.53 *(±3.24)*	4 – 16		
PDMS-II Grasping[a]					
DMD	8/8 (100%)	8.63 *(±1.41)*	6 - 10	0.323	[-2.101 – 0.719]
TD	19/19 (100%)	9.32 *(±1.70)*	5 - 13		
PDMS-II Object Manipulation[a]					
DMD	7/8 (87.5%)	5.43 *(±1.90)*	2 – 8	<0.001*	[-5.924 – -2.719]
TD	16/19 (84.2%)	9.75 *(±1.61)*	7 – 13		
PDMS-II Visual-Motor Integration[a]					
DMD	7/8 (87.5%)	6.57 *(±1.90)*	4 – 9	0.001*	[-5.447 – -1.621]
TD	19/19 (100%)	10.11 *(±2.16)*	7 – 15		

n = number of participants ; SS = Scaled/Standard Scores ; CI = Confidence Interval ;
[a]parametric independent two sample t-test ; *p<0.05

4.4 Older group

The median total score of the PUL 2.0 of the DMD boys (37.00) was significantly lower compared to the TD boys (p=0.001). Nearly all TD boys scored a maximum score of 42 on this test. When analyzing the three levels separately, a significant difference was found between both groups on high, middle and distal level (p=0.001, p=0.005, p=0.005). This is visualized in Fig. 3. For the item scores of the high level, boys with DMD showed problems with executing anteflexion of the shoulder with weight (500g). On the middle level, lower scores were found on the items moving a weight (1kg) on a table and stacking five cans. Distally, the boys with DMD had problems with tearing a paper and tracing a path with a pencil.

Fig. 4a shows the box plots of the PDMS-II grasping subdomain. The median standard score of the DMD group was 7.00 which was significantly lower compared to the median standard score of 10.00 of the TD group (p=0.002). The DMD group experienced difficulties with several items (e.g. grasping a marker, (un)buttoning a button and touching each finger to thumb).

On the PDMS-II object manipulation subdomain, the boys with DMD scored a mean standard score of 5.78 versus 10.19 for the TD boys (p<0.001). The boys with DMD showed difficulties with throwing a ball over and underhand (10ft.), hitting a target by tossing a tennis ball over and underhand, bouncing a tennis ball to a wall and catching a tennis ball with only their hands.

The mean standard score of the PDMS-II visual-motor integration subdomain of the DMD group was significantly lower compared to the TD group (p<0.001).

The boys with DMD appeared to have difficulties with the following items: copying a cross/square, cutting a circle/square, connecting dots, folding a paper and coloring between the lines. Details of these results can be found in Table 4.

Fig. 4b shows the mean standard scores and standard deviations of PDMS-II object manipulation and visual-motor integration subdomains for the DMD and TD group aged 3.5y – 6y.

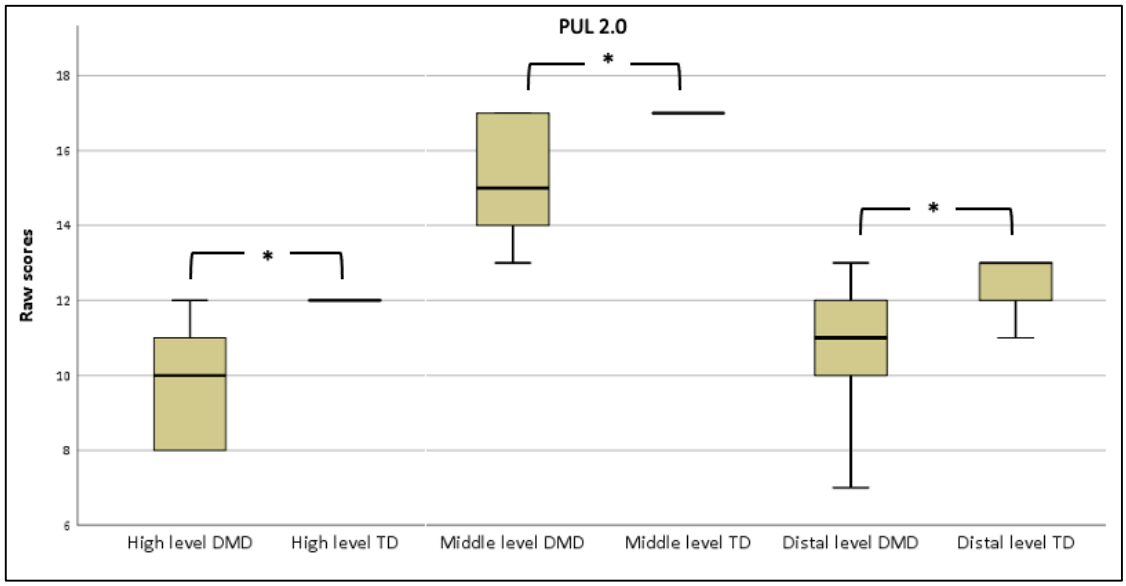

Fig. 3. Box plots of median Raw Scores and Interquartile Range (IQR) of the PUL 2.0 high, middle and distal level from DMD and TD groups aged 3.5y – 6.5y *(*significant difference in median scores)*

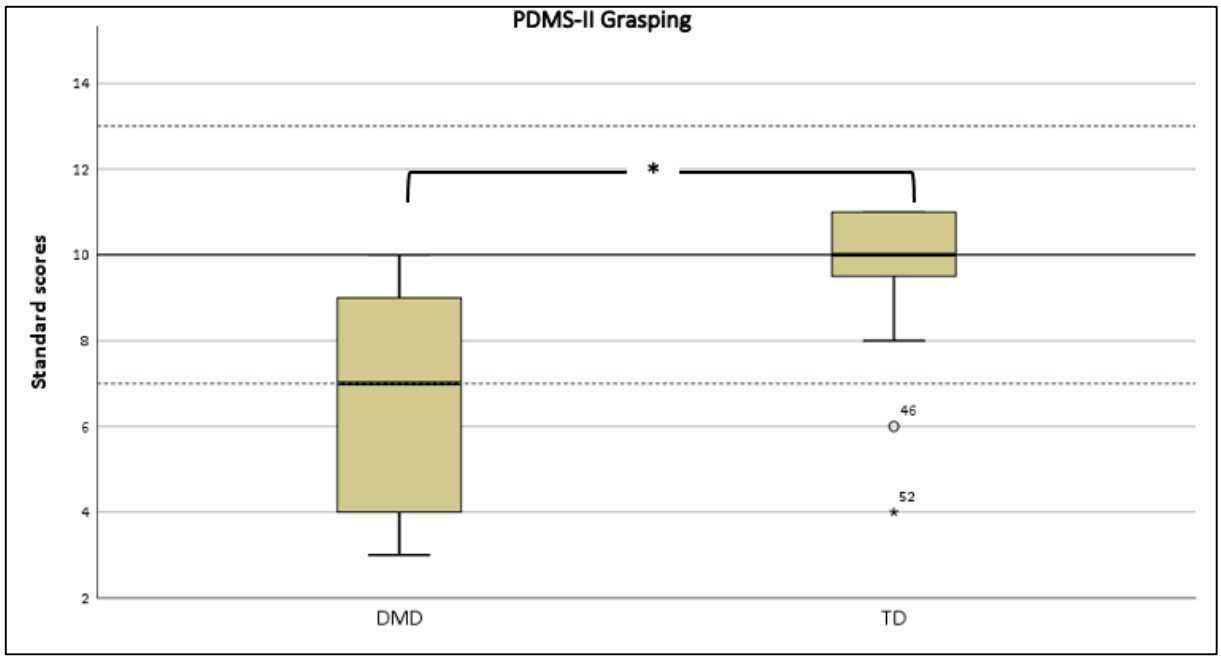

Fig. 4a. Box plots of median Standard Scores and Interquartile Range (IQR) of the PDMS-II Grasping from DMD and TD groups aged 3.5y – 6y *(* significant difference in median scores, dotted line = mean ±1 SD, bold line = mean)*

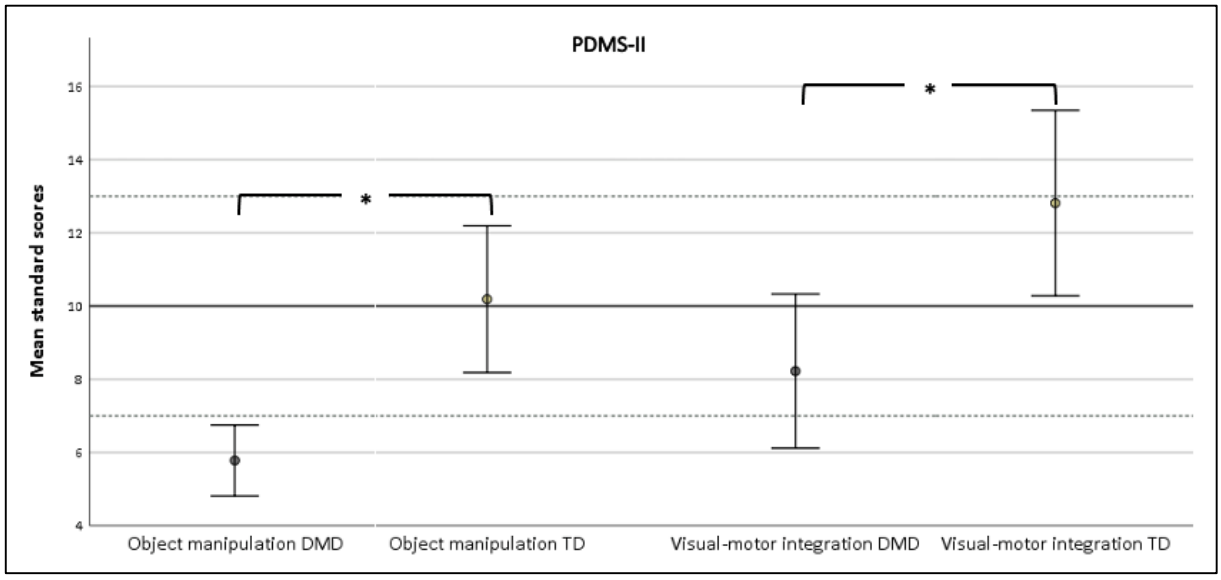

Fig. 4b. Mean Standard Scores and Standard Deviations of PDMS-II Object Manipulation and Visual-Motor Integration for DMD and TD groups aged 3.5y – 6y *(*significant difference in mean scores, dotted line = mean ±1 SD, bold line = mean)*

Table 4

Results Older Group

Group	n (% of total)	Median *(IQR)*	Range	p-value
PUL 2.0 Total[b]				
DMD	9/10 (90%)	37.00 *(8)*[1]	28 – 42	0.001*
TD	15/16 (93.8%)	42.00 *(1)*[1]	40 – 42	
PUL 2.0 High Level[b]				
DMD	9/10 (90%)	10.00 *(4)*[1]	8 – 12	0.001*
TD	15/16 (93.8%)	12.00 *(0)*[1]	12 – 12	
PUL 2.0 Middle Level[b]				
DMD	9/10 (90%)	15.00 *(3)*[1]	13 – 17	0.005*
TD	15/16 (93.8%)	17.00 *(0)*[1]	17 – 17	
PUL 2.0 Distal Level[b]				
DMD	9/10 (90%)	11.00 *(3)*[1]	7 – 13	0.005*
TD	15/16 (93.8%)	13.00 *(1)*[1]	11 – 13	
PDMS-II Grasping[b]				
DMD	9/10 (90%)	7.00 *(5)*[2]	3 – 10	0.002*
TD	16/16 (100%)	10.00 *(2)*[2]	4 – 11	
Group	**n (% of total)**	**Mean SS *(SD)***	**Range**	**p-value**	**95%CI**
PDMS-II Object Manipulation[a]					
DMD	9/10 (90%)	5.78 *(±0.97)*	4 – 7	<0.001*	[-5.646 – -3.173]
TD	16/16 (100%)	10.19 *(±2.01)*	6 – 13		
PDMS-II Visual-Motor Integration[a]					
DMD	9/10 (90%)	8.22 *(±2.11)*	6 – 13	<0.001*	[-6.655 – -2.525]
TD	16/16 (100%)	12.81 *(±2.54)*	7 – 17		

n = number of participants ; SS = Standard Scores ; CI = Confidence Interval

[a]parametric independent two sample t-test; [b]Non-parametric Mann-Whitney U test; * p<0.05

[1]Raw Score ; [2]Standard Score

5 Discussion

UL function and fine motor skills are important for the execution of school skills and activities of daily living. The ability to sufficiently perform these activities are important to be self-reliant (e.g. feed themselves). Since there is little evidence concerning UL function and fine motor skills of young boys with DMD under the age of six, this study aimed to partially close this gap. We investigated whether there is already a difference in UL function and fine motor skills between TD boys and boys with DMD aged zero to 6.5 years old. We also aimed to gain more insight in these differences (i.e. specific items/subdomains).

The results of the total group showed a difference in UL function for all three investigated PDMS-II subdomains. These results had the biggest statistical power, because data of all the participants (except one) could be analyzed. To gain further insight in when these differences occurred, and what these differences were, the younger and older groups were analyzed.

In the younger group (0 - 3.5y), our results did show a significant difference in PDMS-II object manipulation and visual-motor integration subdomains. Also, the Bayley-III fine motor skills scaled scores were significantly different between younger TD boys and boys with DMD. This last finding is in line with Connolly et al. (2013). They found low mean fine motor function scaled scores (7.9) compared to normative values (p=0.001). This was found in boys with DMD with a mean age of 1.9y (±0.7y). Our sample of young boys with DMD (mean age 2.23y) scored a lower mean scaled score (4.75) in comparison with Connolly et al. (2013).

In contrast to the other results of the younger group regarding fine motor skills (Bayley-III fine motor skills and PDMS-II visual-motor integration), the PDMS-II grasping subdomain did not show a significant difference. This could indicate that younger children with DMD do not have problems with fine motor skills. The discrepancy in our findings could be explained by the fact that fine motor skills can be divided into two types of skills. The pure fine motor skills like picking up food pellets and the more complex fine motor skills such as pen and paper tasks and building a tower with blocks. The Bayley-III fine motor skills contains both pure and complex fine motor skills in contrast to the PDMS-II, where these skills are separately assessed in the grasping (pure fine motor skills) and visual-motor integration (complex fine motor skills) subdomains. During analysis of the different test items, younger boys with DMD seemed to score relatively well on the pure fine motor items like picking up and inserting coins into a notch. They experienced more problems with more complex items, such as pencil grasps and drawing a horizontal/vertical line.

A possible explanation for the lower scores on the more complex fine motor skills could be that these skills require more cognitive processing. Cotton, Voudouris, and Greenwood (2001) found that boys with DMD scored one standard deviation below the normal IQ of TD children. This could be due to the lack of dystrophin protein in the brain, which could have an impact on the organization of various brain structures (e.g. neocortex) (Muntoni et al., 2003). Nevertheless, Wingeier et al. (2011) found a broad range of cognitive abilities in boys with DMD. This means that in some cases, the cognitive abilities could partially explain the lower scores on pen and paper tasks.

In the older group (3.5y - 6.5y), all scores regarding fine motor skills (PDMS-II grasping and visual-motor integration) of the boys with DMD were significantly lower than those of the TD group. When looking at the test items, similar findings were found as in the younger group.

Namely that the boys with DMD perceived more difficulties with the more complex fine motor items, such as cutting a circle/square.

The older boys also experienced problems with the more gross motor UL items of the PUL 2.0 and the PDMS-II object manipulation subdomain. Items regarding different ball skills and lifting a weight through anteflexion of the shoulder were found to be difficult. To execute these items sufficient, UL strength is necessary. McDonald et al. (1995) found that there is a strong annual decline in UL strength starting from the age of five in boys with DMD. A lack of strength could have influenced the performance on these gross motor UL items. Nevertheless, no literature is available regarding UL strength in boys with DMD under the age of five.

Besides strength, trunk control is also important. Bulut, Alemdaroğlu-Gürbüz, Topaloğlu, Yılmaz, and Karaduman (2020) found a moderate to high correlation between trunk control and UL function in boys with DMD. They found that boys with a better trunk control scored higher on the PUL 1.2. These findings are in line with Santos, Maciel, Fávero, Grossklauss, and de Sá (2021). They also observed worse trunk control in ambulant boys with DMD with a mean age of ten (SD ±3.5y) compared to TD boys. Nevertheless, following Sá, Fagundes, Araújo, Oliveira, and Fávero (2016) boys at the same disease stage could have different levels of trunk control. Trunk control could also influence the performance on the ball skills items of the PDMS-II object manipulation subdomain. Since ball skills are performed in a standing position, impairments present in the lower limbs and trunk could also influence the performance on these items.

Our hypothesis was that due to the proximal to distal progression of the disease, early involvement of the shoulder could negatively impact the more distal hand function, resulting in an early difference in UL function and fine motor skills between TD and DMD boys.

This hypothesis could partially be confirmed by our findings. We found that boys with DMD from the age of 3.5y showed difficulties on the high level of the PUL 2.0 which could indicate early involvement of the shoulder. However, boys with DMD also showed difficulties on the PUL 2.0 distal level. They experienced problems with similar test items as in the PDMS-II, namely pen and paper tasks. Nevertheless, from the findings of this study no conclusions can be made whether early shoulder involvement has an impact on the hand function because no correlations between shoulder function and fine motor skills of the DMD boys were investigated.

5.1 Strengths and limitations

This study has its strengths and limitations. One of the strengths is that all assessments were administered by or under supervision of a skilled assessor. Moreover, all assessment scales used were found valid and reliable (Bayley, 2006; Deroma et al., 2013; Folio et al., 2000; Mayhey et al., 2020). Furthermore, this study recruited its own age-matched control group of Flemish TD boys. This positively influenced the comparability of the DMD and TD group (e.g. similar socio-cultural environment). This also ensured a uniform comparison between both groups instead of a different norm group for each test.

One of the limitations of this study was the small sample size of boys with DMD (n=18), in combination with missing values in the statistical analysis. This could negatively influence the generalizability of this study. In order to enlarge the sample size, and consequently the generalizability, an international, multi-center study is needed. Missing values were present when assessment was not possible (i.e. participant too tired/old for test). Another limitation was that strength measurements were not included in the assessments. Literature suggests that before the age of 10, UL strength in boys with DMD is lower compared to TD children (M. Janssen et al., 2017; Mattar & Sobreira, 2008; McDonald et al., 1995; Pizzato et al., 2014). This could indicate that UL strength was a possible confounder which was not taken into account in the statistical analysis. However, strength measurements are difficult to perform and less reliable in children under the age of five (Tecklin, 2015). Other confounders could be the influence of cognition on fine motor skills, the influence of the mutation location on motor performance and the fact that PDMS-II object manipulation subdomain contains five lower limb items (e.g. kicking a ball).

5.2 Recommendations for future research

In order to increase the insight in UL function and fine motor skills in young boys with DMD, longitudinal studies with larger sample sizes are needed. Possible further research subjects could be:

- The long term influence of an early UL intervention in boys with DMD.
- The influence of cognition on fine motor skills in boys with DMD.
- Comparison of UL strength between boys with DMD and TD boys aged zero to five years old.

6 Conclusion

Up till now, there has been little attention for UL function and fine motor skills in young boys with DMD (<6.5y). The majority of publications focused on the assessment and treatment of lower limb functions and walking. This study showed that there is already a clear difference in UL function and fine motor skills between young boys with DMD and TD boys. This difference is present even before there is known to be loss of strength in the upper extremities (from the age of five). Boys with DMD mainly experienced problems with more complex fine motor skills like pen and paper tasks. To execute these skills, not only motor skills are important, but also cognitive abilities and trunk control could play an important role.

The new insights of this study emphasize the importance of increased awareness for UL function and fine motor skills from parents and physical/occupational therapists, even in the early stages of the disease. Future research with a larger sample size is necessary.

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8 Appendices

8.1 Inschrijvingsformulier

Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - *INFORMATION STUDENT*

Faculteit/School: **Faculteit Revalidatiewetenschappen**
Faculty/School: ***Rehabilitation Sciences***

Stamnummer + naam: **1642756 Caeyers Pieter**
Student number + name

Opleiding/*Programme*: **2 ma revalid. & kine kinderen**

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PART A - MANDATORY - TO BE FILLED OUT BY THE STUDENT

Titel van Masterproef/*Title of Master's thesis:* EARLY UPPER LIMB INVOLVEMENT IN BOYS WITH DUCHENNE MUSCULAR DYSTROPHY AGED UNDER 6.5 YEARS: A CROSS SECTIONAL STUDY

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○ wijzigen - *change to*:

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In geval van samenwerking tussen studenten, naam van de medestudent(en)/*In case of group work, name of fellow student(s)*: VAN HOOF MARTHE

● behouden - *keep*

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PART B - MANDATORY - TO BE FILLED OUT BY THE SUPERVISOR(S)

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De promotor(en) geeft (geven) de student(en) het niet-bindend advies om de bovenvermelde masterproef in de bovenvermelde periode/*The supervisor(s) give(s) the student(s) the non-binding advice:*

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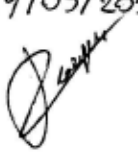
Datum en handtekening student(en)
Date and signature student(s)

24/05/2021



Datum en handtekening promotor(en)
Date and signature supervisor(s)

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Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

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O wijzigen - *change to*:

In geval van samenwerking tussen studenten, naam van de medestudent(en)/*In case of group work, name of fellow student(s)*: CAEYERS PIETER

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O wijzigen - *change to:*

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Wijziging gegevens masterproef in luik A/*Change information Master's thesis in part A:*

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O goedgekeurd mits wijziging van - *approved if modification of:*

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PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)
Date and signature student(s)

24/5/2021

Datum en handtekening promotor(en)
Date and signature supervisor(s)

27/05/2021

8.2 Mail advies promotor

Katrijn KLINGELS do 27 mei 18:11
aan Pieter, Jasmine, mij

Beste Pieter en Marthe,
Proficiat met het afwerken van jullie MP!
In bijlage vinden jullie de documenten.
Met vriendelijke groeten,
Katrijn Klingels

Prof.dr. Katrijn Klingels

Tenure track professor

Pediatrische Revalidatie - Faculteit Revalidatiewetenschappen

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8.3 Inventarisatieformulier

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01/10/2020	Bespreking aanpak masterproef deel 2	Promotor: online Copromotor/Begeleider: Student(e): Student(e):
13/10/2020	Bekijken data	Promotor: online Copromotor/Begeleider: Student(e): Student(e):
23/02/2021	Bespreken vragen	Promotor: online Copromotor/Begeleider: Student(e): Student(e):
15/04/2021	Bespreken methode	Promotor: online Copromotor/Begeleider: Student(e): Student(e):
11/05/2021	Bespreken resultaten	Promotor: online Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
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