How do fine and gross motor skills develop in preschool boys with Duchenne Muscular Dystrophy?

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How do fine and gross motor skills develop in preschool boys with Duchenne Muscular Dystrophy?

Highlights:

- Boys with DMD experience both fine and gross motor problems yet at preschool age
- Preschool boys with DMD do not achieve the same functioning motor level as TD boys
- Evolution of motor skills differs between different motor subdomains
- Cognitive development plays a role in fine and gross motor development

ABSTRACT

Background: Boys with Duchenne Muscular Dystrophy (DMD) experience both fine and gross motor problems. Nowadays, early intervention focuses almost exclusively on gross motor skills.

Aims: We aimed to explore early motor development in preschool boys with DMD and investigate the influence of cognition.

Methods and Procedures: Seventeen boys with DMD (11 months- 6 years) were compared to typically developing (TD) peers and followed-up with the Bayley Scales of Infant and Toddler Development (Bayley-III); Peabody developmental motor scales (PDMS-II) and Motor Function Measure (MFM-20). The longitudinal evolution of fine and gross motor skills was investigated using linear mixed effect models (LMM). Cognition was added to the LMM as a covariate.

Outcomes and Results: Preschool boys with DMD scored lower compared to TD peers on both fine and gross motor skills ($p<0.001$). The evolution of motor development was subscale-dependent. A significant influence of cognition was found on different subscales ($p= 0.002$-0.04).

Conclusions and Implications: Preschool boys with DMD do not achieve the same functioning level as TD boys. Cognition plays a crucial role in the evolution of motor skills. Our results suggest a shift to a broader psychomotor approach including both fine and gross motor skills, also considering the impact of cognition.

Keywords:

Duchenne muscular Dystrophy (DMD), early development, motor skills, fine motor, gross motor, cognition, preschool children

1. INTRODUCTION

The main characteristic of Duchenne Muscular Dystrophy (DMD) is progressive loss of muscle function, which proceeds from proximal to distal limb muscles (Hoffman, Brown, & Kunkel, 1987). In addition to motor problems, DMD is also characterized by delay in cognitive and/or language development and/or adaptive behavioral problems, probably caused by the effect of loss of *dystrophin* protein expression in the brain (Connolly et al., 2013; Cyrulnik et al., 2008).

DMD is already present in early childhood. A delay in gross motor milestones (e.g. crawling, independent walking) is often one of the first symptoms (Norcia, Lucibello, Coratti, Onesimo, & Pede, 2021; van Dommelen, van Dijk, de Wilde, & Verkerk, 2020). Still, a positive evolution in motor skills is seen up until the age of seven (Bushby, Hill, & Steele, 1999; Ciafaloni et al., 2009; Connolly et al., 2014; Coratti et al., 2019; Mazzone et al., 2011). This phase is called the "honeymoon" period. However, young boys with DMD seem not to achieve the same functioning level compared to typically developing (TD) boys (De Sanctis et al., 2015; Henricson et al., 2012; van Dommelen et al., 2020). Longitudinal studies on early gross motor development in DMD are still scarce and use different outcome measures (Connolly et al., 2014; Coratti et al., 2019; Mazzone et al., 2011; Pane et al., 2014). Heterogeneity in outcome measures impairs comparison of results between studies. Most longitudinal studies include "older" boys of >5 years. Moreover, clinical interventional studies have mostly focused on boys >6 years of age. Nowadays, there is a demand for trials in young children to target the disease process at a time when the muscle is still in good condition. Further insights into early gross motor development will be essential for the evaluation process of those trials.

Next to gross motor problems, young boys with DMD also experience fine motor problems and show delays in fine motor milestones (e.g. pincer grasp, drawing) (Connolly et al., 2014, 2013; van Dommelen et al., 2020). However, fine motor skills seem to improve more compared to gross motor skills in infants and young boys with DMD (Connolly et al., 2014; van Dommelen et al., 2020). Little literature exists on the early development of fine motor skills in infants and young boys with DMD.

Prior research also indicated that young DMD boys may show cognitive delays (Connolly et al., 2013; Cyrulnik et al., 2008), which might impact motor development. In TD a link has been found between cognition and motor development, mainly between cognition and fine motor development (Davis, Pitchford, & Limback, 2011). However, in DMD the level of cognitive development also seems to affect gross motor milestones (Mirski & Crawford, 2014; van Dommelen et al., 2020). The influence of cognition on fine and gross motor development of young boys with DMD has not yet thoroughly been investigated. Moreover, the underlying causes of the global developmental delays seen in boys with DMD have not yet been fully elucidated. Type and site of mutation in the *dystrophin* gene, which impacts on the expression of *dystrophin* brain isoforms, seem to exert an influence on early development of young boys with DMD. For instance, boys with mutations downstream of *exon* 44 seem to have a

lower developmental quotient (DQ) compared with boys with other mutations (Chieffo et al., 2015; Pane et al., 2013; Thangarajh et al., 2019). A DQ is used to indicate an infant's growth to maturity across different developmental domains, such as motor and cognitive development.

Overall, the lack of data on early development on one hand and on consistent outcome measures on the other hand, are important barriers to therapy development in young DMD. This study aims to generate more insight in early motor development that might help in optimizing early intervention strategies and clinical trial design in this age group. The objectives of this study were: 1) to compare early fine and gross motor development between infants and young boys with DMD and TD peers; 2) to investigate the evolution of the early fine and gross motor development in young boys with DMD between 0 and 6 years old; 3) to investigate the influence of cognition on early motor development in infants and young boys with DMD.

2. MATERIALS AND METHODS

2.1. Participants

Infants and young boys diagnosed with DMD, aged between 0 and 6 years were recruited from the Neuromuscular Reference Centre (NMRC) of the University Hospitals Leuven. The inclusion criteria were 1) genetically diagnosed DMD; 2) willing and able to participate in the study.

The assessments took place during their half-yearly clinic visit at the NMRC. A second appointment was made if the assessments were not completed due to lack of time, or concentration and/or cooperation problems of the child during the clinic visit. The extra assessments were performed at the child's home, daycare, or nursery school.

A TD control group was recruited via different daycare centers or nursery schools. The TD group was used as a reference for the motor assessments in the cross-sectional study. Boys with any neurological, cardiorespiratory, neuromuscular or musculoskeletal disorder were excluded.

Written informed consent was obtained from the parents or legal guardians of the children participating in this study. The study was approved by the Ethics Committee Research UZ/KU Leuven (S59068).

2.2 Study design and assessments

The study was a single centre, so-called mixed cross-sectional and longitudinal study, evaluating the difference in motor performance between infants and young boys with DMD and TD peers at baseline, and the longitudinal evolution of motor skills in the DMD group. Depending on the age of the child, different evaluations were performed (Table 1). All TD boys were only evaluated once. All infants and young boys with DMD were evaluated at baseline and followed-up every 6 months if possible. First, feasibility of the Bayley-III was investigated in 5 infants with DMD. These pre-baseline measurements were also included in the analyses. As all infants and young boys with DMD below the age of 6 known in the NMRC were invited to participate in the study, this resulted in different baseline ages of the

participants. Some of them were already reaching the age limit at baseline, which hampered further follow-up. Also, Covid-19 influenced the follow-up period, resulting in missed follow-ups and deviations in time intervals between measurements. Taken together, this created an unbalanced data set with different numbers of evaluations per subject, missing data and variable time intervals.
The motor assessments were conducted by an experienced physiotherapist with certification on the Bayley-III, while the psychological testing was performed by a clinical psychologist of the NMRC.

Height and weight of each participant was obtained and information regarding therapy/medication and the site of mutation of the boys with DMD was abstracted from the medical records. A distinction was made between mutations downstream of *exon 44* and mutations upstream of *exon 44*, because of the clinical differences in DQ seen between these two groups (Chieffo et al., 2015; Pane et al., 2013; Thangarajh et al., 2019).

Table 1. Outcome measures per age

Age (years)	**0**	**1**	**2**	**3**	**4**	**5**
Fine motor skills	Bayley-III fine motor scale					
	PDMS-II grasping and VMI					
Gross motor skills	Bayley-III gross motor scale					
	PDMS-II stationary, locomotion and object manipulation					
			MFM-20			
Cognition	Bayley-III cognition scale					
					WPPSI-III	

Bayley-III: Bayley Scales of Infant and Toddler Development, third edition; PDMS-II: Peabody Developmental Motor Scales, second edition; MFM-20: Motor Function Measure; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence, third edition

2.2.1 Outcome measures

Age-appropriate outcome measures were used to investigate fine and gross motor development and to determine the baseline cognitive level (Table 1).

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

The Bayley-III is an instrument assessing development of infants and young children between 16 days and 42 months (Bayley N, 2006). This test consists of five distinct scales: cognition; language: receptive and expressive; motor skills: fine and gross; social-emotional skills and adaptive behaviour. Raw scores are converted to scaled scores (mean=10; SD=3) and index scores (mean=100; SD=15). The Bayley-III

is valid and reliable (Bayley, 2006; Deroma et al., 2013; Van Baar, Steenis, Verhoeven, & Hessen, 2014).

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

The PDMS-II assesses gross and fine motor abilities from birth through 6 years of age. The gross motor domain contains four subscales: reflexes (up to 11 months), stationary, locomotion and object-manipulation. The fine motor domain contains two subscales: grasping and visual-motor integration. Raw scores are converted to standard scores (mean=10; SD=3) per domain and a fine, gross and total motor quotient (mean=100; SD=15) can be calculated. The PDMS-II has been found valid and reliable (Chien & Bond, 2009; Tavasoli, Azimi, & Montazari, 2004).

Motor Function Measurement for Neuromuscular diseases (<7 years old) (MFM-20)

The MFM-20 is a quantitative evaluation scale that measures functional motor abilities in persons with neuromuscular diseases between two and seven years of age. The scale is divided into three functional domains: standing and transfers; axial and proximal motor function; and distal motor function. The raw scores are expressed as a percentage in relation to the maximum score. Sub scores for each domain and a total score can be calculated. The MFM-20 has been shown to be reliable and valid in young children with neuromuscular diseases (De Lattre et al., 2013).

Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III-NL)

The WPPSI-III is a norm-referenced test designed to evaluate cognitive ability and can be used in children starting from the age of 2 years 6 months. Children have to complete 7 core subscales: information, vocabulary, word reasoning, block design, matrix reasoning, picture concepts and coding. Reliability and validity are proven by different studies. A total, verbal and performance IQ can be calculated (mean=100; SD=15). Reliability and validity is proven by different studies (*Community-University Partnership for Study of Children, Youth, and Families. Review of the Wechsler Preschool and Primary Scale of Intelligence- third editon (Canadian) 2011*, 2011; Wechsler, 2002).

2.3. Data analyses

Descriptive statistics were used to document general and clinical characteristics (age, height, weight, baseline cognition, mutation site,…) of the boys with DMD and TD control group. Data distribution was checked by the Shapiro-Wilk and visual inspection of the data. Parametric test statistics were applied since almost all data were normally distributed.

To compare baseline characteristics and the different motor outcomes between both groups, independent t-tests were used.

The longitudinal evolution of fine and gross motor skills in young boys with DMD was investigated using linear mixed effect models (LMM). These methods were required to accommodate the unbalanced

dataset and the correlation between the repeated measurements by modelling the variance both between and within the participants. The motor scores were defined as the responses. In the mean structure, the time course of the measurements within the participants (i.e., longitudinal effect) and the age at the first assessment (i.e., cross-sectional effect of increasing baseline age) were defined as fixed effects. Depending on their relationship with the responses, higher-order terms were added in the LMM (e.g. baseline age squared, if a quadratic relationship was seen). Subsequently, the longitudinal effect might also depend on the baseline age, so the interaction between time and baseline age (Time x Baseline age) was also included as fixed effect in the LMM. To model the variability among the boys with DMD, random effects consisting of a random intercept (to model the variability in starting value) and a random slope (to model the variability in progression rate) for the time effect were added in the LMM.

The workflow as also described by Vandekerckhove et al. was used to build the LMMs.(Vandekerckhove, Hauwe, & Beukelaer, 2022; Verbeke & Molenaers, 2000; Verbeke & Molenberghs, 1997) First, Loess regressions were performed to explore the mean structure. Second, the random-effect structure was defined by inspecting the individual observed profiles and the observed variance function (i.e., change in squared residuals calculated from the Loess regressions over time) as well as performing an informal analysis to check if the observed profiles could be well-explained by a specific linear regression function. Third, a formal test was performed to determine if the random-effect structure could be reduced. A likelihood ratio test compared a model with a random intercept (i.e., assuming constant variance) to a model with random intercept and slope (i.e., allowing the variance to change over time). Lastly, a reduction of the mean structure was investigated by performing F tests. After building the LMM, empirical Bayes estimates were calculated to determine outliers and influential factors.

All motor scores can be defined as responses as followed:

$$Responses_{ij} = \beta_0 + \beta_1 \times Time + \beta_2 \times Bas\_age + \beta_3 \times Bas\_age^2 + \beta_4 \times Bas\_age \times Time + \beta_5 \times Bas\_age^2 \times Time + b_{1i} + b_{2i} \times Time + \varepsilon_{ij}$$

With β_0= intercept; β_1 = regression coefficients for Time; $\beta_{2\ and\ 3}$ = regression coefficients for Bas_age and Bas_age^2; $\beta_{4\ and\ 5}$ = regression coefficients for the interaction effects between Bas_age and Time; b_{1i} = random intercept; b_{2i} = random slope for time and ε_{ij} = measurement error.

Both Time and Bas_age were expressed in years.

In the end, we investigated the influence of cognition on the evolution of the different motor scores by adding it to the LMM as a covariate.

All statistical analyses were performed using SAS ®, version 9.4 and/or IBM SPSS Statistics 28.

3. RESULTS

3.1. Study participants

A total of 17 boys with DMD and 17 TD control boys were included in the study. The mean age was 3 years 8 months (± 1 year 6 months) with a range between 11 months and 6 years in both groups. The mean height and weight were respectively 98.22 cm (±11.37 cm) and 15.73 kg (±4.45 kg) for the DMD group and 104 cm (±14.26 cm) and 16.23 kg (±4.08 kg) for the control group.

In the DMD group 11 boys had a mutation upstream of *exon* 44 and 6 boys had a mutation downstream of *exon* 44. Mean baseline cognition score (based on the Bayley-III or WPPSI-III) was 85.13 (± 13.53), about 1 SD below the average mean. Cognition scores were missing for two boys, because of the influence of native language on the WPPSI-III scores. The total number of evaluations was 46, with mean number of evaluations per boy of 3 (range: 1-5).

Eleven boys with DMD received corticosteroids or participated in a clinical trial by the end of this study. The mean age of initiating medical therapy was 4 years 7 months. Twelve of them received physical therapy, with a focus on gross motor skills, the mean starting age was 3 years 7 months. Individual characteristics and number of assessments of the boys with DMD are summarised in Appendix A.

3.2. Baseline comparison DMD-TD

No significant differences were found between both groups regarding age, height and weight ($p=0.20$-0.99). Infants and young boys with DMD scored significantly lower on the Bayley-III Fine Motor (FM) and Gross Motor (GM) scale ($p<0.001$). The mean Bayley-III FM scale scores (SS) of the boys with DMD was 5.18 (±2.40), between 1 and 2 SD below the expected mean of 10 (SD=3) and mean Bayley-III GM SS was 3.91 (±1.51), more than 2 SD below the expected mean. The TD boys received average mean SS on both scales (Table 2). The Bayley-III Total Motor (TM) Index Score (IS) was also significantly lower in infants and young boys with DMD (67.27, more than 2 SD below the expected mean of 100 (SD=15)).

The same findings were seen regarding the PDMS-II, namely significantly lower scores on all domains in the DMD group with a mean Fine Motor Quotient (FMQ) of 84.47 (±7.67) and a mean Gross Motor Quotient (GMQ) of 71.65 (±5.82), respectively around 1 and 2 SD below the expected mean, resulting in a mean Total Motor Quotient (TMQ) of 74.71 (±5.81), almost 2 SD below the expected mean of 100 (SD=15). Again, as expected, average mean scores were found in the TD group. An overview of all mean subscale scores for both groups and between group test statistics can be found in Table 2.

Also, the percentage of the total MFM scores were significantly lower in the DMD group (85.52% ±7.45) compared to the TD group (96.56% ±5.43) ($p<0.001$).

Table 2. Between group comparisons at baseline

	Expected Mean (SD)	Number	DMD Mean (SD)	TD Mean (SD)	p-value
Age		17	3y 8mo (18mo)	3y 8mo (18mo)	0.99
Height		17	98.22 (11.37)	104 (14.26)	0.20
Weight		17	15.73 (4.45)	16.23 (4.08)	0.73
Bayley-III FM SS	10 (3)	11	5.18 (2.40)	11.64 (2.73)	<0.001
Bayley-III GM SS	10 (3)	11	3.91 (1.51)	11.82 (3.60)	<0.001
Bayley-II TM IS	100 (15)	11	67.27 (7.16)	110.55 (17.69)	<0.001
PDMS-II FMQ	100 (15)	17	84.47 (7.67)	103.53 (11.44)	<0.001
PDMS-II GMQ	100 (15)	17	71.65 (5.82)	106.24 (6.64)	<0.001
PDMS-II TMQ	100 (15)	17	74.71 (5.81)	105.29 (7.81)	<0.001
PDMS- II Stationary	10 (3)	17	6.76 (1.52)	11.71 (1.40)	<0.001
PDMS-II Locomotion	10 (3)	17	4.29 (0.69)	10.94 (1.60)	<0.001
PDMS-II Object manipulation	10 (3)	16	5.63 (1.41)	10.31 (1.40)	<0.001
PDMS-II Grasping	10 (3)	17	7.41 (2.29)	9.41 (1.87)	0.009
PDMS-II VMI	10 (3)	17	7.41 (2.18)	11.76 (2.61)	<0.001
MFM total	100%	16	85.52 (7.45)	96.56 (5.43)	<0.001

SD= Standard Deviation; DMD= Duchenne Muscular Dystrophy; TD= Typically Developing; FM SS= Fine Motor Scaled Score; GM SS= Gross Motor Scaled Scores; TM IS= Total Motor Index Scores; PDMS-II: Peabody Developmental Motor Scales, Second edition; FMQ= Fine Motor Quotient; GMQ= Gross Motor Quotient; TMQ= Total Motor Quotient; VMI= Visual Motor Integration; MFM total= Motor Function Measure Total Score

3.3 Longitudinal fine and gross motor development in DMD

The results of the LMM are presented in Tables 3–4. The intercepts and estimates of fixed effects with corresponding p-values are presented per subdomain. The 95% confidence intervals of fixed effects' estimates and random-effect and residual covariance structure of the linear mixed effect models are presented in Appendices B and C.

3.3.1 Bayley-III

Eleven boys between 11 months and 3 years 6 months were evaluated with the Bayley-III, seven out of them were followed-up two to four times. Individual estimated evolutions of FM and GM SS and TM IS are demonstrated in Figures 1a, b and c. Overall, we did not find any longitudinal effect and also no significant effect of baseline age, presumably because of the limited number of evaluations. However, the best fit models presume a stable evolution over time of FM and GM SS and TM IS in this young age group. Stable SS or IS mean an increase in raw scores and thus a positive evolution of motor development, parallel to the evolution seen in TD over time.

Table 3. Regression coefficients for fixed effects as a result linear mixed effect models for the Bayley-III Fine and Gross Motor Scaled Scores and Total Motor Index Scores

	Fixed effects					
	Regression coefficients					
	Intercept		Longitudinal effects		Cross-sectional effects	
			Time		Bas_age	
Variable	β_0	**p-val**	β_1	**p-val**	β_2	**p-val**
FM	2.44	0.18	NA	/	1.32	0.06
GM	4.17	0.003	NA	/	-0.32	0.45
TM	58.96	<0.0001	NA	/	3.06	0.28

Bas_age= Baseline age; p-val= p-value; FM= Fine Motor; GM= Gross Motor; TM= Total Motor; NA= Not Applicable

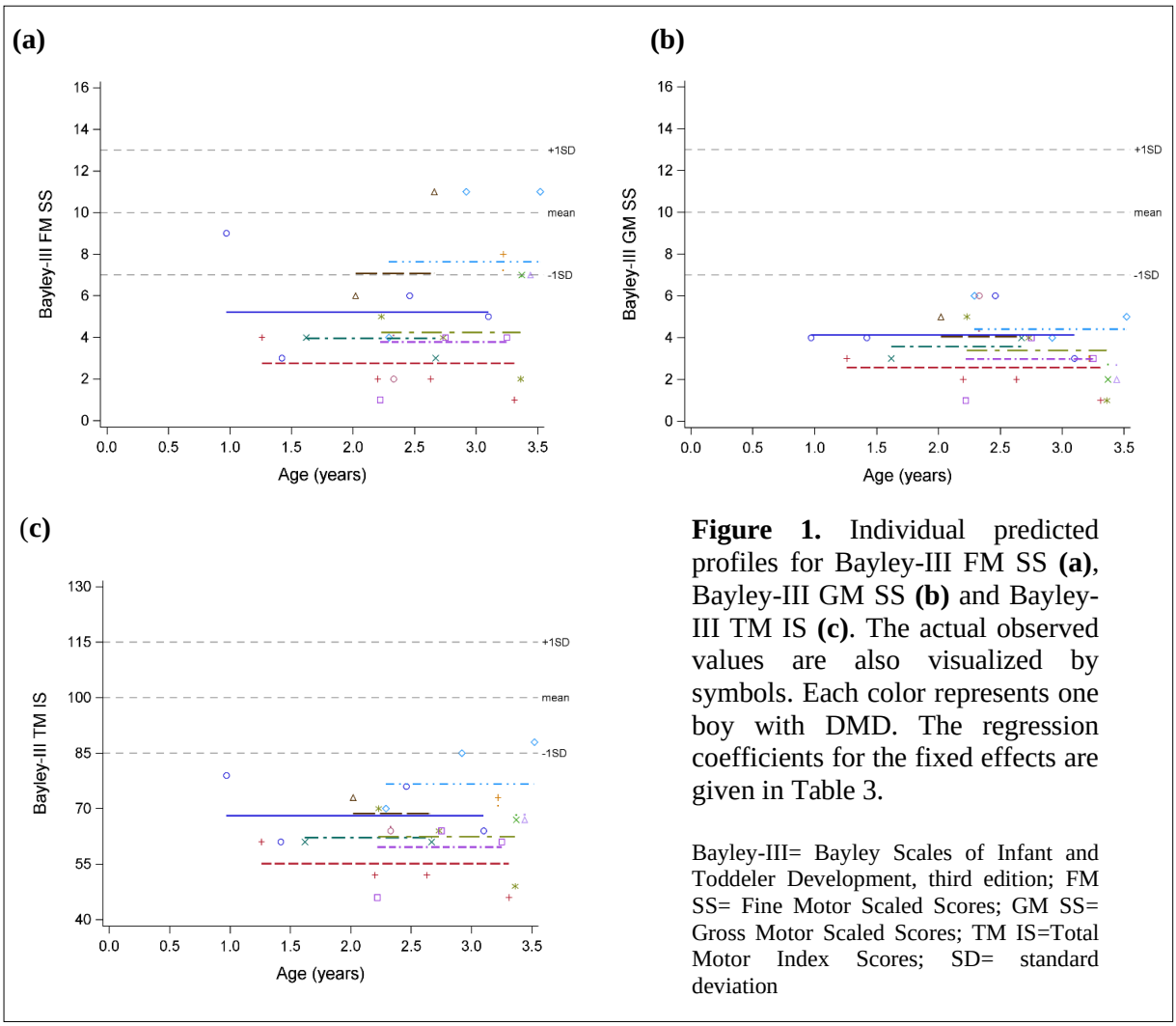

Figure 1. Individual predicted profiles for Bayley-III FM SS **(a)**, Bayley-III GM SS **(b)** and Bayley-III TM IS **(c)**. The actual observed values are also visualized by symbols. Each color represents one boy with DMD. The regression coefficients for the fixed effects are given in Table 3.

Bayley-III= Bayley Scales of Infant and Toddeler Development, third edition; FM SS= Fine Motor Scaled Scores; GM SS= Gross Motor Scaled Scores; TM IS=Total Motor Index Scores; SD= standard deviation

3.3.2 PDMS-II

Eleven out of 17 boys between 11 months and 6 years old were followed up with the PDMS-II. Individual estimated evolutions of the different PDMS-II quotients and subscale SS are demonstrated in figures 2a, b, c and 3a, b, c, d and e. Overall, negative longitudinal effects were found for the different subscales of the PDMS-II, and most of them were also related to baseline age.

A longitudinal decrease of 16.77 points per year was found for the FMQ and a decrease of 18.52 points per year with increasing baseline age. The longitudinal change in FMQ over time was also related to baseline age. First FMQs seem to decrease until around the age of 4, followed by increases in FMQ (Figure 2a). A smaller longitudinal effect was seen for GMQ, a decrease of 6.66 points per year. With increasing baseline age, the GMQ decreased with 10.58 points per year. We found also first a decrease in GMQ followed by a small increase starting from around the age of 5 (Figure 2b). TMQ showed similar evolutions, with a longitudinal negative effect related to baseline age (Figure 2c). TMQ also first decreases followed by a small increase around the age of 4 years 6 months.

Stationary SS show a negative longitudinal effect of 2.39 points per year. The longitudinal effect was also related to baseline age. Before the age of 5 a clear decrease in stationary scaled scores is found followed by a stabilisation around the age of 5. No longitudinal effect was found for locomotion. Locomotion SS decreased with 0.88 points per year with increasing baseline age. Object manipulation showed a small negative longitudinal and baseline age effect, a decrease of 1.23 points per year and also a decrease of 1.83 points per year with increasing baseline age. Grasping SS decreased longitudinally with 5.26 points per year and also with 6.36 points per year with increasing basline age. Also, an interaction effect between time and baseline age was found, resulting in a decrease in SS followed by an increase, with the tipping point around the age of 4. For the VMI SS a small longitudinal and baseline age effect was found, with an interaction effect between both time and baseline age, resulting in relatively stable scores over time.

Table 4. Regression coefficients for fixed effects as a result linear mixed effect models for the different PDMS-II subscales and the MFM-20 dimensions.

	Fixed effects											
	Regression coefficients											
	Intercept		Longitudinal		Cross-sectional effects				Interaction effects			
			Time		Bas_age		Bas_age^2		Time x Bas_age		Time x Bas_age^2	
Variable	$\boldsymbol{\beta_0}$	**p-val**	$\boldsymbol{\beta_1}$	**p-val**	$\boldsymbol{\beta_2}$	**p-val**	$\boldsymbol{\beta_3}$	**p-val**	$\boldsymbol{\beta_4}$	**p-val**	$\boldsymbol{\beta_5}$	**p-val**
FMQ	110.87	<0.0001	-16.77	0.03	-18.52	<0.0001	2.64	<0.0001	6.01	0.003		
GMQ	90.15	<0.0001	-6.66	0.005	-10.58	0.0001	1.30	0.0008			0.45	0.01
TMQ	96.18	<0.0001	-12.77	0.03	-13.77	<0.0001	1.85	<0.0001	4.05	0.009		
Stat	12.02	<0.0001	-2.39	0.01	-2.35	0.006	0.22	0.03	0.51	0.05		
Loc	4.98	<0.0001			-0.88	0.02	0.15	0.01				
ObjMan	8.40	<0.0001	-1.23	0.03	-1.83	0.005	0.26	0.003			0.10	0.04
Grasp	17.84	<0.0001	-5.26	0.02	-6.36	<0.0001	0.81	<0.0001	1.78	0.004		
VMI	9.26	0.0001	-1.07	0.03	-2.14	0.09	0.39	0.046	0.43	0.009		
MFMD1	43.43	<0.0001	8.69	<0.0001	7.11	<0.0001						
MFMD2	90.16	<0.0001	5.20	0.01	1.86	0.02			-0.95	0.04		
MFMD3	93.16	<0.0001	1.89	0.07	1.05	0.09						
MFMtot	72.76	<0.0001	4.91	<0.0001	3.59	<0.0001						

Bas_age= baseline age; p-val= p-value; FMQ= Fine Motor Quotient; GMQ= Gross Motor Quotient; TMQ= Total Motor Quotient; Stat= Stationary; Loc= locomotion; ObjMan= Object Manipulation; Grasp= grasping; VMI= Visual Motor Integration; MFM= Motor Function Measure; MFMD1= MFM Dimension 1; MFMD2= MFM Dimension 2; MFMD3= MFM Dimension 3; MFMtot= MFM Total score

3.3.3 MFM-20

MFM-20 standing and transfer scores (D1) showed a longitudinal increase of 8.69% per year and also an increase of 7.11% per year with increasing baseline age. Smaller longitudinal (5.20% per year) and cross-sectional effects (1.86% per year with baseline age) were seen for axial and proximal motor functions (D2), with also an interaction effect resulting in an increase of percentages until around the age of 4 to 5 years olds, followed by a stabilisation. Because of very stable and mostly maximum scores over time, no significant fixed effects were found for distal motor functions (D3). The MFM total scores also increased 4.91% per year and 3.59% per year with increasing baseline age.

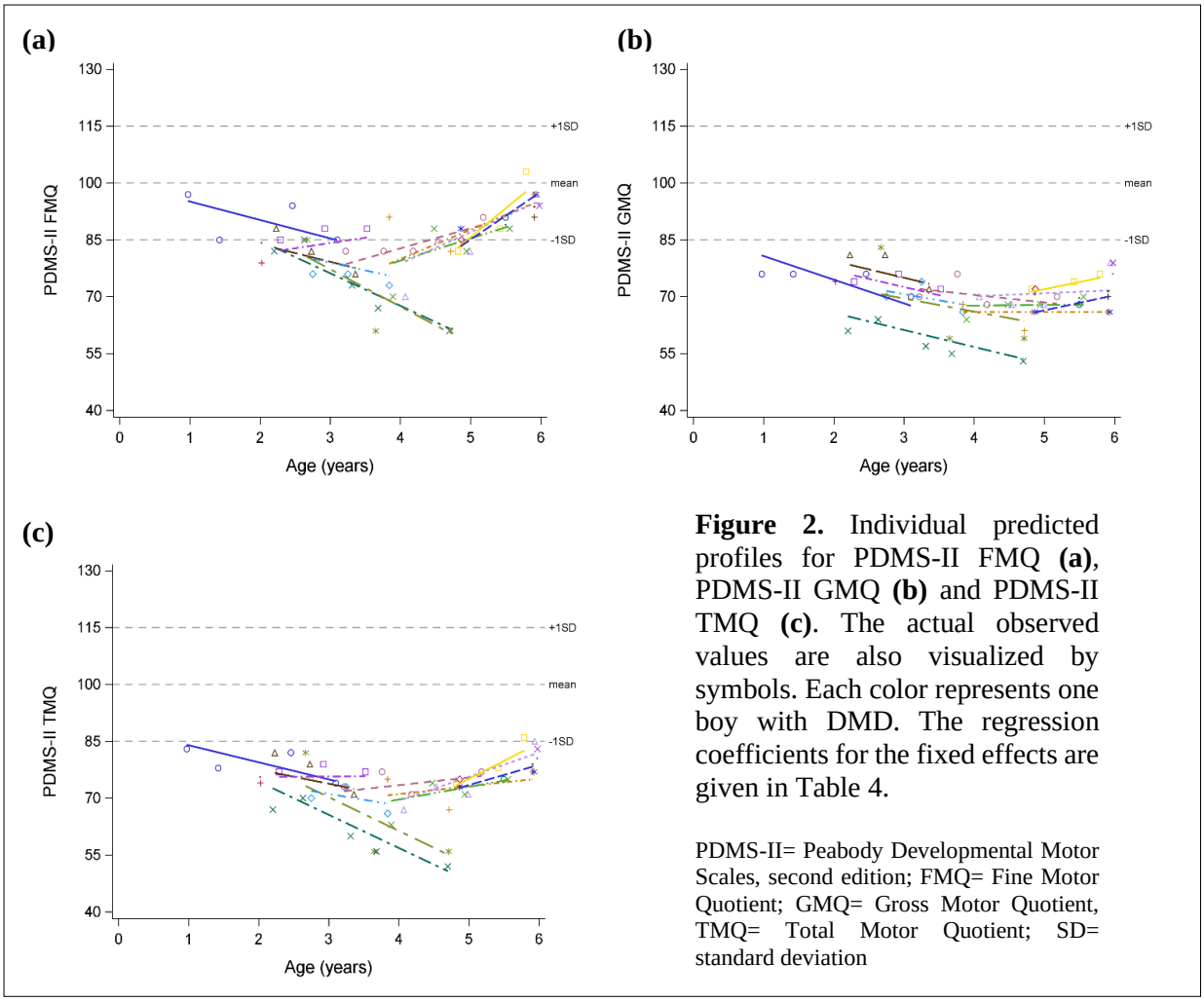

Figure 2. Individual predicted profiles for PDMS-II FMQ **(a)**, PDMS-II GMQ **(b)** and PDMS-II TMQ **(c)**. The actual observed values are also visualized by symbols. Each color represents one boy with DMD. The regression coefficients for the fixed effects are given in Table 4.

PDMS-II= Peabody Developmental Motor Scales, second edition; FMQ= Fine Motor Quotient; GMQ= Gross Motor Quotient, TMQ= Total Motor Quotient; SD= standard deviation

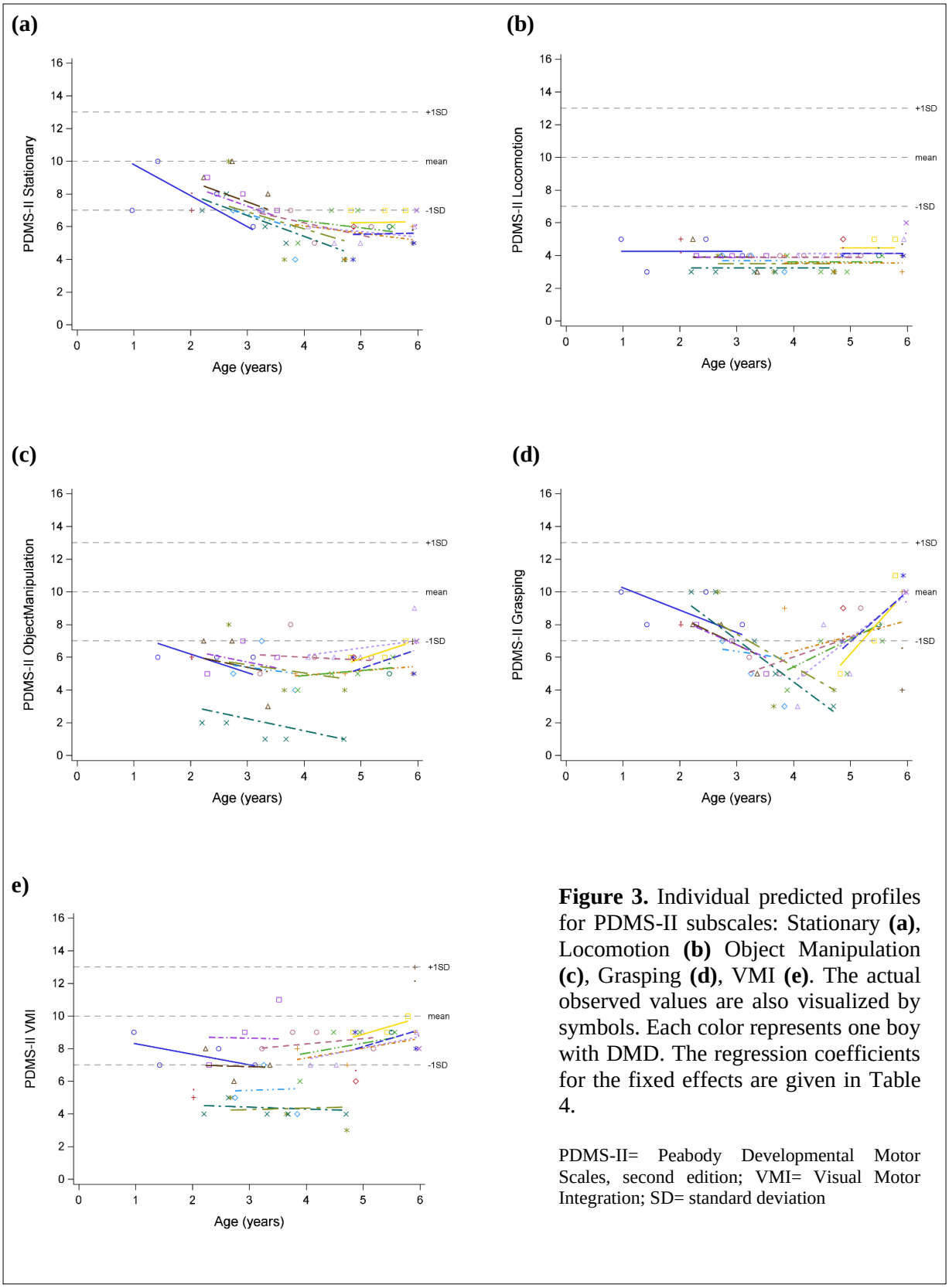

Figure 3. Individual predicted profiles for PDMS-II subscales: Stationary **(a)**, Locomotion **(b)** Object Manipulation **(c)**, Grasping **(d)**, VMI **(e)**. The actual observed values are also visualized by symbols. Each color represents one boy with DMD. The regression coefficients for the fixed effects are given in Table 4.

PDMS-II= Peabody Developmental Motor Scales, second edition; VMI= Visual Motor Integration; SD= standard deviation

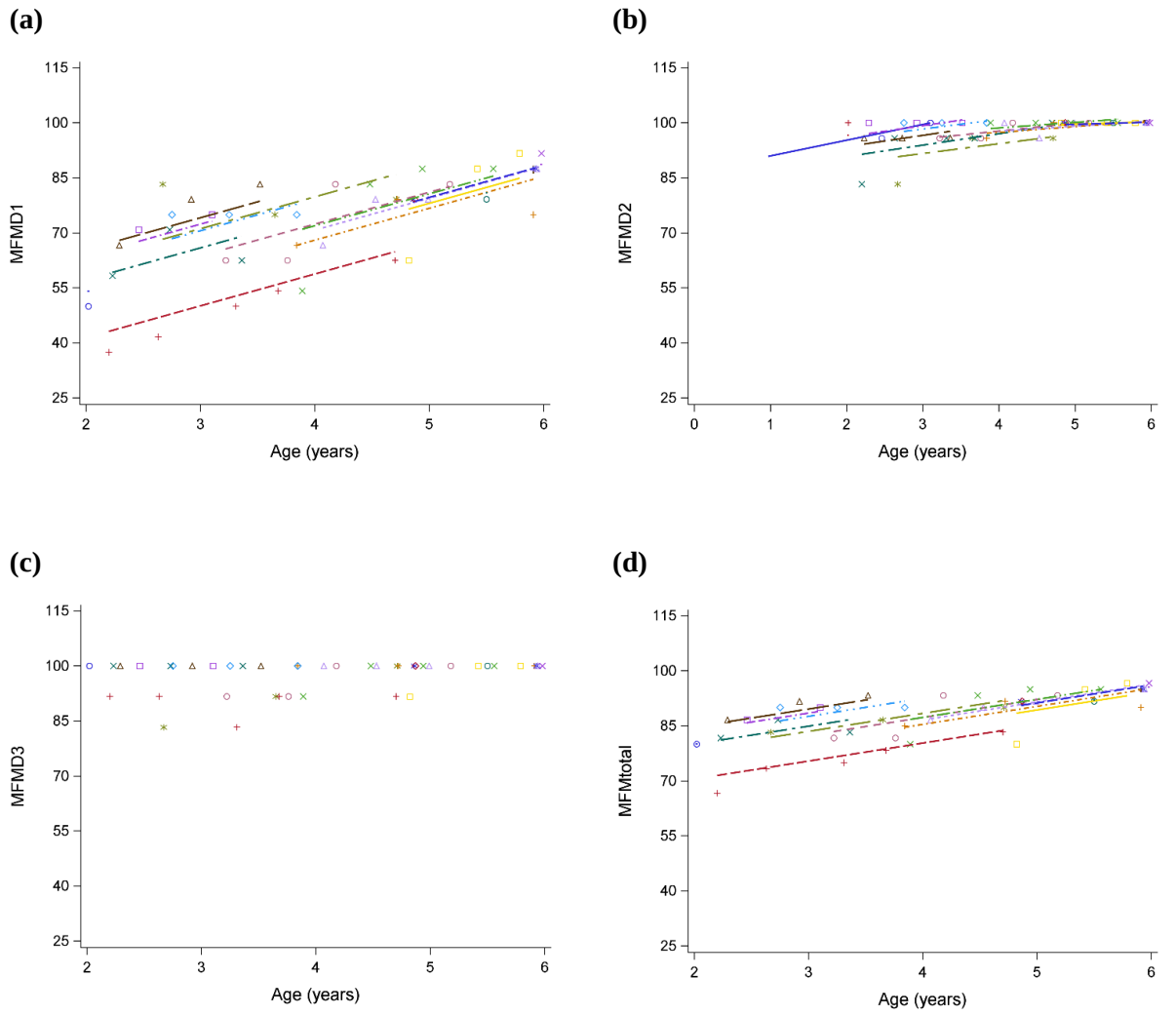

Figure 4. Individual predicted profiles for the Motor Function Measure (MFM): Standing and transfers (Dimension 1) **(a)**, Axial and proximal functions (Dimension 2) **(b)** Distal functions (Dimension 3) **(c)**, Total score **(d)**. The actual observed values are also visualized by symbols. Each color represents one boy with DMD. The regression coefficients for the fixed effects are given in Table 4.

MFMD1= Standing and Transfers; MFMD2= Axial and proximal functions; MFMD3= Distal functions; MFMtotal= Total MFM Score; SD= standard deviation

3.4. Influence of baseline cognition on the evolution of motor development.

Baseline cognition of the DMD boys significantly interacted with the FM SS, GM SS and TM IS of the Bayley-III (p=.002; p=0.03 and 0.005 respectively), meaning that there is a significant influence of the level of baseline cognition on the evolution of motor skills in young boys with DMD between 11 months and 3.5 years old.

We also found a significant influence of baseline cognition on the evolution of the TMQ of the PDMS-II (p=0.06) and the locomotion (p= 0.003), object manipulation (p=0.02) and visual motor integration subscales (p=0.01). The same was found for the MFM-20 total score (p=0.04) and trends were found for the MFM-20 dimensions scores (p=0.05-0.07).

Observation of the individual results of the DMD boys demonstrated overall higher scores in boys with mutations upstream of *exon 44.* The group of boys with mutations downstream of *exon* 44 was smaller and demonstrated heterogeneous results.

4. DISCUSSION

4.1. Fine and gross motor development in infants and preschool boys with DMD

Our study explored in detail early fine and gross motor development in infants and preschool boys with DMD using mixed cross-sectional and longitudinal design. In addition, the influence of the cognitive level on the evolution of fine and gross motor skills was also explored.

Despite the known proximal to distal loss of muscle function, with the lower limbs affected more in the early stage (Chelly & Desguerre, 2013), infants and young boys with DMD underperform on fine motor skills compared to TD peers. These results are in line with the research of Connolly et al. (2013-2014) (Connolly et al., 2014, 2013). Using the Bayley-III, stable fine motor SS were found, meaning that there is still an improvement of function. On the PDMS-II we found a decreasing-increasing trend for the fine motor subscales scores. Overall, lower fine motor scores might be related to the more general developmental delay seen in DMD, as the different developmental domains interact with each other (Connolly et al., 2013; Cyrulnik et al., 2008; Pane et al., 2013). However, the influence of the other developmental domains on fine motor development in DMD is not yet clearly described. If we zoom in into specific fine motor domains, we found that VMI SS of the PDMS-II remained relatively stable over time, however a slight decreasing-increasing trend was seen with a tipping point around the age of 4. The mean VMI SS (7.41) was also lower compared to the expected mean of 10 (SD=3). Grasping SS seem to decline clearly during the first years of life, followed by an increase also starting from around the age of 4. A possible explanation of the clear negative-positive evolution of the grasping curve might be the importance of the pencil grasp in his different forms. From the age of 35 to 71 months, managing different pencil grasps are the most important items of the PDMS-II subscale grasping. Only limited other items are included to make a differentiation in scores. We noticed that most boys with DMD experienced difficulties with managing the right pencil grasp and drawing/copying figures, resulting in lower scores, especially on the grasping scale. When they went to preschool, mastering pencil grasp was

exercised at school and we noticed that the scores on the grasping scale also started to increase. The same might be seen for VMI skills that are exercised at school. These findings might demonstrate the importance of therapy on fine motor skills already early in life, as this can have a positive influence on the fine motor evolution of boys with DMD. The evolution of VMI and grasping scores carries over in the fine and total motor quotient scores of the PDMS-II, showing the same decreasing-increasing evolution.

Regarding gross motor development, individual Bayley-III GM SS fluctuated, but overall stable trends were found over time with SS about 1.5 to 2.5 SD below the expected mean. Connolly et al. (2014) found decreasing trends in Bayley-II GM SS over 12 months (Connolly et al., 2014). PDMS-II GMQs decreased until around the age of 5 and then slightly increased. Stationary SS declined until the ages of 4 to 5 years and remained stable from then on. The decline in stationary SS might be related to the known proximal to distal loss of muscle function in DMD boys, as a lot of the stationary items rely on proximal muscle control. However, as described before, the decrease in GMQs and stationary SS scores is followed by an increase or stabilisation around the ages of 4 to 5. This might be an effect of medical therapy. Most of the boys included in the study started with corticosteroids between these ages. The stabilisation in stationary SS might be a straight effect of the corticosteroid treatment. Multiple boys also received physical therapy, which also almost exclusively focused on gross motor skills. However, starting ages and reasons for referral for therapy varied e.g. some boys started already at a very young age because of postural asymmetry.

Object manipulation and locomotion SS remained relatively stable over time. However, locomotion SS were clearly lower. These results are in line with Parson et al. (2004), who found lower scores and decreasing trends of locomotor scores on the GMDS over time in 16 DMD boys aged between two and three years (Parsons, Clarke, & Bradley, 2004). One possible explanation of the lower locomotion SS might be the fact that the item hierarchy might not be applicable for infants and young boys with DMD. According to the manual of the PDMS-II, you have to abort the assessment after 3 consecutive negative items, however many of the boys with DMD were able to perform higher classified items after early abortion of the test assessment e.g. some boys were not able to jump up or down and/or climbing stairs without support or alternated, which resulted in 3 consecutive negative items. Even though they were able to perform a higher classified item as walking on tiptoes but they did not receive any score for this anymore.

MFM-20 standing and transfers scores showed a clear improvement over time in boys with DMD. However, none of them reached the maximum score of 100%. The average scores of the axial, proximal and distal subscale were higher compared to the standing and transfer subscale and most boys reached a maximum score around the age of 4.5 years. However, a maximum score on the MFM-20 subscales is expected around age of 2 years in TD children (De Lattre et al., 2013). The results on the MFM-20 confirm again that young boys will improve in motor function, but still underperform compared to TD boys. De Lattre et al. (2013) found similar results in a cross-sectional study, investigating the validity

of the MFM-20 in 194 TD children and 88 children with neuromuscular disorders aged between two and seven years old. Their results showed comparable scores of 80% on the standing and transfers subscale and maximum scores reached at the axial and proximal motor function subscale and 90% on the distal motor function subscale in boys with DMD between 2 and 7 years. The difference in evolution between the subscales of the MFM-20 could be explained by the fact that items of the standing and transfers subscale require the use of the lower limbs in a standing position, whereas items of the axial, proximal and distal subscales are mostly conducted seating. This trend was also seen in the clearly lower SS on the locomotion and stationary subscales of the PDMS-II and corresponds to the known proximal to distal loss of muscle function and strength, with the lower limbs more affected in the early stage of the disease (Chelly & Desguerre, 2013).

Mean baseline cognition of the DMD boys was 1 SD below the average mean. Baseline cognition was found to have a significant influence on different (sub)scales of the Bayley-III, PDMS-II and MFM-20. This provides evidence that higher cognitive levels could lead to a better development of fine motor skills as well as gross motor skills.

Regarding fine motor development, baseline cognition significantly interacted with the evolution of VMI SS of the PDMS-II. This suggests that cognition plays an important role in the ability to translate visual imaging into accurate motor actions. Chieffo et al. (2015) examined 41 boys between four and six years old and found a significant correlation between PIQ of the WPPSI-III and eye-hand coordination subscales of the GMDS (Chieffo et al., 2015). The influence of cognitive development on fine motor skills has been investigated extensively in TD children and children with neurodevelopmental disorders (e.g. ADHD). Brain development seems to play a crucial role in the acquisition of fine motor skills (Davis et al., 2011; Klupp, Möhring, Lemola, & Grob, 2021). Imaging studies have shown an overlap of activation between areas initially thought to control just one function, suggesting an underlying neural network that serves both cognitive and motor functioning (Abe & Hanakawa, 2009). As cognitive development is this important in the development of TD children, it cannot fail to play a crucial role in the fine motor development of DMD boys. Especially, knowing that the isoform Dp140, which is affected in mutations downstream of *exon 44*, has been connected to brain involvement and thus to more severe cognitive impairment (Rasic et al., 2014; Taylor et al., 2010; Thangarajh et al., 2019; Wingeier et al., 2011).

Baseline cognition also significantly interacted with the evolution of the TMQ, locomotion and object manipulation SS of the PDMS-II and the MFM-20 total score. A possible explanation of the interaction of cognition with the locomotion and object manipulation GM subscales of the PDMS-II, might be that these subscales require more command understanding as the items are more complex. However, the first items of the locomotion subscale include overall developmental milestones such as standing, creeping and walking independently. Mirski et al. investigated the relationship between delay of independent walking and cognitive impairment in DMD boys and they also found that boys with DMD having cognitive impairments were three times more likely to have a delay in walking. They suggest that a

delay in walking should be considered as a consequence of impairment in broader neurologic development as seen in DMD and not only as a motor problem (Mirski & Crawford, 2014).

4.2. Reflection on strengths and limitations of the study

This study was subjected to some limitations. First, the number of assessments of each DMD boy was different. Reasons include reaching the age limit, Covid-19 measures and lockdowns or not showing up to their half yearly consultation at the NMRC. However, the missing data were considered in the statistical analyses. Secondly, the boys with DMD enrolled in the study at different ages. Influencing factors, such as therapy and use of medication were not implemented in the model but described in detail. Some boys followed physical therapy with focus on stretching of the lower limbs and most of them received medical treatment by the end of this study. Future research is necessary to investigate more in detail the influence of therapy and medication on fine and gross motor development in a larger sample of young boys with DMD.

Despite these limitations, our study is one of the first studies that thoroughly explored the evolution of different fine and gross motor skills in a young cohort of boys with DMD under the age of six years. Moreover, we investigated the influence of cognition on both fine and gross motor development in young DMD boys.

5. CONCLUSIONS

Our study confirms that young boys with DMD gain in fine and gross motor skills, however most of them do not achieve the same functioning level compared to TD boys. In addition, our work shows that the level of cognitive development plays a crucial role in the evolution of fine and gross motor skills. These new insights in the evolution of early development could be of added value for future clinical trials in young boys with DMD. Subsequently, increased alertness to early symptoms, e.g. developmental delay, may advance the age of diagnosis, as well as associated early intervention. Nowadays early intervention in infants and young boys with DMD focuses almost exclusively on gross motor skills. However, the results of this study suggest a shift to a broader psychomotor approach including both fine and gross motor skills, also considering cognition.

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Appendix A. Individual characteristics of the Duchenne group

Subject ID	Baseline_age	Age_last assessment	Number of assessments	Height (cm)	Weight (kg)	Baseline cognition score	Mutation type and site	Start corticosteroids/medication	Start physical terapy
DMD1 +	5y 11mo	5y 11mo	1	110	18	95	Deletion exon 45-52	4y 10mo	/
DMD2 △	2y 2 mo	4y 8mo	5	92	14	60	Deletion exon 51	4y 3mo	10mo
DMD3 ✳	2y 8mo	4y 8mo	3	86	10	70	Duplication exon 2	4y 8mo	1y 5mo
DMD4 ○	3y 2mo	5y 2mo	4	92	14	80	Deletion exon 45	4y 5mo	3y 7mo
DMD5 □	4y 9mo	5y 9mo	3	105	20	98	Deletion exon 46-52	5y 2mo	5y 3mo
DMD6 ×	5y 11mo	5y 11mo	1	116	25	90	Deletion exon 3-7	/	/
DMD7 ✶	4y 10mo	5y 11mo	2	104	16	90	Frameshift mutation exon 24	4y 9mo	5y 11mo
DMD8 +	3y 10mo	5y 10mo	3	105	19	90	Deletion exon 45	4y 8mo	4y 2mo
DMD9 ×	3y 10mo	5y 6mo	4	108	21	88	Deletion exon 45-50 51 skip	4y 11mo	1y 9mo
DMD10 △	4y 0mo	5y 11mo	4	97	17	116	Deletion exon 45-50	4y 6mo	4y 11mo
DMD11 □	2y 3mo	3y 6mo	3	97	11	85	Deletion exon 49-52	/	/
DMD12 +	2y 0mo	2y 0m	1	86	11	75	Duplication exon 8-13	/	/
DMD13 ◇	2y 9mo	3y 10mo	3	97	11	70	Deletion exon 46-51	/	11mo
DMD14 ◇	4y 10mo	4y 10mo	1	106	17	-	Frameshift mutation exon 8	4y 6mo	/
DMD15 ○	11mo	3y 1mo	4	72	8	90	Deletion exon 45	/	1y 9mo
DMD16 △	2y 2mo	3y 4mo	3	86	12	80	Deletion exon 48-50	3y 2mo	/
DMD17 ○	5y 6mo	5y 6mo	1	107	17	-	Deletion exon 8-41	/	4y 3mo

Subject ID= subject identification; cm= centimeters; kg= kilograms; DMD= Duchenne Muscular Dystrophy; y= years; mo= months; -: no score avaiable; /: not yet started

Appendix B. 95% confidence intervals of fixed effects' estimates

Fixed effects

	Regression coefficients					
	Intercept	Longitudinal	Cross-sectional effects		Interaction effects	
		Time	Bas_age	Bas_age^2	Time x Bas_age	Time x Bas_age^2
Variable	$\boldsymbol{\beta_0}$	$\boldsymbol{\beta_1}$	$\boldsymbol{\beta_2}$	$\boldsymbol{\beta_3}$	$\boldsymbol{\beta_4}$	$\boldsymbol{\beta_5}$
FM SS	-1.36 - 6.24		-0.03 - 2.68			
GM SS	1.88 - 6.47		-1.21 - 0.56			
TM IS	42.42 - 75.49		-2.87 - 9.00			
FMQ	101.71 - 120.02	-31.06 - -2.47	-24.38 - -12.65	1.88 - 3.41	2.40 - 9.61	
GMQ	79.93 - 100.37	-11.15 - -2.17	-15.50 - -5.67	0.59 - 2.00		0.11 - 0.79
TMQ	87.72 - 104.64	-23.78 - -1.76	-18.42 - -9.13	1.22 - 2.47	1.14 - 6.95	
Stat	8.72 - 15.33	-4.19 - -0.59	-3.96 - -0.73	0.02 - 0.42	-0.006 - 1.02	
Loc	3.90 - 6.05		-1.59 - -0.17	0.03 - 0.27		
ObjMan	5.70 - 11.10	-2.34 - -0.12	-3.04 - -0.62	0.10 - 0.42		0.005 - 0.20
Grasp	12.86 - 22.84	-9.62 - -0.90	-8.79 - -3.94	0.49 - 1.13	0.64 - 2.92	
VMI	5.45 - 13.05	-2.03 - -0.10	-4.63 - 0.35	0.008 - 0.77	0.11 - 0.75	
MFMD1	27.66 - 59.20	4.93 - 12.44	4.09 - 10.13			
MFMD2	82.56 - 97.76	1.24 - 9.15	0.38 - 3.34		-1.85 - -0.05	
MFMD3	NA	NA	NA			
MFMtot	64.95 - 80.57	3.41 - 6.41	2.08 - 5.08			

Bas_age= Baseline age; FM SS= Fine Motor Scaled Score; GM SS= Gross Motor Scaled Scores; TM IS= Total Motor Index Scores; FMQ= Fine Motor Quotient; GMQ= Gross Motor Quotient; TMQ= Total Motor Quotient; VMI= Visual Motor Integration; MFMD1= MFM Dimension 1; MFMD2= MFM Dimension 2; MFMD3= MFM Dimension 3; MFM total= Motor Function Measure Total Score; NA= not applicable

Appendix C. Random-effect and residual covariance structure of the linear mixed effect models

	Random effects		Residual
	Variance random intercept	Variance random slope	Variance residual
Variables	**$\sigma^2(b_{1i})$**	**$\sigma^2(b_{2i})$**	**$\sigma^2(\varepsilon_{ij})$**
FM SS	3.75		5.45
GM SS	0.92		1.71
TM IS	53.38		66.24
FMQ	0	29.13	26.54
GMQ	16.64		18.50
TMQ	4.38	18.73	17.43
Stat	0.24		1.49
Loc	0.15		0.34
ObjMan	1.22		1.35
Grasp	2.25	2.16	2.76
VMI	2.51		1.17
MFMD1	45.62		50.95
MFMD2	5.44		6.57
MFMD3	NA	NA	NA
MFMtot	13.09		10.96

b_{1i} = random intercept; b_{2i} = random slope for time and ε_{ij} = measurement error; FM SS= Fine Motor Scaled Score; GM SS= Gross Motor Scaled Scores; TM IS= Total Motor Index Scores; FMQ= Fine Motor Quotient; GMQ= Gross Motor Quotient; TMQ= Total Motor Quotient; VMI= Visual Motor Integration; MFMD1= MFM Dimension 1; MFMD2= MFM Dimension 2; MFMD3= MFM Dimension 3; MFM total= Motor Function Measure Total Score; NA= not applicable