Early motor, cognitive, language, behavioural and social emotional development in infants and young boys with Duchenne Muscular Dystrophy- A systematic review

Peer-reviewed author version

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ABSTRACT

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disorder caused by mutations in the *dystrophin* gene. Deficiency of the dystrophin protein causes not only motor, but also cognitive, language, behavioural and social emotional problems. This is the first systematic review investigating five early developmental domains in boys with DMD between 0 and 6 years old. Interactions between different domains and links with mutation types and sites were explored.

A systematic search was performed in PubMed, Web of Science and Scopus. An adapted version of the Scottish Intercollegiate Guidelines Network (SIGN) Checklists for case-control and cohort studies was used to evaluate quality.

Fifty-five studies of high or acceptable quality were included. One was an RCT of level 1b; 50 were cohort studies of level 2b; and four were an aggregation of case-control and cohort studies receiving levels 2b and 3b. We found that young boys with DMD experienced problems in all five developmental domains, with significant interactions between these. Several studies also showed relationships between mutation sites and outcomes.

We conclude that DMD is not only characterised by motor problems but by a more global developmental delay with a large variability between boys. Our results emphasise the need for harmonisation in evaluation and follow-up of young boys with DMD. More high-quality research is needed on the different early developmental domains in young DMD to facilitate early detection of difficulties and identification of associated early intervention strategies.

Keywords:

Duchenne Muscular dystrophy, Motor development, Cognitive development, Language development, Behavioral development, Social emotional development

1. INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disorder caused by mutations in the *dystrophin* gene, which affects boys more frequently than girls. Female carriers mostly show no evidence of muscular weakness. DMD is the most common form of muscular dystrophy in childhood, affecting 1 in 5000 male births.[1] It causes deficiency of the protein dystrophin in muscle fibres and in the central nervous system. It is characterised by progressive muscle weakness.[2] In boys, in early childhood, DMD may present as a delay in reaching gross motor milestones.[3,4] Although studies report gains in motor function over the first years, young boys with DMD most often do not achieve the same functional level as do typically developing (TD) children.[5–8] Later, a decline in motor functioning is seen, leading to loss of ability to walk and wheelchair dependency around the age of 12-13 years.[5–7] Subsequently, progressive cardiac and respiratory involvement result in reduced life expectancy.[9]

In addition to motor problems, cognitive, language, behavioural and social emotional problems are often seen in boys with DMD.[10–14] The effect of lack of dystrophin in the brain is not fully understood, but studies have found a link with neurodevelopmental and behavioural problems.[15,16] Overall, boys with DMD have an intelligent quotient (IQ) about one standard deviation below normal.[13,17] Furthermore, language deficits have been reported in boys with DMD. Expressive communication seems to be more often affected than receptive communication.[12,15] Boys with DMD appear to score worse in subjects like sentence and story recall than their healthy siblings.[15] Also, behavioural problems and social emotional problems are often reported in boys with DMD. The prevalence of Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD) among boys with DMD is higher than in the healthy population.[18]

Often, there is a delay between the first signs and symptoms of DMD and the final diagnosis. The mean age of diagnosis is 5 years.[19,20] However, symptoms of delay in achieving developmental milestones, such as motor milestones (e.g. independent walking), language milestones and/or cognitive delays, should raise suspicions and prompt earlier diagnosis.[21]

Therefore, the aim of this review is to summarise the different early developmental domains in preschool boys with DMD. We aim to identify and map early gross and fine motor skills, cognition, language (expressive and receptive), behavioural and social emotional development, and to investigate the relation between those domains in boys with DMD between 0 and 6 years old, considering type and site of the mutations. These insights may provide a better overview of early development in DMD, possibly contributing to an earlier diagnosis and suggesting early and targeted treatment strategies adapted to the individual young boy with DMD.

2. MATERIALS AND METHODS

2.1 Protocol and search strategy

This systematic review follows the PRISMA 2020 statement: an updated guideline for reporting systematic reviews.[22]

The databases PubMed, Scopus and Web of Science (WOS) were searched up to September 2022, using an extensive number of keywords to answer the question: '*What is known about early motor, cognitive, language and behavioural development in infants and young boys with DMD between 0 and 6 years old*'. A concept map was created to decide how the concepts were combined using AND and OR Boolean operators (Appendix A1). In Scopus and WOS, Boolean operators W/0 and NEAR/0 were used to combine terms about 'age', 'old' and 'year'. The different search strategies can be found in Appendix A2. No limits or filters were imposed resulting in a broad overview of the literature, with only the WOS databases 'Zoological Record' and 'Derwent Innovations Index' not being selected.

2.2 Study selection

Two independent reviewers (JH and SP) selected relevant studies by screening first on title/ abstract and then on full text. The following inclusion criteria were applied:

- Population: studies describing boys with DMD between 0 and 6 years old or, studies that included boys older than 6 years were also included if data could be extracted from younger boys between 0 and 6 years old.
- Outcome: outcome measures must contain information on at least one of the different developmental domains: motor, cognitive, language, behavioural and social emotional;
- Design and language: case studies, case-control studies, prospective studies, retrospective studies, cross-sectional studies, and longitudinal studies in English or Dutch. Reviews were screened for relevant references.

The presence of a (TD) control group was not used as an inclusion criterium. However, we included information on this in the data extraction and synthesis of results as we mean that it might be important for the interpretation of results.

Articles were excluded if they met following exclusion criteria:

- Population: different age range; diseases other than DMD; animal studies; studies of relatives of people with DMD (parents, mothers, siblings, female carriers);
- Outcome: studies describing therapy or treatment concepts for DMD, studies not linked to any developmental domain;
- Design and language: validity and reliability studies on outcome measures; studies in languages other than English and Dutch

2.3 Quality assessment

The quality of included studies was assessed with an adapted version of the Scottish Intercollegiate Guidelines Network, 2012 methodology checklists (SIGN checklist) for case-control and cohort studies. The checklist comprises two sections: internal validity and overall assessment of the study. The two most important questions of subsection 'selection of subjects' from the case-control checklist were added to the cohort checklist. More specifically these questions were: 'Are cases clearly defined and differentiated from possible controls?', and 'Is it evident that controls are non-cases?' Studies were assessed as high quality (++), acceptable (+), or low quality (-) regarding the presence of bias and confounding. Furthermore, an extra question about level of evidence, based on the table of Portney and Watkins, was added.[23] The levels assigned to include studies were as follows: 1b. individual RCT; 2b. individual cohort study; 3b. individual case control study; 4. case-series or poor quality cohort and case-control studies; 5. expert opinion or bench research. Critical assessment of included studies using the adapted version of the SIGN checklist can be found in Table 1. Quality assessment was performed by two reviewers (JH and SP).

2.4 Data extraction and synthesis of results

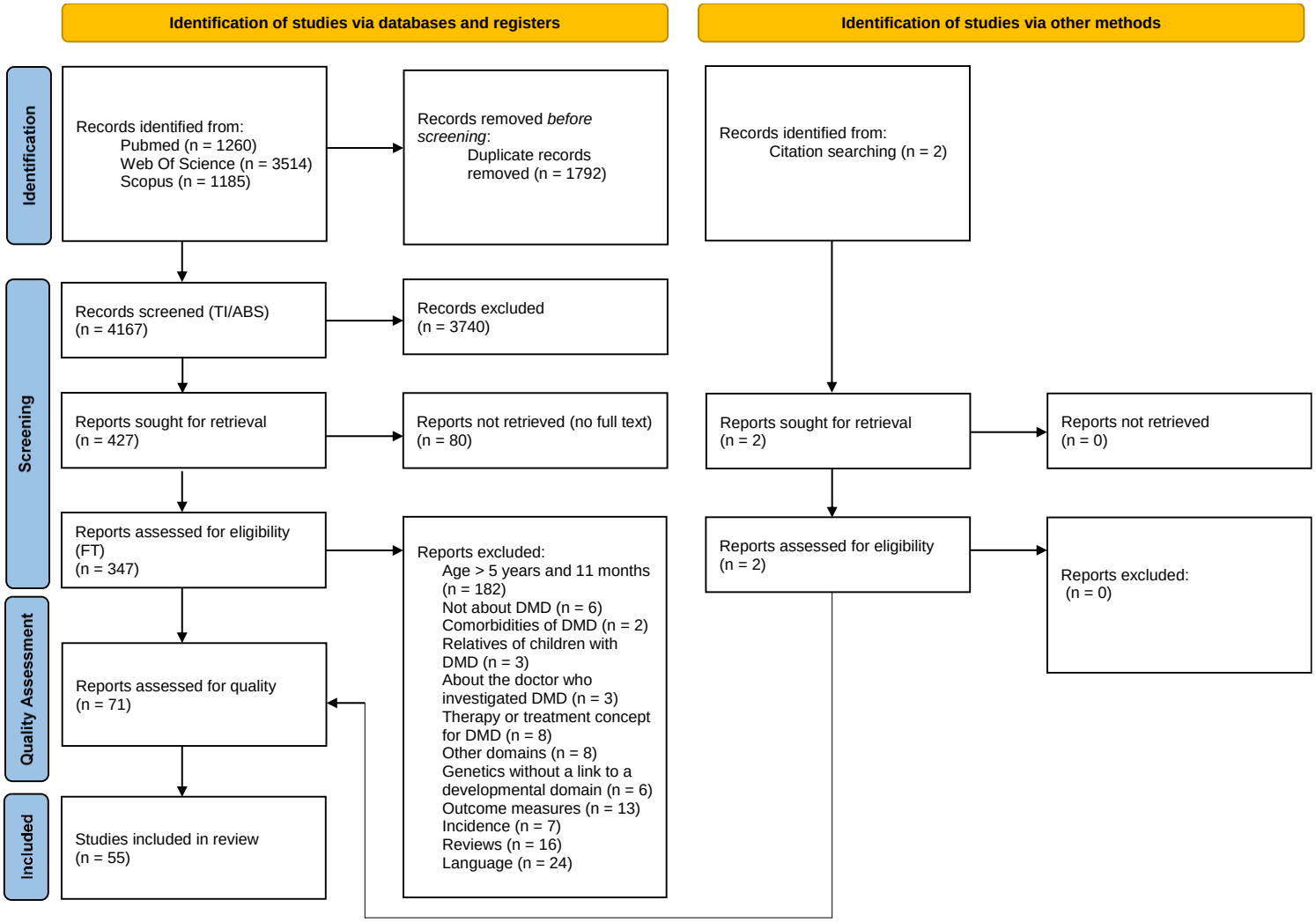
The following data were extracted from the selected studies: information about the *population* (number of participants, age, anthropometric values, corticosteroid use, mutation type and site or other influencing factors, possible control group (TD children; Becker Muscular Dystrophy BMD,..)*; study design (*cross-sectional, longitudinal retrospective or prospective)*; developmental outcome and outcome measures* (motor, cognitive, language, behavioural, social emotional); *results* (motor, cognitive, language, behavioural, social emotional). Data were extracted from each individual study by one reviewer and accuracy checked by the second reviewer (SP and JH).

3. RESULTS

3.1 Study selection

Searches in November 2021 and September 2022 found 5959 publications, 1260 in PubMed, 3514 in Web of Science and 1185 in Scopus. After deduplication, screening on title and abstract and on full text, 69 studies met the inclusion criteria. Reference screening revealed two additional studies, yielding 71 studies for quality assessment; data were extracted from 55. A PRISMA flow chart of the search process can be found in Figure 1.

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

3.2 Results of quality assessment

Detailed information on the quality assessment of the included studies is given in Table 1.

Sixteen studies were assessed as low quality (-), creating a risk of bias or confounding.[24–39] All but two were case-studies with evidence levels 3b or 4; the two were cohort studies from 1965 and 1981.[24,33] Seven did not address an appropriate or clearly focused question, leading to reduced internal validity.[24,25,28,32,33,36,39] Only one case study compared boys with DMD to a control group.[25] Four studies described only unusual cases with DMD or had few patients in the required age range, so their results were not directly generalisable to this review's target group.[30,33,38,39] In one study, outcomes were not clearly defined.[30] We excluded these low-quality studies before data extraction.

The remaining 55 studies were of acceptable (+) (37) or high quality (++) (18). One study was an RCT with evidence level 1b;[40] 50 were cohort studies of level 2b;[3,4,7,8,12,13,16,41–83]; and four studies were an aggregation of case-control and cohort studies with evidence levels 2b and 3b.[84–87] Overall, potential confounders were considered in these studies and reliable assessment methods and, where possible, control groups were used. However, no confidence intervals were given in these studies.

Table 1. Critical appraisal of the included studies using an adapted version of the SIGN methodology checklist

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Dubowitz (1965)	N	NA	N	NA	0%	NA	NA	NA	Y	N	NA	N	N	N	N	N	-	Y	Y	2b
Rosman & Kakulas (1966)	N	Y	N	NA	8%	Y	Y	Y	Y	Y	Y	N	N	N	Y	N	-	Y	Y	3b
Marsh & Munsat (1974)	Y	N	N	NA	15%	Y	NA	NA	Y	N	NA	Y	Y	N	Y	N	+	Y	N	2b
Winarno et al. (1976)	N	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	N	N	N	NA	NA	-	Y	Y	4
Leibowitz &Dubowitz (1981)	Y	NA	N	NA	?	NA	NA	NA	Y	N	NA	Y	Y	N	Y	N	+	Y	N	2b
Allsop & Ziter (1981)	N	NA	N	NA	0%	NA	NA	NA	Y	?	NA	Y	Y	N	N	N	-	Y	N	2b
Scott et al. (1982)	Y	NA	N	NA	7%	N	NA	NA	Y	N	NA	Y	Y	N	Y	N	+	Y	Y	2b
Crisp (1982)	Y	NA	N	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	N	N	N	-	Y	Y	2b
Renier et al. (1983)	Y	?	NA	NA	NA	NA	N	?	Y	NA	NA	Y	N	N	NA	NA	-	Y	Y	4
Komoto et al. (1984)	N	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	NA	NA	-	Y	Y	4
Kaplan et al. (1986)	Y	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	N	NA	NA	-	Y	Y	4
Smith et al. (1989)	Y	Y	N	NA	0%	NA	NA	NA	Y	N	Y	Y	Y	N	Y	N	+	Y	Y	2b
Smith et al. (1990)	Y	Y	N	NA	0%	NA	NA	NA	Y	N	Y	Y	Y	N	Y	N	+	Y	Y	2b
Smith et al. (1991)	Y	Y	N	NA	0%	NA	NA	NA	Y	N	Y	Y	Y	N	N	N	+	Y	Y	2b
Covone et al. (1991)	Y	NA	N	NA	?	NA	NA	NA	Y	N	NA	Y	Y	N	?	N	-	Y	N	2b

Topaloglu et al. (1993)	N	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	NA	NA	-	Y	N	4
Lenk (1996)	Y	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	N	NA	NA	-	Y	Y	4
Iwanczak et al. (2000)	Y	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	NA	NA	-	Y	Y	4
Jay & Vajsar (2001)	N	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	NA	NA	-	Y	Y	4
Hyde et al. (2001)	Y	NA	N	NA	0%	NA	NA	NA	Y	N	NA	Y	Y	N	Y	N	+	Y	N	2b
Essex & Roper (2001)	N	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	NA	NA	-	Y	Y	4
Parsons et al. (2004)	Y	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	Y	?	N	+	Y	Y	2b
Beenakker et al. (2005)	Y	Y	N	NA	NA	NA	Y	Y	Y	N	Y	Y	N	N	Y	N	+	Y	Y	2-3b
Cyrulnik et al. (2007)	Y	Y	N	NA	NA	NA	Y	Y	Y	N	Y	Y	Y	Y	Y	N	++	Y	Y	2b
Cyrulnik et al. (2008)	Y	Y	N	NA	NA	NA	Y	Y	Y	N	Y	Y	Y	Y	Y	N	++	Y	Y	2b
Desguerre et al. (2009)	Y	NA	N	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	N	Y	N	+	Y	Y	2b
Taylor et al. (2010)	Y	NA	N	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	Y	Y	N	++	Y	Y	2b
Erturk et al. (2010)	Y	NA	NA	NA	0%	NA	NA	NA	N	NA	NA	Y	N	Y	NA	NA	-	N	N	4
Waring & Woodyatt (2011)	Y	Y	Y	NA	NA	NA	Y	Y	Y	?	Y	Y	Y	N	N	N	+	Y	Y	2-3b
Wingeier et al. (2011)	Y	NA	Y	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	N	Y	N	+	Y	Y	2b

Mazzone et al. (2011)	Y	NA	Y	NA	0%-10%	Y	NA	NA	Y	NA	NA	Y	Y	N	Y	N	++	Y	Y	2b
Donald et al. (2011)	Y	Y	Y	NA	NA	NA	Y	Y	Y	NA	Y	Y	Y	N	?	N	+	Y	Y	2-3b
Doglio et al. (2011)	Y	Y	N	NA	NA	NA	Y	Y	Y	NA	Y	Y	Y	Y	?	N	+	Y	Y	2-3b
Pane et al. (2013)	Y	NA	Y	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	?	N	+	Y	Y	2b
Henricson et al. (2013)	Y	NA	Y	NA	?	Y	NA	NA	Y	NA	NA	Y	Y	Y	?	N	+	Y	Y	2b
Mazzone et al. (2013)	Y	NA	N	NA	0%	NA	NA	NA	Y	NA	NA	Y	Y	N	Y	N	++	Y	Y	2b
Connolly et al. (2013)	Y	NA	N	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	N	?	N	+	Y	Y	2b
Pane et al. (2014a)	Y	NA	NA	NA	15%	Y	NA	NA	Y	NA	NA	Y	N	N	?	N	+	Y	Y	2b
Sarrazin et al. (2014)	Y	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	NA	N	+	Y	Y	2b
Pane et al. (2014b)	Y	NA	Y	NA	8%	Y	NA	NA	Y	NA	NA	Y	Y	N	Y	N	++	Y	Y	2b
Mirski & Crawford (2014)	Y	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	?	N	+	Y	Y	2b
Rasic et al. (2014)	Y	NA	Y	NA	NA	NA	NA	NA	Y	NA	NA	N	Y	Y	Y	N	+	Y	Y	2b
Pane et al. (2014c)	Y	?	Y	NA	0%	NA	NA	NA	Y	?	Y	Y	Y	N	Y	N	++	Y	Y	2b
Connolly et al. (2014)	Y	NA	NA	NA	26%	?	NA	NA	Y	NA	NA	?	Y	N	?	N	+	Y	Y	2b
Chieffo et al. (2015)	Y	NA	Y	NA	?	NA	NA	NA	Y	?	NA	Y	Y	N	Y	N	++	Y	Y	2b
De Sanctis et al. (2015)	Y	Y	Y	NA	0%	NA	NA	NA	Y	?	Y	Y	Y	N	Y	N	++	Y	Y	2b

Davidson et al. (2015)	Y	Y	Y	NA	0%	NA	NA	NA	Y	?	NA	Y	Y	N	Y	N	++	Y	N	2b
Mercuri et al. (2016)	Y	Y	Y	NA	?	NA	NA	NA	Y	?	Y	Y	Y	N	?	N	+	Y	Y	2b
Buckon et al. (2016)	Y	NA	Y	NA	2%	?	NA	NA	Y	?	NA	Y	Y	N	?	N	+	Y	Y	1b
Ricotti et al. (2016)	Y	NA	NA	NA	0%	NA	NA	NA	Y	?	NA	Y	Y	N	Y	N	++	Y	N	2b
Alfano et el. (2017)	Y	Y	Y	NA	?	NA	NA	NA	Y	?	Y	Y	Y	N	Y	N	++	Y	Y	2b
Gissy et al. (2017)	Y	NA	Y	NA	NA	NA	NA	NA	Y	NA	NA	Y	?	N	N	N	+	Y	Y	2b
Arora et al. (2018)	Y	Y	N	NA	?	NA	NA	NA	Y	N	Y	Y	Y	N	?	?	+	Y	Y	2b
Thangarajh et al. (2018)	Y	NA	Y	NA	?	NA	NA	NA	Y	N	NA	Y	Y	N	Y	N	++	Y	Y	2b
Singh et al. (2018)	Y	NA	Y	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	N	N	N	+	Y	Y	2b
Fowler et al. (2018)	Y	NA	Y	NA	?	NA	NA	NA	Y	N	NA	Y	Y	N	?	N	+	Y	Y	2b
Brogna et al. (2018)	Y	NA	N	NA	0%	NA	NA	NA	Y	N	NA	Y	Y	N	N	N	+	Y	N	2b
Lee et al. (2018)	Y	NA	Y	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	N	N	+	Y	N	2b
Brogna et al. (2019)	Y	NA	Y	NA	6%	?	NA	NA	Y	N	NA	Y	Y	N	Y	N	++	Y	Y	2b
Muntoni et al. (2019)	Y	NA	Y	NA	NA	NA	NA	NA	Y	NA	NA	Y	N	N	Y	N	+	Y	Y	2b
Thangarajh et al. (2019)	Y	NA	Y	NA	?	NA	NA	NA	Y	N	NA	Y	Y	N	N	N	+	Y	Y	2b

Pereira et al. (2020)	Y	NA	Y	NA	0%	NA	NA	NA	Y	NA	Y	Y	N	N	N	N	+	Y	Y	2b
Dommelen et al. (2020)	Y	Y	Y	NA	NA	NA	NA	NA	Y	NA	Y	Y	N	N	Y	N	++	Y	Y	2b
Wang et al. (2021)	Y	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	Y	Y	NA	NA	-	Y	Y	4
Norcia et al. (2021)	Y	Y	Y	NA	NA	NA	Y	Y	Y	NA	Y	Y	N	N	Y	N	++	Y	Y	2b
Thangarajh et al. (2021)	Y	Y	Y	NA	?	NA	NA	NA	Y	N	Y	Y	Y	Y	Y	N	++	Y	Y	2b
Donovan et al. (2021)	Y	Y	Y	NA	50%	?	Y	Y	Y	N	Y	Y	Y	Y	Y	N	++	Y	Y	2b
Brogna et al. (2021)	Y	NA	Y	NA	13%	NA	NA	NA	Y	N	NA	Y	N	N	N	N	+	Y	Y	2b
Mayhew et al. (2022)	Y	NA	Y	NA	16%	NA	NA	NA	Y	N	NA	Y	Y	N	N	N	+	Y	Y	2b
Yan-Li Ma et al. (2022)	Y	Y	Y	NA	NA	NA	Y	Y	Y	NA	NA	Y	N	N	N	N	+	Y	Y	2b
Chieffo et al. (2022)	Y	Y	N	NA	NA	NA	Y	Y	Y	N	NA	Y	Y	N	N	N	+	Y	Y	2b

SIGN Methodology checklist: Cohort Studies

S1: Internal Validity

1. The study addresses an appropriate and clearly focused question.

Internal Validity: Selection of subjects

2. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.
3. The study indicates how many of the people asked to take part did so, in each of the groups being studied.
4. The likelihood that some eligible subject might have the outcome at the time of enrolment is assessed and taken into account in the analysis.
5. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.
6. Comparison is made between full participants and those lost to follow up, by exposure status.
7. Cases are clearly defined and differentiated from possible controls?
8. It is clearly established that controls are non-cases?

Internal Validity: Assessment

9. The outcomes are clearly defined.
10. The assessment of outcome is made blind to exposure status. If the study is retrospective, this may not be applicable.
11. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.
12. The method of assessment of exposure is reliable.
13. Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.
14. Exposure level or prognostic factor is assessed more than once.

Internal Validity: Confounding

15. The main potential confounders are identified and taken into account in the design and analysis.

Internal Validity: Statistical Analysis

16. Have confidence intervals been provided?

S2: Overall assessment of the study

17. How well was the study done to minimise the risk of bias or confounding?
18. Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?
19. Are the results of this study directly applicable to the patient group targeted in this guideline?
20. Level of evidence.

Possible Answers:

Y: Yes
N: No
NA: not applicable
[?]: Can’t say
[-]: low quality
[+]: acceptable
[++]: high quality

3.3. Results data extraction

3.3.1 Characteristics of the study participants

Participant characteristics for the included studies are fully described in Appendix B. The ages of boys (and men) with DMD ranged between 0 months and 35 years and 1 month, with the age range of the controls being from 8 months to 32 years. Of course, the data extracted pertained to boys below the age 6. Twenty-three studies gave information about mutation sites and type; twenty described glucocorticoid use; only nine gave anthropometric values for the populations.

3.3.2 Description of the developmental domains

3.3.2.1 Motor development

Motor development was described in 46 studies, though using different outcome measures.[3,4,7,8,12,13,40–45,48–56,58–70,72,74–77,79–84,88] First, the achievement of motor milestones and results for general (motor) developmental tools are discussed. Subsequently, results for muscle strength are described, followed by results for different timed tests and walking tests. Finally, results using disease-specific evaluation tools are discussed.

Most boys with DMD achieved gross and fine motor milestones at a later age than healthy children.[4,12,68,74] The three milestones most likely to be achieved later in very young boys with DMD were sitting unaided, walking, and climbing stairs.[3] The age of independent walking was delayed and differed significantly from TD children ($p < 0.001$) and from children with Becker Muscular Dystrophy (BMD) ($p < 0.05$).[79] Desguerre et al. (2009) and Gissy et al. (2017) found that 30% of the children with DMD walked at 17 to 19 months, 23% at 20 to 24 months and 8% later than 24 months.[45,65] They also found that 56% of the boys with DMD had never been able to run and 31% had never been able to climb stairs without support.[45]

Significant differences were found between boys with DMD and TD children in all domains of the Bayley-III Scales ($p < 0.0001$ to $p = 0.002$).[52] The scores on the motor subscales were significantly lower than for TD children ($p < 0.0001$) with gross motor skills more affected than fine motor skills.[52] Lower gross motor scores were also significantly associated with increasing age ($p = 0.02$).[59] Buckon et al. (2016) also found significant decreases of scores on Walking/Running/Jumping dimension skills of the Gross Motor Function Measure (GMFM) with increasing age ($p = 0.046$).[40] Children with DMD performed more poorly than controls on fine motor skills, based on the Developmental NEuroPSYchological Assessment (NEPSY) and Wide Range Assessment of Visual Motor Abilities (WRAVMA).[13] Boys with DMD were delayed relative to familial controls, with the largest differences on the motor scales of the Vineland Adaptive Behaviour Scales (VABS).[13] They also showed significantly lower scores on all subscales of the Griffiths' Mental Development Scales (GMDS) than healthy controls, with the highest discrepancy for the locomotor subscale ($p < 0.001$) which was also strongly negatively correlated with age.[3,41–43,49]

Pane et al. (2013) and Chieffo et al. (2015) found higher Developmental Quotients (DQs) in boys with mutations upstream of or in exon 44 than in boys with mutations downstream of exon 44.[49,60] A significant difference was reported according to site of mutation in favour of boys with mutations upstream of exon 44 for the eye and hand coordination subscale ($p < 0.009$), but not on the locomotor subscale ($p < 0.277$).[49]

Muscle strength was evaluated with the Composite Muscle Score (CMS), manual muscle testing (MMT) using the Medical Research Council (MRC) scale, myometry or (handheld) dynamometry (HHD). Overall, muscle strength was higher in younger boys with DMD than in older boys but, even for younger boys, values compared unfavourably with TD boys.[44,83,84] Beenakker at al. (2005) reported that mean total muscle force of boys with DMD was 2 SD below the expected mean.[84] Buckon et al. (2016) compared isometric and isokinetic concentric knee extensor/flexor strength of 4-7 year old boys with DMD with a normative age-matched data.[40] Corticosteroid and coricosteroid naïve boys with DMD showed less than 50% of isometric and isokinetic concentric knee extensor/flexor strength of controls.[40] A gradual decline in strength in boys with DMD with an overall trend for loss of total muscle strength was associated with age.[40,44,88] Both Hyde et al. (2001) and Doglio et al. (2011) reported significant strength reductions with age in the lower limb muscles, using MRC and MMT respectively.[44,88] The same trends were found in volitional muscle strength assessed using the Biodex System isokinetic dynamometer.[40] Beenakker et al. (2005) found significant negative correlations between the 9m run test and lower limb and proximal muscle forces ($p = 0.047$ and $p = 0.046$).[84]

Several studies used timed function tests (TFTs) (time to rise from floor (TRF), 10m timed tests (10MTT), timed 4 stairs climb (4SC) or walking tests (six-minutes walking test (6MWT)) to evaluate motor development in young boys with DMD. These needed significantly more time to rise from the floor than healthy controls.[8,43,88] In DMD, times also increase with increasing age.[50,66,80] Buckon et al. (2016) found that young boys with DMD (4-7 years old) needed significantly less time than older boys (> 8 years old).[40] Similar findings were reported for the 4SC, with younger boys with DMD needing more time than healthy controls and decreasing velocity with increasing age.[50,66] Speed or times on the 10MTT were also significantly worse in young boys with DMD than in healthy controls.[6,8,43,66,88] Younger boys with DMD (<5 years 6 months to 7 years) achieved better results on the 10MTT than older ones.[6,50,80] For the 100m timed test (100MTT), lower speed was found in the DMD group than age-matched healthy controls, though young boys (4 to 6 years old) with DMD were still able to improve their times.[64] Pereira et al. (2020) showed that running times had already worsened starting from the age of 4 and also, for walking, young boys with DMD lose ground compared to healthy controls starting from the age of 6.[8] Scott et al. (1982) also found significant correlations between age and walking time on the TWT for both the 28-feet and the 150-feet distance, with faster times in younger boys.[83]

Results on the 6MWT showed significantly better results in boys with DMD under the age of seven compared to older boys.[51,75,80] However, younger boys with DMD (aged 5 to 7 years) walked only about

75% of the distance achieved by healthy controls.[66] Changes in walking distance were (significantly) correlated with age in boys with DMD.[6,7,51,55,66]

Brogna et al. (2019) found a significant correlation between 6MWT results and the groups below and above six seconds on the TRF.[7] Donovan et al. (2021) showed a decline in step count with increasing age, with boys with DMD aged between 5 and 7 years still achieving significantly better results than older boys. They also found significant relationships between step activity, functional abilities (including TFTs) and strength.[76] Subsequently, gait analysis was performed in young boys with DMD: significant differences in temporal and stride parameters and increased cadences and decreased step lengths were reported in boys with DMD between 5 years and 6 years 8 months old.[88] Based on StepWatch activity, a significant decrease in the percentage of low frequency strides (-5%) and increased percentage of high frequency strides (+4%) were found in boys with DMD between 4 and 7 years old.[69] Finally, more disease specific tools for neuromuscular disorders or DMD were used. Motor ability scores were significantly worse in boys with DMD than in healthy controls.[43,44,83,88] Connolly et al. (2013) found significant increases in scores with age with the Hammersmith Functional Motor Scales-Expanded (HMFSE) in young boys between 0 and 3 years old ($p < 0.001$).[52] However, in older boys, motor ability scores seemed to reduce with age.[83] North Star Ambulatory Assessment (NSAA) total scores were significantly higher in boys under the age of 7 years 2 months ($p < 0.002$), than for older boys with DMD.[48,49,53,72,80] Young boys with DMD between 3 and 5 years old were not able to obtain a full score on the NSAA and scored significantly lower than controls.[61,63] Finally, improvements in Performance of Upper Limb (PUL) scores were found in young boys with DMD.[58] However, while almost all TD boys achieved maximum scores around the age of 5, young boys with DMD did not achieve the same functional level. In the younger DMD group (<5 years of age), the difference in scores with TD peers was mainly obvious at the shoulder level dimension.[58,70,77] In TD, PUL scores remained stable after the age of 5, whereas in the DMD cohort a steady deterioration in scores was found.[58]

3.3.2.2 Cognitive development

Cognitive development was investigated in 19 studies, using different outcome measures.[12,13,59,60,67,68,73,78,81,82,85,41,42,45–47,52,54,57] In young boys with DMD (0 to 3 years old), Bayley-III cognition scores showed a significant shift to the left on the normal distribution curve ($p < 0.0001$).[52] Also on the GMDS, young boys with DMD scored significantly lower than controls.[41,42,60] Another study showed delays in mental milestones in 14% of patients with DMD.[68] Two studies reported a global cognitive delay in DMD compared to controls.[13,56] Boys with DMD seem to score significantly lower compared to standardised normative data on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI).[46] Half of the boys with DMD showed normal cognitive development, but around 16% had borderline intelligence, 26% encountered learning difficulties (IQ 85-70) and 11 to 17% had an intellectual disability (IQ<70).[54,68] Wingeier et al. (2011) found no significant association between IQ and age.[47]

Desguerre et al. (2009) described four clusters of boys with DMD: cluster A (20%); B (28%); C (22%) and D (30%).[45] Most boys in cluster A showed moderate or severe intellectual disabilities and 86% had more than three years of school delay. In cluster B, most showed moderate intellectual disabilities and poor motor outcomes, with 26% having more than 3 years of school delay. In cluster C, boys had normal intelligence and delayed motor impairment. In cluster D, boys had normal intelligence but poor motor outcomes; 86% attended ordinary education.[45]

Thangarajh et al. (2019) found that boys with mutations downstream of 45 had significantly more learning difficulties ($p < 0,03$).[73] Chieffo et al. (2015) found a significant difference in WPPSI scores between boys with mutations upstream of exon 44 and those with mutations in exons 44-45 for Full Scale Intelligence Quotient ($p < 0.003$). Loss of the distal dystrophin isoform Dp140 was associated with cognitive disability.[54,68,82]

3.3.2.3 Language development

Twelve studies described language development.[3,12,78,85,13,41,42,49,52,59,67,73] Young boys with DMD showed delayed language milestones.[3] When children with DMD scored late on constructing complete sentences, they were more likely to perform poorly on measures of single-word vocabulary ($p < 0.001$).[12] Young boys with DMD between 8 months and 7 years of age scored significantly lower on the language parts of the GMDS, the Reynell Developmental Language Scales (RDLS), on the GDMS hearing-speech subscales ($p < 0.001$), and both on Bayley-III receptive and expressive language subscales ($p < 0.002$).[3,12,13,41,42,52] Based on the RDLS, both verbal comprehension and expressive language scores were lower in boys with DMD than in age-matched controls.[41,42] Within the DMD group lower scores were found for expressive language than for verbal comprehension ($p < 0.001$).[42] Boys with DMD were more likely to read later than their unaffected siblings ($p < 0,001$).[12] Waring & Woodyatt (2011) reported results for phonological awareness in five boys with DMD aged between 4 years 10 months and 6 years 9 months, measured with the Preschool and Primary Inventory of Phonological Awareness (PIPA): boys with DMD scored significantly lower than the control group on tests of Syllable Segmentation ($p < 0.035$), Rhyme Awareness ($p < 0.009$), Alliteration Awareness ($p < 0.011$) and Phoneme Isolation ($p < 0.041$).[85] Chieffo et al. (2022). described language difficulties in a cohort of 20 boys with DMD using the Batteria per la Valutazione del Linguaggio in Bambini dai 4 ai 12 anni (BVL 4-12). Abnormal scores (= -2 standard deviations (SD)) were found for lexical and syntactic comprehension in 10% of the boys with DMD. In terms of language production, abnormal scores were found on denomination (in 5%), articulation (in 80%) and, for oral repetition skills, on word repetition (in 20%) and on sentence repetition (in 80%).[78]

Pane et al. (2013) found significant differences in favour of boys with mutations upstream of exon 44 for the hearing-speech subscale of the GDMS ($p<0.0012$).[49] In 2019, Thangarajh et al. (2019) described language difficulties in a cohort of 196 boys with DMD between 4 years 1 month and 8 years using a parental review.[73] They found significantly more language delay in boys with mutations downstream of

exon 45 (48%) (p = 0.005). These boys were also later with talking (p=0.03).[73] There were no significant differences among DMD mutation subtypes for speech delay.[73]

3.3.2.4 Behavioural development

Behavioural development was described in ten studies.[12,13,42,52,59,71,73,74,86,89] Several reported behavioural problems in boys with DMD between the ages of 1 month and 7 years.[13,42,52,59] A significant difference was found between controls and boys with DMD on the Behaviour Screening questionnaire (BSQ) ($p < 0.001$).[42] Based on the adaptive behaviour questionnaire of the Bayley-III and the VABS, boys with DMD showed significant delays in adaptive behaviour skills compared to unaffected children ($p < 0.05$).[13,52,59] In line with these results, retrospective data of 76 boys with DMD showed significant delays of adaptive behaviour and personal/social behaviour milestones compared to TD children ($p < 0.01$), based on the Dutch Development Instrument (DDI).[74] No significant differences in behavioural development were found between boys with DMD who achieved milestones like walking, sitting and crawling on time compared with boys who were delayed in these milestones, using the Child Behaviour Check List (CBCL).[12]

In a cross-sectional study of different types of behaviour, measured by the IOWA Conners scale (ICS), 8% of boys with DMD met the criteria for inattentive-impulsive-overactive (IO) and 5% for oppositional-defiant (OD) behaviours (including 8% of those with mutations downstream of exon 45 but only 1% of those with mutations upstream of exon 45).[73] Moreover, using parental reported measures, Attention Deficit Hyperactivity Disorder (ADHD) frequency appeared also to be higher in boys with mutations downstream of exon 45, though not significantly ($p = 0.06$).[73] Ricotti et al. (2016) described one boy within the age range of this review, who was suggestive for having Autism Spectrum Disorder (ASD).[89]

3.3.2.5 Social emotional development

Social emotional development was described in nine studies.[13,16,49,57,59,60,67,73,74] Based on the DDI, young boys with DMD achieved milestones of personal/social behaviour and communication later than TD children. Reported in the youngest age group (2 to 3 months), this was confirmed at a later age (12 to 48 months) ($p < 0.01$).[74] Young boys with DMD scored significantly delayed from the control group ($p < 0.001$) on the personal-social subscale of the GMDS.[41]

A significant difference according to site of mutation in favour of boys with mutations upstream of exon 44 was also found with this subscale.[49] Cyrulnik et al. (2008) found that 20 children with DMD between 3 and 6 years of age were delayed relative to familial controls on VABS in communication, daily living and socialisation (1 SD lower than controls).[13] Three boys (within the age range of this review) scored DQs of 82, 96 and 105 on the social emotional Vineland-Doll Scale (VDS).[57]

3.3.2.6 Interaction between developmental domains

In 10 studies, interactions between the five different developmental domains were described.[3,12,13,42,49,52,56,60,82,86] A correlation was found in the DMD group between the locomotor subscale and the other subscales of the GMDS.[42] Chieffo et al. (2015) reported in a longitudinal study of 41 boys with DMD a significant correlation ($p < 0.0001$) between total IQ (WPPSI III) and DQ (GMDS), even when the locomotor subscale was excluded.[60] Furthermore, they found a significant correlation between VIQ and the hearing and speech subscale ($p < 0.0032$) and between PIQ and the performance ($p < 0.0001$) and eye and hand coordination ($p < 0.0001$) subscales.[60]

Parson et al. (2004) explored the relationship between language and motor milestones in 18 boys with DMD. No interaction was found between delays in walking and delayed language development.[3]

Three studies described the association between language and cognitive development.[12,13,52] Connolly et al. (2013) found a significant correlation between the language and cognitive subscales of the Bayley-III ($p < 0.0001$).[52] Subsequently, Cyrulnik et al. (2007) found that boys scoring late on constructing complete sentences were more likely to perform poorly on single-word vocabulary ($p < 0.001$) and also on visuospatial reasoning ($p = 0.002$).[12] Cyrulnik et al. (2008) also found that communication scores were strongly associated with cognitive outcomes ($p < 0.001$), though motor scores were not.[13] Three other studies reported results for associations between cognitive and motor development. A significant association was found between cognitive delay, such as in visuospatial reasoning, and delay in walking. Boys with DMD who walked at or after 16 months of age had three times the risk of also progressing more slowly at school.[12,56] On the other hand, Leibowitz & Dubowitz (1981) found no interaction between IQ and degree of disability.[82]

Finally, a significant association between parent-reported adaptive behaviours and child cognitive performance ($p < 0.05$) was described in boys with DMD.[13]

4. DISCUSSION

4.1 Different developmental domains and their interactions

When investigating early development in young preschool boys with DMD, most studies pay attention to gross motor development because delays in gross motor milestones are one of the first clear symptoms. However, DMD is also known to be associated with cognitive, language, behavioural and social emotional deficits. Therefore, insights into the different developmental domains are necessary to contribute to early intervention and in addition may lead to more targeted therapeutic approaches.

Gross motor milestones, such as independent walking, are achieved later in boys with DMD than in TD children. Overall, gross motor skills are more affected than fine motor skills,[12,13,45,52,54,59,65,68,74] but the latter are also already affected in young boys with DMD.[74] It is not yet clear which specific fine motor tasks are the most difficult. Van der Fels et al. (2014) found a correlation between fine motor skills and cognition in TD children.[90] While the main focus of therapy in young boys with DMD lies in gaining

gross motor skills, the results of this study favour a shift to a broader psychomotor approach, including both gross and fine motor skills in infants and young boys with DMD.

A strong negative correlation is found between gross motor function and age.[3,13,40–44,49,52,59,83,84,88] This mirrors the degenerative disease process of DMD at the level of the muscles. Boys with DMD show a gradual decline in muscle strength, especially for knee extensors and hip flexors, with an overall trend for loss associated with age.[40,44,83] Significant muscle weakness is already apparent in young boys with DMD regardless of corticosteroid treatment.[40] The variability in results for muscle strength can be attributed to the variability in disease progression between boys with DMD. The low reliability of strength measurements in young children could also contribute to these differences. Additionally, the velocity of execution of functional tasks is reduced in young boys with DMD compared to TD children, further decreasing with age.[8,64,66,80] The TFTs rely on explosive power and thus muscle strength, which is reduced from a young age in boys with DMD. Also, the results for walking tests show deterioration of gait in DMD compared to healthy children and distances achieved correlate negatively with the age, starting from the age of 6 to 7 years.[7,8,40,48,51,53,64,66,83] The attention and compliance required to perform walking tests such as the 6MWT may be an additional challenge for young boys with DMD. Despite improvements in function up until the age of seven, they never achieve the same functional level as healthy children, and the difference only increases.[5–8,40,72] However, the time when boys with DMD reach a plateau in motor skills or start declining is not clearly defined and varies from subject to subject and with different functional skills. Only one study described the relation between site of mutation and motor development. No significant difference was found according to mutation site for gross motor skills, but one was found for fine motor skills in favour of boys with mutations upstream of exon 44.[49]

Various studies report on motor function in boys with DMD, starting from the age of 5 years and older, but still little is known about younger boys with DMD. Most studies focus only on gross motor development while fine skills were less mapped. In addition, many different outcome measures were used. These findings warrant further investigation of gross and fine motor function in young boys with DMD.

Next, we investigated the evidence about early cognitive development in DMD. DMD is caused by a mutation in the dystrophin gene which affects the amount of dystrophin protein in muscle fibres but also in the central nervous system. The effect of loss of dystrophin in the brain is less well described, but a link with intellectual disability has been found.[15] A global cognitive delay has been reported in boys with DMD compared to controls, especially in the performance, practical reasoning, verbal comprehension, reading, visuospatial skills, attention and memory domains.[12,13,41,42,56,78] Connolly et al. (2013) found a shift to the left in the normal distribution for the cognitive subscale of the Bayley-III.[52] Subsequently, reduced intellectual functioning in school-age boys with DMD is reported, with an overall intelligent quotient (IQ) about 1 SD below the average IQ.[13,54,59,68] However, variability is seen in cognitive development in young boys with DMD, which might be explained by the site of the mutation.

Ricotti et al. (2016) reported that mutations towards the distal 3', which also involve the short brain-expressed isoforms Dp140 and Dp71, have more devastating effects on the neurocognitive phenotype of DMD.[16] Full-scale IQ scores differ between boys with mutations upstream of exon 44 and those who have mutations in and downstream of exons 44-45.[45,60,73] Moreover, mutations before exon 30 only affect long dystrophin isoforms: these mutations are positively correlated with IQ.[45] Not all studies take site of mutation into account.

Preschool boys with DMD also experience delays in language milestones (speaking first words, speaking full sentences).[3,12] However, these results should be interpreted with caution since they rely on parental report and thus create the possibility of interviewer or recall bias. Cross-sectional data on language development using different evaluation tools show that young boys with DMD experience difficulties with receptive and expressive language, compared to TD children.[3,12,13,41,42,59,78] Greater language delay was found in boys with mutations downstream of exon 45. These mutations lead to a different maturation process and delay in the language domain compared to TD children.[49,60] No differences in language delay were found among the different DMD mutations subtypes.[73] Type and site of mutation are not always taken into account in the analysis of results, making it possible that there is large variability in levels of language impairment in young boys with DMD. There is also no consensus about language evaluation tools.

Boys with DMD younger than 6 years also show differences in behavioural development when compared with TD boys. The main problem in boys with DMD is in adaptive behaviour and the achievement of these milestones.[13,42,52,59,74] No distinction is made between boys with different mutations, making it highly possible that there is a large variability within behavioural development in boys with DMD. Also, different evaluation tools were used. Aside from delays in adaptive behaviour, different types of behavioural problems have been reported in boys with DMD. Forty percent of boys with DMD have been found to have behavioural and social emotional problems.[91] Moreover, the prevalence of a diagnosis of neuropsychiatric behavioural disorders (e.g. ASD, ADHD, OCD, …) among boys with DMD is higher than in the healthy population.[16,18] The frequency of ADHD and other behavioural problems seems higher in boys with mutations downstream of exon 45.[73] These results suggest that not all boys experience behavioural problems. However, these data are based on only one study using parental reports, allowing for the chance of recall bias or interviewer bias.

Finally, different social emotional characteristics were found in young boys with DMD from TD children.[13,41,57] Young boys with DMD achieve milestones of personal and social behaviour and communication later than TD boys.[74] Similar results were described by Darke et al. (2006), who found approximately 40% of children with DMD aged between 5 and 13 years to have social emotional and behavioural problems.[91] However, social emotional development in young boys with DMD has not been deeply investigated yet.

We also described interactions between the different developmental domains. A correlation between motor functioning and the other developmental domains was reported, suggesting that worse motor function is related to greater delays in other developmental domains.[42,86] Further, a correlation is reported between cognitive abilities and general DQ, suggesting that cognition influences global development.[60] In addition, mutations upstream of exon 44 seem to have a less substantial influence on DQ than those downstream of exon 44.[49,60] Further, strong correlations were found between language impairments and cognitive delays,[12,13,52] between delays in walking and cognitive problems,[12,56] and between adaptive behaviour and cognitive performance.[13] In contrast, Leibowitz and Dubowitz et al. (1981) report no interaction between degree of disability and IQ.[82] Parsons et al. (2004) found no relationship between delays in language and motor milestones.[3] These differences in results could be explained by the wide variability of phenotypes of young boys with DMD because of different mutation types and sites in the DMD gene. Alternatively, these contradictions could also be related to differences in the quality of the relevant studies and the use or non-use of validated evaluation tools, such as the Bayley-III scales.

We can conclude for each domain that further research, using uniform outcome measures, taking type and site of mutation into account, preferably using longitudinal designs, is needed in order to extend knowledge about the different developmental domains and to understand their inter-relationship in young boys with DMD below the age of six.

4.2 Strengths and limitations of the literature review

This is the first review to explore five different developmental domains and the relation between domains in young boys with DMD, including additionally findings on the influence of type and site of mutation. To ensure that all the available literature on this topic was included, a wide search strategy with an extensive number of combinations of MeSH-terms and keywords was formulated and conducted in three different databases (PubMed, Web of Science and Scopus). This resulted in numerous hits and a large number of included studies. However, the quality of the studies was rather moderate. Pooling and comparing results were difficult due to the wide range of evaluation tools used in the different studies. Another limitation of this review is the complexity of the quality assessment. Because of the wide variety of designs of included studies, an adapted version of the SIGN checklist for case-control and cohort studies was used, which could have influenced the quality assessment. Nevertheless, we feel that this checklist was the most appropriate one to detect different biases in the included studies.

4.3 Implications and recommendations for future research

This review shows that infants and young boys with DMD experience more than only motor problems. Further, a large variability in phenotypes of DMD was found. Better insights in these different phenotypes and relations with the different types and sites of mutations seen in DMD could provide a better overview of early development in this population. Furthermore, these insights might contribute to

earlier detection of difficulties, facilitating early intervention strategies adapted to the individual young boy with DMD.

The results of this study also emphasise the need for harmonisation in evaluation and follow-up of young boys with DMD. A standardised longitudinal protocol to evaluate the different developmental domains in these boys, if widely used, would facilitate the comparison of development of different DMD populations.

5. CONCLUSIONS

This review aimed to identify and map the literature on the early motor, cognitive, language, behavioural, and social emotional development in infants and young boys with DMD between 0 and 6 years old. Preschool boys with DMD score more poorly in different developmental domains than TD children. Furthermore, significant interactions between several developmental domains were found. There are indications that type and site of mutation can explain the wide variability in outcomes in young boys with DMD. Evidence on the early development of young boys with DMD is still scarce. Therefore, more high-quality research with longitudinal designs into the different early developmental domains in young boys with DMD is needed to provide a greater awareness of symptoms and their associated early intervention strategies.

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REFERENCES

1. Mendell JR, Shilling C, Leslie ND, et al. Evidence-Based Path to Newborn Screening for Duchenne Muscular Dystrophy. *Ann Neurol*. 2012;71(3):304-313. doi:10.1002/ana.23528

2. Hoffman E, Brown R, Kunkel L. Dystrophin: The protein product of the Duchenne muscular dystrophy locus. *Cell*. 1987;51(6):919-928. doi:10.1016/0092-8674(87)90579-4

3. Parsons EP, Clarke AJ, Bradley DM. Developmental progress in Duchenne muscular dystrophy: Lessons for earlier detection. *Eur J Paediatr Neurol*. 2004;8(3):145-153. doi:10.1016/j.ejpn.2004.01.009

4. Norcia G, Lucibello S, Coratti G, Onesimo R, Pede E. Early Gross Motor Milestones in Duchenne Muscular Dystrophy. 2021;8:453-456. doi:10.3233/JND-210640

5. McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. *Muscle Nerve*. 2010;41 (4)(April):500-510. doi:10.1002/mus.21544

6. Mazzone E, Vasco G, Sormani MP, et al. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. *Neurology*. 2011;77:250-256. doi:10.1212/WNL.0b013e318225ab2e

7. Brogna C, Coratti G, Pane M, et al. Long-term natural history data in Duchenne muscular dystrophy ambulant patients with mutations amenable to skip exons 44 , 45 , 51 and 53. *PLoS One*. 2019;14(6): e0218683. doi:10.1371/journal.pone.0218683

8. Pereira AC, Prufer de Queiroz Campos Araujo A, Goncalves Ribeiro M. Can simple and low-cost motor function assessments help in the diagnostic suspicion of Duchenne muscular dystrophy ? *J Pediatr (Rio J)*. 2020;96:503-510. doi:10.1016/j.jped.2019.02.003

9. Landfeldt E, Thompson R, Sejersen T, McMillan HJ, Kirschner J, Lochmüller H. Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. *Eur J Epidemiol*. 2020;35(7):643-653. doi:10.1007/s10654-020-00613-8

10. Cotton S, Voudouris NJ, Greenwood KM. Intelligence and Duchenne muscular dystrophy: Full-Scale, Verbal, and Performance intelligence quotients. *Dev Med Child Neurol*. 2001;43(7):497-501. doi:10.1111/j.1469-8749.2001.tb00750.x

11. Hinton VJ, De Vivo DC, Fee RJ, Goldstein E, Stern Y. Investigation of Poor Academic Achievement in Children with Duchenne Muscular Dystrophy. *Learn Disabil Res Pr*. 2004;19(3):146-154. doi:10.1111/j.1540-5826.2004.00098.x

12. Cyrulnik SE, Fee RJ, De Vivo DC, Goldstein E, Hinton VJ. Delayed Developmental Language Milestones in Children with Duchenne's Muscular Dystrophy. *J Pediatr*. 2007;150(5):474-478. doi:10.1016/j.jpeds.2006.12.045

13. Cyrulnik SE, Fee RJ, Batchelder A, Kiefel J, Goldstein E, Hinton VJ. Cognitive and adaptive deficits in young children with Duchenne muscular dystrophy (DMD). *J Int Neuropsychol Soc*. 2008;14(5):853-861. doi:10.1017/S135561770808106X

14. Hinton VJ, Nereo N, Fee R, Cyrulnik SE. Social Behavior Problems in Boys with Duchenne Muscular Dystrophy. *J Dev Behav Pediatr*. 2006;27(6):470-476. doi: 10.1097/00004703-200612000-00003

15. Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, Stern Y. Selective deficits in verbal working memory associated with a known genetic etiology: The neuropsychological profile of Duchenne muscular dystrophy. *J Int Neuropsychol Soc*. 2001;7(1):45-54. doi:10.1017/S1355617701711058

16. Ricotti V, Mandy WPL, Scoto M, et al. Neurodevelopmental, emotional, and behavioural problems in Duchenne muscular dystrophy in relation to underlying dystrophin gene mutations. *Dev Med Child Neurol*. 2016;58(1):77-84. doi:10.1111/dmcn.12922

17. Jane Prosser E, Murphy EG, Thompson MW. Intelligence and the gene for duchenne muscular dystrophy. *Arch Dis Child*. 1969;44(234):221-230. doi:10.1136/adc.44.234.221

18. Hendriksen JGM, Vles JSH. Neuropsychiatric Disorders in Males With Duchenne Muscular Dystrophy: Frequency Rate of Attention-Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder, and Obsessive—Compulsive Disorder. *J Child Neurol*. 2008;23(5):477-481. doi:10.1177/0883073807309775

19. Bushby KMD, Hill A, Steele JG. Failure of early diagnosis in symptomatic Duchenne muscular dystrophy. *Lancet*. 1999;353(9152):557-558. doi:10.1016/s0140-6736(98)05279-9

20. Ciafaloni E, Fox DJ, Pandya S, et al. Delayed Diagnosis in Duchenne Muscular Dystrophy: Data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). *J Pediatr*. 2009;155(3):380-385. doi:10.1016/j.jpeds.2009.02.007

21. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010;9(1):77-93. doi:10.1016/S1474-4422(09)70271-6

22. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMC*. 2021;10(1):89. doi: 10.1186/s13643-021-01626-4

23. Portney L, Watkins M. *Foundations of Clinical Research: Pearson New International Edition (3rd Edition)*.; 2013.

24. Dubowitz V. Intellectual impairment in muscular dystrophy. *Arch Dis Child*. 1965;40(211):293-301. doi:10.1136/adc.40.211.296

25. Rosman NP, Kakulas BA. Mental deficiency associated with muscular dystrophy. *Brain*. 1966;89(4):769-788. doi: 10.1093/brain/89.4.769

26. Lenk U, Oexle K, Voit T, et al. A cysteine 3340 substitution in the dystroglycan-binding domain of dystrophin associated with Duchenne muscular dystrophy, mental retardation and absence of the ERG b-wave. *Hum Mol Genet*. 1996;5(7):973-975. doi:10.1093/hmg/5.7.973

27. Iwańczak F, Stawarski A, Potyrała M, Siedlecka-Dawidko J, Agrawal GS. Early symptoms of Duchenne muscular dystrophy - Description of cases of an 18-month-old and an 8-year-old patient. *Med Sci Monit*. 2000;6(3):592-595.

28. Jay V, Vajsar J. The Dystrophy of Duchenne. *Lancet*. 2001;357(9255):550-552. doi: 10.1016/s0140-6736(00)04052-6

29. Essex C, Roper H. Lesson of the week: Late diagnosis of Duchenne's muscular dystrophy presenting as global developmental delay. *BMJ*. 2001;323(7303):37-38. doi: 10.1136/bmj.323.7303.37

30. Erturk O, Bilguvar K, Korkmaz B, et al. A patient with duchenne muscular dystrophy and autism demonstrates a hemizygous deletion affecting dystrophin. *Am J Med Genet Part A*. 2010;152(4):1039-1042. doi:10.1002/ajmg.a.33312

31. Wang L, Lin J, Xiong F, et al. A rare case of monozygotic triplets with Duchenne Muscular Dystrophy. *Neuromuscul Disord*. 2021;31(5):456-461. doi:10.1016/j.nmd.2021.02.005

32. Winarno S, Arman I, Waloejo S, Kristanti L. Progressive Muscular Dystrophy (Duchenne Type) (Case Report). *Paediatr Indones*. 1976;16:361-364.

33. Allsop KG, Ziter FA. Loss of Strength and Functional Decline in Duchenne's Dystrophy. *Arch Neurol*. 1981;38(7):406-411. doi:10.1001/archneur.1981.00510070040004

34. Crisp DE, Ziter FA, Bray PF. Diagnostic Delay in Duchenne ' s Muscular Dystrophy. *JAMA*. 1982;274(4):478-480. doi: 10.1001/jama.247.4.478

35. Renier WO, Nabben FA, Hustinx TW, et al. Congenital adrenal hypoplasia, progressive muscular dystrophy, and severe mental retardation, in association with glycerol kinase deficiency, in male sibs. *Clin Genet*. 1983;24(4):243-251. doi:10.1111/j.1399-0004.1983.tb00078.x.

36. Komoto J, Usui S, Otsuki S, Terao A. Infantile autism and Duchenne muscular dystrophy. *J Autism Dev Disord*. 1984;14(2):191-195. doi: 10.1177/0883073818774439

37. Kaplan L, Osborne P, Ellas E. The diagnosis of muscular dystrophy in patients referred for language delay. *J Child Psychol Psychiatry*. 1986;27(4):545-549. doi: 10.1111/j.1469-7610.1986.tb00641.x

38. Covone A, Lerone M, Romeo G. Genotype-phenotype correlation and germline mosaicism in DMD/BMD patients with deletions of the dystrophin gene. *Hum Genet*. 1991;87(3). doi: 10.1007/bf00200919

39. Topaloglu H, Dinçer P, Gögüs S, Ayter S, Topçu M. Unusual case of duchenne muscular dystrophy (DMD). *Pediatr Neurol*. 1992;8(5):410. doi: 10.1016/j.nmd.2021.02.005

40. Buckon C, Sienko S, Bagley A, et al. Can quantitative muscle strength and functional motor ability differentiate the influence of age and corticosteroids in ambulatory boys with Duchenne muscular dystrophy? *PLoS Curr*. 2016;8: ecurrents.md.1ced64dff945f8958221fddcd4ee60b0).doi:10.137 1/currents.md.1ced64dff945f8958221fddcd4ee60b0

41. Smith R A, Sibert JR, Wallace SJ, Harper PS. Early diagnosis and secondary prevention of Duchenne muscular dystrophy. *Arch Dis Child*. 1989;64(6):787-790. doi:10.1136/adc.64.6.787

42. Smith R A, Sibert JR, Harper PS. Early development of boys with Duchenne muscular dystrophy. *Dev Med Child Neurol*. 1990;Jun 32(6):519-527. doi:10.1111/j.1469-8749.1990.tb16978.x

43. Smith R A, Newcombe R g, Sibert JR, Harper PS. Assessment of locomotor function in young boys with Duchenne Muscular Dystrophy. *Muscle and Nerve*. 1991;14(5):462-469. doi:10.1002/mus.880140513

44. Hyde SA, Steffensen BF, Flyotrup I, et al. Longitudinal data analysis: An application to construction of a natural history profile of Duchenne muscular dystrophy. *Neuromuscul Disord*. 2001;11(2):165-170. doi:10.1016/S0960-8966(00)00175-9

45. Desguerre I, Christov C, Mayer M, et al. Clinical heterogeneity of Duchenne muscular dystrophy (DMD): Definition of sub-phenotypes and predictive criteria by long-term follow-up. *PLoS One*. 2009;4(2):e4347. doi:10.1371/journal.pone.0004347

46. Taylor PJ, Betts GA, Maroulis S, et al. Dystrophin gene mutation location and the risk of cognitive impairment in duchenne muscular dystrophy. *PLoS One*. 2010;5(1):e8803. doi:10.1371/journal.pone.0008803

47. Wingeier K, Giger E, Strozzi S, et al. Neuropsychological impairments and the impact of

dystrophin mutations on general cognitive functioning of patients with Duchenne muscular dystrophy. *J Clin Neurosci*. 2011;18(1):90-95. doi:10.1016/j.jocn.2010.07.118

48. Mazzone E, Vasco G, Sormani MP, et al. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. *Neurology*. 2011;77(3):250-256. doi:10.1212/WNL.0b013e318225ab2e

49. Pane M, Scalise R, Berardinelli A, et al. Early neurodevelopmental assessment in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2013;23(6):451-455. doi:10.1016/j.nmd.2013.02.012

50. Henricson EK, Abresch RT, Cnaan A, et al. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcomes. *Muscle Nerve*. 2013;48(1):55-67. doi:10.1002/mus.23808.

51. Mazzone ES, Pane M, Sormani MP, et al. 24 Month Longitudinal Data in Ambulant Boys with Duchenne Muscular Dystrophy. *PLoS One*. 2013;8(1):e52512. doi:10.1371/journal.pone.0052512

52. Connolly AM, Florence JM, Cradock MM, et al. Motor and cognitive assessment of infants and young boys with Duchenne Muscular Dystrophy: Results from the Muscular Dystrophy Association DMD Clinical Research Network. *Neuromuscul Disord*. 2013;23(7):529-539. doi:10.1016/j.nmd.2013.04.005

53. Pane M, Mazzone ES, Sivo S, et al. Long term natural history data in ambulant boys with duchenne muscular dystrophy: 36-month changes. *PLoS One*. 2014;9(10):e108205. doi:10.1371/journal.pone.0108205

54. Sarrazin E, Hagen M Von Der, Schara U, Von Au K, Kaindl AM. Growth and psychomotor development of patients with Duchenne muscular dystrophy. *Eur J Paediatr Neurol*. 2014;18(1):38-44. doi:10.1016/j.ejpn.2013.08.008

55. Pane M, Mazzone ES, Sormani MP, et al. 6 minute walk test in Duchenne MD patients with different mutations: 12 month changes. *PLoS One*. 2014;9(1):e83400. doi:10.1371/journal.pone.0083400

56. Mirski KT, Crawford TO. Motor and cognitive delay in Duchenne muscular dystrophy: Implication for early diagnosis. *J Pediatr*. 2014;165(5):1008-1010. doi:10.1016/j.jpeds.2014.07.006

57. Rasic M V., Vojinovic D, Pesovic J, et al. Intellectual ability in the duchenne muscular

dystrophy and dystrophin gene mutation location. *Balk J Med Genet*. 2014;17(2):25-36. doi:10.2478/bjmg-2014-0071

58. Pane M, Mazzone ES, Fanelli L, et al. Reliability of the Performance of Upper Limb assessment in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2014;24(3):201-206. doi:10.1016/j.nmd.2013.11.014

59. Connolly AM, Florence JM, Cradock MM, et al. One Year Outcome of Boys with Duchenne Muscular Dystrophy Using the Bayley-III Scales of Infant and Toddler Development. *Pediatr Neurol*. 2014;June, 50(6):557-563. doi:10.1038/jid.2014.371

60. Chieffo D, Brogna C, Berardinelli A, et al. Early neurodevelopmental findings predict school age cognitive abilities in duchenne muscular dystrophy: A longitudinal study. *PLoS One*. 2015;10(8):e0133214. doi:10.1371/journal.pone.0133214

61. De Sanctis R, Pane M, Sivo S, et al. Suitability of North Star Ambulatory Assessment in young boys with Duchenne muscular dystrophy. *Neuromuscul Disord*. 2015;25(1):14-18. doi:10.1016/j.nmd.2014.09.015

62. Davidson ZE, Ryan MM, Kornberg AJ, Walker KZ, Truby H. Strong correlation between the 6-minute walk test and accelerometry functional outcomes in boys with duchenne muscular dystrophy. *J Child Neurol*. 2015;30(3):357-363. doi:10.1177/0883073814530502

63. Mercuri E, Coratti G, Messina S, et al. Revised North Star Ambulatory Assessment for Young Boys with Duchenne Muscular Dystrophy. *PLoS One*. 2016;11(8):e01060195. doi:10.1371/journal.pone.0160195

64. Alfano LN, Miller NF, Berry KM, et al. The 100-meter timed test: Normative data in healthy males and comparative pilot outcome data for use in Duchenne muscular dystrophy clinical trials. *Neuromuscul Disord*. 2017;27(5):452-457. doi:10.1016/j.nmd.2017.02.007

65. Gissy JJ, Johnson T, Fox DJ, et al. Delayed onset of ambulation in boys with Duchenne muscular dystrophy: Potential use as an endpoint in clinical trials. *Neuromuscul Disord*. 2017;27(10):905-910. doi:10.1016/j.nmd.2017.06.002

66. Arora H, Willcocks RJ, Lott DJ, et al. Longitudinal timed function tests in Duchenne Muscular Dystrophy: Imaging DMD cohort natural history. *Muscle Nerve*. 2018;58(5):631-638. doi:10.1002/mus.26161.Longitudinal

67. Thangarajh M, Spurney CF, Gordish-Dressman H, et al. Neurodevelopmental Needs in Young Boys with Duchenne Muscular Dystrophy (DMD): Observations from the Cooperative International Neuromuscular Research Group (CINRG) DMD Natural History Study (DNHS). *PLoSCurr*.2018;10:ecurrents.md.4cdeb6970e54034db2bc3dfa54b4d987.

doi:10.1371/currents.md.4cdeb6970e54034db2bc3dfa54b4d987

68. Singh RJ, Manjunath M, Preethish-Kumar V, et al. Natural history of a cohort of Duchenne muscular dystrophy children seen between 1998 and 2014: An observational study from South India. *Neurol India*. 2018;66(1):77-82. doi:10.4103/0028-3886.222881

69. Fowler EG, Staudt LA, Heberer KR, et al. Longitudinal community walking activity in Duchenne muscular dystrophy. *Muscle and Nerve*. 2018;57(3):401-406. doi:10.1002/mus.25743

70. Brogna C, Cristiano L, Tartaglione T, et al. Functional levels and MRI patterns of muscle involvement in upper limbs in Duchenne muscular dystrophy. *PLoS One*. 2018;13(6):e0199222. doi:10.1371/journal.pone.0199222

71. Lee AJ, Buckingham ET, Kauer AJ, Mathews KD. Descriptive Phenotype of Obsessive Compulsive Symptoms in Males With Duchenne Muscular Dystrophy. *J Child Neurol*. 2018;33(9):572-579. doi:10.1177/0883073818774439

72. Muntoni F, Domingos J, Manzur AY, et al. Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy. *PLoS One*. 2019;14(9):e0221097. doi:10.1371/journal.pone.0221097

73. Thangarajh M, Hendriksen J, McDermott MP, Martens W, Hart KA, Griggs RC. Relationships between DMD mutations and neurodevelopment in dystrophinopathy. *Neurology*. 2019;93(17):E1597-E1604. doi:10.1212/WNL.0000000000008363

74. van Dommelen P, van Dijk O, de Wilde JA, Verkerk PH. Early developmental milestones in Duchenne muscular dystrophy. *Dev Med Child Neurol*. 2020;62(10):1198-1204. doi:10.1111/dmcn.14623

75. Thangarajh M, Bello L, Gordish-Dressman H. Longitudinal motor function in proximal versus distal DMD pathogenic variants. *Muscle Nerve*. 2021;64(4):467-473. doi:10.1002/mus.27371

76. Donovan JL, Taivassalo T, Senesac CR, et al. Walking activity in a large cohort of boys with Duchenne Muscular Dystrophy. *Muscle Nerve*. 2021;23(2):192-198. doi:10.1002/mus.27119.

77. Brogna C, Cristiano L, Verdolotti T, et al. Longitudinal motor functional outcomes and magnetic resonance imaging patterns of muscle involvement in upper limbs in duchenne muscular dystrophy. *Med*. 2021;57(11):1267. doi:10.3390/medicina57111267

78. Chieffo DPR, Moriconi F, Mastrilli L, et al. Language Development in Preschool Duchenne Muscular Dystrophy Boys. *Brain Sci*. 2022;12(9):1252. doi:10.3390/brainsci12091252

79. Ma YL, Zhang WH, Chen GH, et al. Walking alone milestone combined reading-frame rule

improves early prediction of Duchenne muscular dystrophy. *Front Pediatr*. 2022;10(1):985878. doi:10.3389/fped.2022.985878

80. Mayhew AG, Moat D, McDermott MP, et al. Functional outcome measures in young, steroid-naïve boys with Duchenne muscular dystrophy. *Neuromuscul Disord*. 2022;32(6):460-467. doi:10.1016/j.nmd.2022.02.012

81. Marsh GG, Munsat TL. Evidence for early impairment of verbal intelligence in Duchenne muscular dystrophy. *Arch Dis Child*. 1974;49(2):118-122. doi:10.1136/adc.49.2.118

82. Leibowitz D, Dubowitz V. Intellect and Behaviour in Duchenne Muscular Dystrophy. *Dev Med Child Neurol*. 1981;23(6):577–590. doi: 10.1111/j.1469-8749.1981.tb02039.x

83. Scott O, Hyde S, Goddard C, Dubowitz V. Quantitation of muscle function in children: A prospective study in duchenne muscular dystrophy. *Muscle Nerve*. 1982;5(4):291-301. doi:10.1002/mus.880050405

84. Beenakker EAC, Maurits NM, Fock JM, Brouwer OF, Hoeven JH Van Der. Functional ability and muscle force in healthy children and ambulant Duchenne muscular dystrophy patients. *Eur J Paediatr Neurol*. 2005;9:387-393. doi:10.1016/j.ejpn.2005.06.004

85. Waring P, Woodyatt G. Phonological awareness skills in young boys with Duchenne muscular dystrophy. *Int J Disabil Dev Educ*. 2011;58(2):155-168. doi:10.1080/1034912X.2011.570503

86. Donald KAM, Mathema H, Thomas KGF, Wilmshurst JM. Intellectual and behavioral functioning in a South African cohort of boys with Duchenne muscular dystrophy. *J Child Neurol*. 2011;26(8):963-969. doi:10.1177/0883073811399149

87. Pernigotti P, Doglio L, Pavan E, Frigo C. Early signs of pathological pattern evaluated by gait analysis in Duchenne muscular dystrophy patients. *Gait Posture*. 2009;27:e27. doi: 10.1016/j.gaitpost.2008.10.044

88. Doglio L, Pavan E, Pernigotti I, Petralia P, Frigo C, Minetti C. Early signs of gait deviation in Duchenne muscular dystrophy. *Eur J Phys Rehabil Med*. 2011;47(4):587-594.

89. Ricotti V, Jägle H, Theodorou M, Moore AT, Muntoni F, Thompson DA. Ocular and neurodevelopmental features of Duchenne muscular dystrophy: A signature of dystrophin function in the central nervous system. *Eur J Hum Genet*. 2016;24(4):562-568. doi:10.1038/ejhg.2015.135

90. van der Fels IMJ, te Wierike SCM, Hartman E, Elferink-Gemser MT, Smith J, Visscher C. The relationship between motor skills and cognitive skills in 4-16 year old typically developing children: A systematic review. *J Sci Med Sport*. 2015;18(6):697-703.

doi:10.1016/j.jsams.2014.09.007

91. Darke J, Bushby K, Couteur A, McConachie H. Survey of behaviour problems in children with neuromuscular diseases. *Eur J Paediatr Neurol*. 2006;10(3):129-134. doi: 10.1016/j.ejpn.2006.04.004

Appendix A1. Concept Map using Boolean operators

AND			
	Muscular Dystrophy, Duchenne	Child*	Child development
	Duchenne Muscular Dystrophy	Child, preschool	Infant development
	Duchenne-Type Progressive Muscular Dystrophy	Preschool Child*	Growth and development
	Duchenne Type Progressive Muscular Dystrophy	Toddler*	Milestone*
	Duchenne	Infant*	Motor skill*
	DMD	Newborn Infant*	Movement*
		Newborn*	Motor activit*
		Neonate*	Extremit*
		Children younger than 6 years of age	Psychomotor performance*
		Age < six years	Visual motor coordination*
		Bab*	Perceptual Motor Performance*
		Boy*	Sensory Motor Performance*
		Kid*	Language Development
		Age	Language*
		Ages	
		Preschool age*	Language Acquisition
		Pre-school age*	Communication*
		Preschooler*	Social Communication*
		Pre-schooler*	Cognition*
		<1 year of age	Cognitive Function*
OR		1 year of age	Adaptation, Psychological
		2 years of age	Psychologic Adaptation
		2 years old	Adjustment
		3 years of age	Coping Skill*
		3 years old	Behavio*
		4 years of age	Adaptive behavio*
		4 years old	Coping behavio*
		5 years of age	Emotional Intelligence*
		5 years of old	Social Intelligence*
		Age < 6 years	Emotional Adjustment*
		0	Psychological Adjustment*
		1	Emotional Adaptation*
		2	
		3	
		4	
		5	
		One	
		Two	
		Three	
		Four	
		Five	

Appendix A2. Search strategies for the different databases

PubMed:

- ("Muscular Dystrophy, Duchenne"[Mesh] OR “Duchenne Muscular Dystrophy”[tiab] OR Duchenne[tiab] or Duchenne*[tiab] OR DMD[tiab] OR DMDS[tiab]) AND ("Child"[Mesh] OR Child*[tiab] OR preschool*[tiab] OR “preschool*”[tiab] OR ”pre-school*”[tiab] OR toddler*[tiab] OR "Infant"[Mesh] OR Infan*[tiab] OR Newborn*[tiab] OR Neonate*[tiab] OR baby[tiab] OR babies[tiab] OR boy[tiab] OR boys[tiab] OR Kid[tiab] OR Kids[tiab] OR ((0[tiab] OR 1[tiab] OR 2[tiab] OR 3[tiab] OR 4[tiab] OR 5[tiab] OR 6[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab]) AND (age[tiab] OR ages[tiab] OR aged[tiab] OR old[tiab] OR year*[tiab]))) AND ("Child Development"[Mesh] OR “Child development”[tiab] OR “Infant Development”[tiab] OR "Growth and Development"[Mesh] OR “Growth and Development”[tiab] OR “Milestone*”[tiab] "Motor Skills"[Mesh] OR “Motor Skill*”[tiab] OR "Movement"[Mesh] OR “Movement*”[tiab] OR "Motor Activity"[Mesh] OR “Motor Activit*”[tiab] OR "Extremities"[Mesh] OR “Extremit*”[tiab] OR "Psychomotor Performance"[Mesh] OR “Psychomotor Performance*”[tiab] OR “Visual Motor Coordination*”[tiab] OR “Perceptual Motor Performance*”[tiab] OR “Sensory Motor Performance*”[tiab] OR "Language"[Mesh] OR “Language*”[tiab] OR "Language Development"[Mesh] OR “Language Development”[tiab] OR “Language Acquisition”[tiab] OR "Communication"[Mesh] OR “Communication*”[tiab] OR “Social Communication*”[tiab] OR "Cognition"[Mesh] OR “Cognition*”[tiab] OR “Cognitive Function*”[tiab] OR "Adaptation, Psychological"[Mesh] OR “Psychologic Adaptation”[tiab] OR “Adjustment”[tiab] OR “Coping Skill*”[tiab] OR “Behavio*”[tiab] OR “Adaptive Behavio*”[tiab] OR “Coping Behavio*”[tiab] OR "Emotional Intelligence"[Mesh] OR “Emotional Intelligence*”[tiab] OR “Social Intelligence*”[tiab] OR "Emotional Adjustment"[Mesh] OR “Emotional Adjustment*”[tiab] OR “Psychological Adjustment*”[tiab] OR “Emotional Adaptation*”[tiab])

Web of Science (WOS):

- (TS=(“Duchenne Muscular Dystrophy” OR “Duchenne*” OR “DMD” OR “DMDS”)) AND (TS=((“Child*” OR “Preschool*” OR “Preschool*” OR “infan*” OR “toddler*” OR “Newborn*” OR “neonate*” OR “boy” OR “boys” OR “baby” OR “babies” OR “kid” OR “kids”) OR ((“0” OR “1” OR “2” OR “3” OR “4” OR “5” OR “6” OR “one” OR “two” OR “three” OR “four” OR “five” OR “six”) NEAR/0 (“age” OR “ages” OR “aged” OR “old” OR “year” OR “years”)))) AND (TS=(“Child development” OR “Infant Development” OR “Growth and Development” OR “Milestone*” OR “Motor Skill*” OR “Movement*” OR “Motor Activit*” OR “Extremit*” OR “Psychomotor Performance*” OR “Visual Motor Coordination*” OR “Perceptual Motor Performance*” OR “Sensory Motor Performance*” OR “Language*” OR “Language Development” OR “Language Acquisition” OR “Communication*” OR “Social Communication*” OR “Cognition*” OR “Cognitive Function*” OR “Adaptation, Psychological” OR “Psychologic Adaptation” OR “Adjustment” OR “Coping Skill*” OR “Behavio*” OR “Adaptive Behavio*” OR “Coping Behavio*” OR “Emotional Intelligence*” OR “Social Intelligence*” OR “Emotional Adjustment*” OR “Psychological Adjustment*” OR “Emotional Adaptation*”))

Scopus:

- (TITLE-ABS-KEY(“Duchenne muscular dystrophy” OR Duchenne OR Duchenne* OR DMD OR DMDS)) AND (TITLE-ABS-KEY ((child* OR preschool* OR “preschool*” OR infan* OR toddler* OR newborn* OR neonate* OR boy OR boys OR baby OR babies OR kid OR kids) OR ((0 OR 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR one OR two OR three OR four OR five OR six) W/0 (age OR ages OR aged OR old OR year OR years)))) AND (TITLE-ABS-KEY (“Child development” OR “Infant Development” OR “Growth and Development” OR “Milestone*” OR “Motor Skill*” OR “Movement*” OR “Motor Activit*” OR “Extremit*” OR “Psychomotor Performance*” OR “Visual Motor Coordination*” OR “Perceptual Motor Performance*” OR “Sensory Motor Performance*” OR “Language*” OR “Language Development” OR “Language Acquisition” OR “Communication*” OR “Social Communication*” OR “Cognition*” OR “Cognitive Function*” OR “Adaptation, Psychological” OR “Psychologic Adaptation” OR “Adjustment” OR “Coping Skill*” OR “Behavio*” OR “Adaptive Behavio*” OR “Coping Behavio*” OR “Emotional Intelligence*” OR “Social Intelligence*” OR “Emotional Adjustment*” OR “Psychological Adjustment*” OR “Emotional Adaptation*”))

Appendix B. Results data extraction of the included studies arranged by publication date (n=55)

Source	N°	Population	Study design	Developmental domain and evaluation tool	Results
Marsh & Munsat (1974)	**81**	**DMD** (n = 34): Age: 5-15y	Cross-sectional	Cognitive: - WISC Motor: - Physical independence rating	Only one boy (5y8mo) in the age range of this review WISC: - Verbal IQ: 80 - Performance IQ: 87 - Full scale IQ: 82 Physical independence rating: - 5: ambulatory unlimited
Leibowitz & Dubowitz (1981)	**82**	**DMD** (n = 57): Age: 3.10-13.7y	Cross-sectional	Cognitive: - WPPSI (4-6.5y) - SBIS (3.10 and 4.4y) - RBQ-B - RBQ-A Motor: - VFS	WPPSI: - Verbal scale IQ: 85 (SD 17) - Performance scale IQ: 93 (SD 18) - Full-scale IQ: 88 (SD 18) - WPPSI scores slightly higher compared to the older children SBIS: - 3.10y: < 43 - 4.4y: 60 RBQ-B - Younger children scored higher on the RBQ-B, type of disturbance did not correlate to age RBQ-A - No significant correlation between age and scores on this test VFS - No link between degree of disability and IQ - Most children: ambulation stage 2

Scott et al. (1982)	**83**	**DMD** (n = 61): Age: 4.3-11.8y	Longitudinal - 3y prospective - Follow up at 3 to 4mo (1977-1979)	Motor: - MRC grading - Myometry - Motor ability score - TWT	MRC grading: - %MRC higher in younger children Myometry (kg) - KE: 5.4 (SD 1.7), KF: 5.4 (SD 1.2), HF: 5.0 (SD 1.3), HE: 2.8 (SD 1.9), HA: 4.0 (SD 1.2), FD: 4.8 (SD 1.2), SA: 2.0 (SD 0.6), WE: 2.0 (SD 0.6) - For all ages: lower values compared to lower limits of normal muscle strength Motor ability score: - Higher in younger children - Decline on sequential assessments - Correlation with %MRC TWT: - Significant correlation between age and walking time - Younger boys: shorter walking times
Smith et al. (1989)	**41**	**DMD** (n = 33) Age: 0.8-6.4y **Control** (n = 21) Age: matches DMD group	Cross- sectional	Cognitive/motor/language - GMDS Language/cognitive - RDLS - PPVT	GMDS: - DMD boys scored significantly lower than controls on all subscales; greatest discrepancy for locomotor and hearing-speech subscales ($p < 0.001$) - Boys diagnosed in the asymptomatic phase → lowest mean age + still showed developmental delay - Boys presenting locomotor problems later → higher mean age + the lowest locomotor score - Lowest mean language score in boys with developmental delay RDLS - Significant difference between DMD boys and controls for verbal comprehension scale A and expressive language scale ($p < 0.001$)

Smith et al. (1990)	**42**	**DMD** (n = 33) Age: 0.83-6.67y **Control** (n = 33) Age: 1.67-6.83y	Longitudinal - Prospective: follow-up of 1y with a 6-monthly interval	Cognitive/motor/language - GMDS Language/cognitive - RDLS - BPVS Behaviour - BSQ	GMDS: - Significant difference between DMDs and controls at each visit ($p < 0.001$) - DMD: low scores on all subscales, with the lowest scores on the locomotor and speech subscales - DMD: significant decrease of locomotor scores over one year ($p < 0.001$) - DMD: lower correlation between locomotor subscale and other subscales compared to control group - DMD: locomotor subscale strongly negatively correlated with age RDLS & BPVS: - Significant difference between DMDs and controls at each visit ($p < 0.001$) - DMD: delayed language development - DMD: lower scores on expressive language compared to verbal comprehension BSQ: - Significant difference between DMDS and controls ($p < 0.001$) - DMD: BSQ scores strongly negatively correlated with all the other scales, except the locomotor scale (GMDS), performance scale (GMDS) and the BPVS
Smith et al. (1991)	**43**	**DMD** (n = 33) Age: 0.83-6.67y **Control** (n = 21) Age: 1.67-6.83y	Longitudinal - Prospective: follow-up of 1y with a 6mo interval	Motor - HMAS - GMDS - MRC scale	HMAS - DMD: Increase in developmental abilities with age, which was markedly different from normal GMDS - Significant differences between means of DMDs and controls at each assessment ($p < 0.001$) - Significant difference in mean quotients between assessments I and II, and assessments I and III within DMD group ($p < 0.001$) - DMD: Negative correlation with age

Hyde et al. (2001)	**44**	**DMD** (n = 27) Age: 4.0-10.08y	Longitudinal - Prospective: follow-up of 30mo with the first and second with a 1mo interval and thereafter at 3-monthly intervals	Motor - MRC - Myometry - MA - Walk time	MRC - Overall trend for loss of %MRC associated with age Myometry (kg) - Significant change over time for KE and HF (p = 0.0002 and p = 0.0036) MA - Reduced MA in relation with age Walk time - Annual decrease in %MRC of 5% corresponds to an additional annual increase in walking time of 11% - Total annual increase in walking time of 20%
Parsons et al. (2004)	**3**	**DMD** (n = 18) Age: 2-3y	Longitudinal - Prospective: follow-up to the age of 48mo - Retrospective	Motor/language - Milestones - GMDS (n=16)	Milestones (90% Denver criterion, 97% criterion identified by Neligan and Prudham) - 3 milestones most likely to be late: locomotor activities → walking, climbing stairs and independent sitting - Every boy had at least one late (locomotor) milestone by 24mo o 94% scored late on either sitting or walking, 67% scored late on both o 72% did not sit by 7.6mo, 33% were sitting on 8mo and 9.3mo, 2 boys were not sitting o 89% did not walk at 13.9mo, 22% did not walk at 18.4mo o 71% failed one, or both, of the language and speech milestones o 81% did not walk upstairs at 22.9mo, 60% could not kick a ball at 23mo, 57% could not jump from a low step at 42mo, 53% could not say meaningful sentences at 29mo, 47% could not say single words at 13.7mo, 35% did not cruise at 13mo o Walking upstairs was never achieved by 5 boys, jumping from a low step was never achieved by 6 boys o No link between late walking and delayed language development GMDS - 56% classified as good average, 31% as low or well below average and 13% identified with developmental deficit - The locomotor score decreased over time, the other scores did not Milestones - Up to the age of 24mo only minor symptoms were detected - Full Gowers' sign: 26-60mo

Beenakker et al. (2005)	**84**	**DMD** (n = 16) Age: 5-8y **Control** (n = 270) Age: 4-11y	Cross-sectional	Motor - TFT: 9m run en TRF - HHD	TFT - DMD: severely declined performance with age - DMD: significant negative correlation between time to run 9m and summed leg muscle force ($p = 0.041$) and summed proximal muscle force ($p = 0.046$) HHD - DMD: Mean scores 2SD below mean for total muscle force
Cyrulnik et al. (2007)	**12**	**DMD** (n = 130) Age: 4-14y **Control** (n = 59) Age: 3-16y - Unaffected siblings	Longitudinal - Retrospective Cross-sectional	Cognitive/language/motor - DDST - Copeland and Kimmel - PPVT - RCPM Behaviour - CBCL	DDST & Copeland and Kimmel (milestones) & PPVT & RCPM o DMD: more often late: sitting, crawling, standing, walking, speaking, reading, speaking their first word and speaking in full sentences ($p < 0.001$) compared to unaffected siblings - DMD: when late on constructing complete sentences → more likely to perform poorly on measures of single-word vocabulary ($p < 0.001$) and visuospatial reasoning ($p = 0.002$) than children with DMD who were on-time in this regard - DMD: when delayed on walking → significantly more poorly visuospatial reasoning ($p = 0.02$) CBCL - No significant differences in the behavioural domain between the 2 groups with DMD (on time – late) - DMD: when delayed in walking → no differences in behaviour compared to DMD boys who achieved this milestone on time

Cyrulnik et al. (2008)	**13**	**DMD** (n = 20) Age: 3-6y **Control** (n = 20) Age: 3-9y - Unaffected family	Cross-sectional	Behaviour/cognitive/social emotional/motor/language - VABS - PPVT - CELF-P - EVT - WRAVMA - WPPSI - WISC - NEPSY	VABS - DMD: Significant delays in adaptive behaviour skills compared to unaffected children ($p < 0.05$) - DMD: delayed relative to familial controls in all four areas of functioning; communication, daily living, socialization, motor skills (1SD lower, largest differences: communication and motor scales) PPVT & CELF-P & EVT & WRAVMA & WPPSI & WISC & NEPSY (neuropsychological domains) - DMD: lower scores on receptive language, expressive language, visuospatial skills, fine-motor skills, attention and memory ($p < 0.05$) compared to controls - DMD: global cognitive delay (1SD below controls) - DMD: differed significant from their controls in expressive language, attention and memory domains ($p < 0.05$) - Significant association between parent-reported adaptive behaviours and child cognitive performance ($p < 0.05$) for many variables in both groups - DMD: more stringent criteria ($p < 0.001$), parents' adaptive ratings significantly associated with child's performance - DMD: communication scores ($p < 0.001$) strongly associated with cognitive outcomes whereas motor scores were not

Desguerre et al. (2009)	**45**	**DMD** (n = 75) Age: 4-18y Cluster A - Age at diagnosis: 4.1y±2.1 Cluster B - Age at diagnosis: 5.6y±1.7 Cluster C - Age at diagnosis: 7.2y±1.9 Cluster D - Age at diagnosis: 4.5y±1.9 Mutations: - Deletions (77%) - Point mutations (19%) - Duplications (4%)	Longitudinal - Retrospective (1990-2000, median follow-up: 10.5y, 6mo interval)	Motor - Milestones Cognitive - WISC - School delay	Milestones - Cluster A (early infantile DMD, 20%) Mean age at initial symptoms: 1.3y±0.6, initial symptom=psychomotor delay: 100%, mean age at first walking: 20.0mo ±7.9 93% was never able to run versus 48% in other groups ($p < 0.005$) - Cluster B (classical DMD, 28%) Mean age at initial symptoms: 3.6+/-1.7, initial symptom=psychomotor delay: 11%, initial symptom=abnormal gait: 68%, mean age at first walking: 16.0mo±4.8 Significant better global outcome than A - Cluster C (moderate pure motor DMD, 22%) Mean age at initial symptoms: 3.8y±-2.0, initial symptom= abnormal gait: 44%, mean age at first walking: 15.0mo±3.8 69% of the patients being thin versus 33% in other groups ($p < 0.02$) - Cluster D (severe pure motor DMD, 30%) Mean age at initial symptoms: 3.3y±1.72, initial symptom=abnormal gait: 33%, Mean age at first walking: 16.0mo±3.4 - 56% of patients had delayed walking (> 18mo), 56% had never been able to run, and 31% to climb stairs without support. WISC/School delay - Cluster A Severe Mental retardation: 29%, moderate Mental retardation: 57%, neuropsychological dysfunction: 14%, school delay > 3y: 86% - Cluster B Severe Mental retardation: 6%, moderate Mental retardation: 42%, neuropsychological dysfunction: 52%, school delay > 3y: 26% - Cluster C Neuropsychological dysfunction: 31%, normal mental status: 69% - Cluster D Normal mental status: 100% 86% of the patients attended an ordinary educational establishment versus 38% of C, 26% of B and 21% of A ($p < 0.007$) - Frequency of mutations before exon 30 correlated with IQ ($p < 0.003$)

Taylor et al. (2010)	**46**	**DMD** (n = 62) Age: 4.25-14.83y Mutations - Out-of-frame (n = 58) - In-frame (n = 4)	Cross-sectional	Cognitive - WPPSI	WPPSI - Significant differences compared to normative values for FSIQ, PIQ and VIQ ($p < 0.0001$) There are only 6 boys in the age range of this review o 4.4y: point mutation (exon 23) - FSIQ: 62, VIQ: 53, PIQ: 77, VIQ-PIQ: -24 o 5.2y: out of frame mutation (exon 50) - FSIQ: 84, PIQ: 83, VIQ: 90, VIQ-PIQ: -7 o 5.9: out of frame mutation (exon 49) - FSIQ: 86, VIQ: 93, PIQ: 80, VIQ-PIQ: 13 o 4.8y: out of frame mutation (exon 53) - FSIQ: 96, VIQ: 105, PIQ: 93, VIQ-PIQ: 12 o 5.0y: PTC (exon 56) - FSIQ: 87, VIQ: 78, PIQ: 102, VIQ-PIQ: -24 o 4.8y: PTC (exon 58) - FSIQ: 61, VIQ: 63, PIQ: 67, VIQ-PIQ: -4
Waring & Woodyatt (2011)	**85**	**DMD** (n = 5) Age: 4.10-6.9y **SMA** (n = 5) Age: 4.11-6.9y **Control** (n = 5) Age: 4-6.11y	Cross-sectional	Cognitive/language: - PIPA	PIPA: - DMD: significantly poorer than controls on tests of Syllable Segmentation ($p < 0.035$), Rhyme Awareness ($p < 0.009$), Alliteration Awareness ($p < 0.011$) and Phoneme Isolation ($p < 0.041$) - DMD: significantly poorer on Rhyme Awareness than the SMA group ($p < 0.008$)
Wingeier et al. (2011)	**47**	**DMD** (n = 25) Age: 3-20y Mutations: - Deletions (n = 17) - Duplications (n = 3) - Point mutation (n = 5)	Cross-sectional	Cognitive: - K-ABC - SON-R - REY figure - RWT - RAVLT - RVDLT - CORSI - TAP	There were only 5 boys in the age range of this review: - Motor disabilities: all mild - IQ: 119, 81, 70, 66 and 11 - No significant association between IQ and age

Mazzone et al. (2011)	**48**	**DMD** (n = 106) Treatment: - No GC (n = 10) - GC (n = 55) - IS (n = 41)	Longitudinal (prospective): follow-up at 12mo	Motor: - 6MWT - NSAA - TI	6MWT: - Significant better results under 6.8y ($p < 0.015$) - 12mo change significantly correlated with age: NSAA ($p < 0.001$) and 6MWT ($p < 0.01$) - NSAA: Significant better results under 7.2y ($p < 0.02$) TI: - 10m timed test: significant better results under 5.6y ($p < 0.001$) - 10m speed: significant better results under 5.6y ($p < 0.006$)
Donald et al. (2011)	**86**	**DMD** (n = 17) Age: 4-16y - School-age: 7.6-16.7y (n = 11) - Preschool: 4.7-7y (n = 6) **Control** (n = 13) School-age: 7.2-14.7y (n = 8) Preschool: 4.10-7.1y (n = 5)	Cross-sectional	Behaviour: - GMDS	GMDS: - DMD: Significant lower scores on general quotient of preschool group ($p < 0.03$), even when locomotor skills were not included and on subtest hearing and speech ($p < 0.03$)
Doglio et al. (2011)	**88**	**DMD** (n = 15) Age: 5-6.8y Height: 114cm (SD 0.08) Weight: 20.6kg (SD 4.4) BMI: 15.8 (SD 2.4) **Control** (n = 9) Age-matched Height: 131cm (SD 0.1) Weight: 27.7kg (SD 5.2) BMI: 16 (SD 2.0)	Cross-sectional	Motor: - MMT - HMAS - Gait analysis	MMT: - DMD: significant strength reduction in 86% for tibialis anterior, peroneus, hip adductors and biceps femoris muscles (p ranging from 0.01 to < 0.05) HMAS: - Significant difference in time to rise from floor ($p < 0.01$); 10-meters walking time ($p < 0.05$) and total score ($p < 0.05$) between DMD and controls Gait analysis: - Significant difference in temporal and stride parameters ($p < 0.01$) between DMD and controls - DMD: cadence increased and step length decreased ($p < 0.01$)

Pane et al. (2013)	**49**	**DMD** (n = 81) Age: 7-47mo Mutations: - Mutations upstream of or in exon 44 - Mutations between exon 44 and 55 - Mutations downstream of exon 62 Tr: none were on GC	Cross-sectional	Motor /social emotional/language: - GSMD	GSMD: - Borderline DQ found in 32% - DQ below 70 found in 12.3% - Boys with mutations upstream or in exon 44 had higher DQ than those with mutations downstream exon 44 - Significant difference for total and individual subscale DQ except for the locomotor subscale (p ranging from 0.0007 to < 0.034) - Mean age at independent ambulation was 16.7mo (SD: 4.5) - Significant inverse correlation ($p < 0.01$) between age and locomotor subscale

Henricson et al. (2013)	**50**	**DMD** (n = 340)
		Age: 2-28y
		- 4-6y (n = 53)
		  o Height: 107.9cm (SD 6.2)
		  o Weight: 20.2kg (SD 3.7)
		Tr:
		- GC (n = 210)
		- No GC (n = 82)
		- past GC (n = 48)
			Longitudinal (prospective): follow-up at 3, 6, 9, and 12mo (ambulatory) or 6 and 12mo (non-ambulatory)	Motor:
				- TFT
				- BFS
				- VFS
				- QMT
				- Milestones
					BFS + VFS + Milestones:
					- BFS: 23 scored grade 1, 2 scored grade 2
					- VFS: 19 scored grade 1, 4 scored grade 2 and 2 scored grade 3
					QMT in 4-6y:
					- Hand grip: 10.2 (SD: 3.6)
					- Elbow extensors: 7.0 (SD: 2.8)
					- Elbow Flexors: 7.6 (SD: 2.3)
					- Knee extensors: 15.5 (SD: 7.7)
					- Knee flexors: 9.7 (SD: 3.3)
					TFT:
					- Decrease in velocity with increasing age for all 3 tasks

Mazzone et al. (2013)	**51**	**DMD** (n = 113) Age: 4.1-17y - <7y - >7y Tr: - GC (n = 67) - IS (n = 40) - No GC (n = 6)	Longitudinal (prospective): follow-up at 12mo and 24mo	Motor: - 6MWT - NSAA - TI	6MWT: - Changes significantly different between age groups ($p < 0.001$) - Boys <7: remained stable with a slight increase at 12mo and 24mo NSAA: - Changes significantly different between age groups ($p < 0.001$) - Boys <7: stable the first year with a decrease the second year TI: - Changes significantly different between age groups ($p < 0.001$)

Connolly et al. (2013)	**52**	**DMD** (n = 24) Age: 1mo-3y Mutations: - Deletions (n = 20) - Duplications (n = 1) - Nonsense (n = 3)	Cross-sectional	Motor: - HMFSE - NSAA Cognition/language/motor: - Bayley-III Behaviour: - ABS	Bayley-III: - Significant distribution to the left for all cognitive subscales compared to normal development ($p < 0.0001$) - Significant lower scores on all motor subscales ($p < 0.0001$), with gross motor scores more affected than fine motor scores - Lower gross motor scores were significantly associated with increasing age ($p = 0.02$) - Significant correlation between language and cognition ($p < 0.0001$) ABS: - DMD: scores 1 SD lower compared to normal development HMFSE: - Significant increase in score with age ($p < 0.001$) NSAA: - No correlation with age
Pane et al. (2014a)	**53**	**DMD** (n = 96) Age: 5-16.8y - <7y (n = 28) - >7y (n = 68) 6MWT <350m (n = 34) 6MWT >350m (n = 62) Tr: - GC (n = 42) - No GC (n = 5) - Int St (n = 49)	Longitudinal (prospective): Follow-up at 12mo, 24mo and 36mo	Motor: - 6MWT - NSAA	6MWD: - Significant difference between age groups ($p < 0.001$) - Boys <7y remained stable with a slight increase at 12mo and at 24mo + a small decrease at 36mo - 6MWT changes significantly differed among the 4 groups ($p < 0.001$) NSAA: - Significant difference between age groups ($p < 0.001$) - Boys <7y had a small change over the first year and further decrease at 24mo and at 36m

Sarrazin et al. (2014)	**54**	**DMD** (n = 263) Age: 2-17y Tr: - GC (n = 29) - No GC (n = 234) Mutations: - Deletions (68%) - Point mutations (15%) - Duplications (12%) - Other mutations (5%)	Longitudinal (retrospective): Data from 1975-2011	Motor: - Milestones Cognitive: - School - K-ABC - WISCI	Milestones: - Mean age at walking: 18.3mo. - 30% of boys with DMD did not walk by 18mo of age - 8% walked later than 24 months of age - Mutations located in the most distal part of the gene (upstream of exon 63) have the most severe effect on development o 15 of 18 patients with distal mutations display intellectual disability and 15 of 17 present with delayed or severely delayed motor developmental milestones School + KABC + WISCI: - 57% of patients show normal cognitive development - 26% has learning difficulties (IQ 85-70) - 17% has intellectual disability (IQ < 70) - Loss of Dp140 is associated with cognitive disability
Pane et al. (2014b)	**55**	**DMD** (n = 191) Age: 3.2-15y - <7y (n = 80) - >7y (n = 111) Tr: - GC (n = 176) - No GC (n = 15) Mutations: - Deletions (n = 132) - Duplications (n = 15) - Point mutations (n = 44)	Longitudinal (prospective): follow-up at 12mo	Motor: - 6MWT	6MWT: - Significant heterogeneity among groups with a deletion (p = 0.03), no longer significant when converted to % (p = 0.06) - Range of 215 to 521.50 and mean of 383.09 in the youngest group - Follow-up: range of −95 to 175 and mean of 27.37 in the youngest group
Mirski & Crawford (2014)	**56**	**DMD** (n = 107)	Longitudinal (retrospective): Data from 1989-2012	Motor/cognitive: - Clinical charts	Clinical charts: - 45% was cognitively delayed - 42% was delayed at walking - Strong association between cognitive delay and delay in walking (p < 0.0001) - Boys with DMD who walked at or after 16mo had three times the risk of also progressing more slowly in school

Rasic et al. (2014)	**57**	**DMD** (n = 41) Age: 3-16y Mutations: - Deletions (n = 37) - Duplications (n = 4)	Longitudinal (retrospective): Data from 1992-2013	Cognitive: - WISC - BLS Social emotional: - VDS	There were only three boys in the age range of this review - FSIQ/ DQ: 96, DQ 105 and DQ 82 - Mutations: Out of frame deletion of exons 45-50, 48-50, 45-76
Pane et al. (2014c)	**58**	**DMD** (n = 322) Age: 4.1-35.1y - <5y, 5–7.9y, 8–12.9y, 13–21y and above 21y **Control** (n = 277) Age: - 3-5y (n = 47) - 5-25y (n = 230)	Cross-sectional	Motor: - PUL	PUL: - Improvement of scores in young boys with DMD on each level - Boys with DMD do not achieve the same functioning level compared to TD → <5 years main difference at the shoulder level dimension - Timed items: for items I, J and K, there was a marked overlap between the typically developing and DMD boys until after the age of 10 years
Connolly et al. (2014)	**59**	**DMD** (n = 24) Age: <3y Mutations: - Deletions (n = 16) - Nonsense (n = 2) - Duplication (n = 1)	Longitudinal (prospective): Follow-up at 6mo and 12mo	Motor/cognition/language/social emotional: - Bayley-III Behaviour: - ABS	Bayley-III: - Significant differences between DMD group and typically developing children at baseline in all domains (p ranging from 0.002 to < 0.0001), at 6m and at 12m - Significant increase in fine motor scores at 12m ($p < 0.05$) ABS: - Significant deficits in Functional pre-academic, Health and safety, Leisure, Self-care, Social, and Motor subtests (p ranging from 0.04 to < 0.001) - No significant differences at follow-up

Chieffo et al. (2015)	**60**	**DMD** (n = 41) Age: <4y ->6y Mutations: - Mutations upstream exon 44 (n = 17) - Mutations in exon 44–55 (n = 19) - Mutations downstream of exon 62 (n = 2)	Longitudinal (prospective): followed until school age	Motor/social emotional: - GMDS Cognitive: - WPPSI III	GSMD + WPPSI III: - Significant correlation ($p < 0.0001$) between total IQ and DQ even when the locomotor scale was excluded - Significant correlation between VIQ and hearing and speech Griffith's subscale ($p < 0.0032$) - Significant correlation between PIQ and performance (< 0.0001) and eye and hand coordination (< 0.0001) subscales - Significant difference between boys with mutations upstream exon 44 and those with mutations in exon 44–45 for DQ ($p < 0.01$) and FSIQ ($p < 0.003$)
De Sanctis et al. (2015)	**61**	**DMD** (n = 125) Age: 3-5y Tr: none on GC **Control** (n = 147) Age: 3-5y	Cross-sectional	Motor: - NSAA	NSAA: - None of the boys obtained a full score - Significant difference in items 4 to 6 and total score ($p < 0.0002$) ($p < 0.0057$) ($p < 0.005$) ($p < 0.009$) - DMD boys scored significantly lower than controls except for item 1, 2 and 12 in the youngest age group and 1 and 2 in the other three subgroups
Davidson et al. (2015)	**62**	**DMD** (n = 16) Age: 5.2-13.1y Tr: All but two on GC Weight: 35.7kg (SD 11.9) Height: 124.4cm (SD 7.4) BMI: 22.6 (SD 6.0) **Control** (n = 13) Age: 5-13y Weight: 32.9kg (SD 10.4) Height: 136.5cm (SD 16.1) BMI: 17.2 (SD:2.0)	Cross-sectional	Motor: - 6MWT - StepWatch Activity monitor	There was only one boy in the age range of this review (on GC) - 6MWD: 391m - Mutation: Deletion exon 53-55

Mercuri et al. (2016)	**63**	**DMD** (n = 75) <5y **Control** (n = 171) Age: 2.9-4.8y	Cross-sectional & longitudinal (prospective): Follow-up of 6mo	Motor: - Revised version of the NSAA	Revised version of the NSAA: - DMD: significantly lower total scores compared to controls and lower scores on individual items, except for item 1,2,3,9 and 12 in the 3y group and item 1 and 2 in the other subgroups
Buckon et al. (2016)	**40**	**DMD** (n = 83) Age: 49-180mo 4-7y >8y Tr: - GC (n = 50) o Height: 109.9cm (SD 9.1) o Weight: 21.1kg (SD 5.2) - No GC (n = 33) o Height: 106.7cm (SD 7.0) o Weight: 19kg (SD 3.9)	Cross-sectional	Motor: - Volitional muscle strength - GMFM-88 (standing & walk/run/jump dimensions) - TMT (10-meter run, sit to stand, supine to stand, climb 4-stairs)	Volitional muscle strength: - Significant decrease with age for: isometric hip flexor (p = 0.037), isometric and isokinetic concentric knee extensor (p = 0.017, p = 0.001) and isometric ankle dorsiflexor (p=0.024) strength GMFM-88: - Significant interaction effect for Walking/Running/Jumping dimension skills (p = 0.046), with scores reversing across age - Higher scores in the (younger) naïve group of 4-7 years TMT: - Younger age group (4-7y): significantly less time to perform each TMT
Ricotti et al. (2016)	**89**	**DMD** (n = 16) Age: 4-15y Mutations: - Mutations involving exons 3-13 (n = 7) - Mutations involving exons 44-57 (n = 7) - Mutations downstream of exon 63 (n = 2) Tr: All boys on GC	Cross-sectional	Social emotional/behaviour: - SCDC	There was only one boy in the age range of this review - Nonsense mutation exon 70 - SCDC = 16 ASD - Severe speech delay

Alfano et al. (2017)	**64**	**DMD** (n = 72) Age: 4-12y Mutations: - Deletion (n = 49) - Duplication (n = 8) - Frameshift (n = 8) - Nonsense (n = 7) Tr: - GC (n = 54) - No GC (n = 18) **Control** (n = 599) Age: 4-14y	Cross-sectional & longitudinal (prospective): Follow-up at 1mo and 1y in controls and 5-19mo in DMD	Motor: - 100MTT	100MTT - Significant difference in median speed between DMD and age-matched control group for each age group ($p < 0.01$) - Boys with DMD between the ages of 4 to 6y still improve their 100m time
Gissy et al. (2017)	**65**	MD STARnet: **DMD** (n = 463) DNHS: **DMD** (n = 281) PPMD: **DMD** (n = 366)	MD STARnet: Longitudinal (retrospective): data from 2004 to 2011 & (prospective): annual follow-up DNHS: cross-sectional PPMD: cross-sectional	Motor: - Medical history & examination - Parent questionnaire - Pediatrician's notes - First step survey	- Age of independent walking differed significantly from normally developing children ($p < 0.001$)

Arora et al. (2018)	**66**	**DMD** (n = 92) Age: 5-12.9y Tr: all boys on CS Mutations: - Deletion (67%) - Duplication (10%) - Point mutation/other (21%) 5-6.9y - Weight: 21.3kg (SD 3.4) - Height: 1.11m (SD 0.05) - BMI: 17.2 (SD 1.8) - Brooke score: 1-2 **Control** (n = 45) Age matched -6.9y - Weight: 23.2kg (SD 5.4) - Height: 1.20m (SD 0.08) - BMI: 15.8 (SD 1.4)	Longitudinal: - Prospective Follow-up at 1y, 2y, 3y and 4y	Motor: - 6MWT - TFT	Boys with DMD had impaired functional performance even at 5–6.9 years TFT: - The youngest boys took twice as long as controls to complete the TFTs 6MWD: - Younger aged boys with DMD walked about 75% of the distance measured in controls 6MWT and TFT: - In boys <7 years, no significant changes in function were detected over 1y - 6MWT and TFT significantly correlated with each other

Thangarajh et al. (2018)	**67**	**DMD** (n = 204) Age: 4-8.9y Mutations: - Mutations upstream of DMD exon 45 (n = 53) - Mutations downstream of DMD exon 51 (n = 52) - Mutations between DMD exon 45 and 50 (n = 48) Weight: 22.0kg (SD 5.7) Height: 116.6cm (SD 9.2) Tr: GC at baseline (n = 124)	Longitudinal (prospective): follow-up of 10y - Year 1: 3mo - Year 2: 6mo - Year 3-10: 12mo	Cognitive/Language: - QOL-Questionnaire - School-related activities - Parental review Motor/social emotional/cognitive: - PedsQL	QOL-Questionnaire + school related activities + parental review + PedsQL: - No significant neurodevelopmental challenges, use of services in the age group of 4-6y of age
Singh et al. (2018)	**68**	**DMD** (n = 275) Age at symptom onset: 3.7y (SD 1.9) Mutations: - Proximal deletion (n = 36) - Distal deletion (n = 158) - Combined deletion (n = 10) - Proximal duplication (n = 1) - Distal duplication (n = 1) Tr: 54.5% on GC	Longitudinal (retrospective): Data from 1998 to 2013 & (prospective): Data from 2013 to 2014	Cognitive: - BKS Motor: - Questionnaire	Questionnaire: - Delay in achievement of milestones in 57% - Delay in mental milestones in 14% BKS: - Bright normal (1.1%) - Average intelligence (42%) - Dull normal intelligence (30.6%) - Borderline intelligence (15.9%) - Mild mental retardation (10.9%)

Fowler et al. (2018)	**69**	**DMD** (n = 32) Age: 4.1-11.3y - 4-7y (n = 16) - >8y (n = 16) Height: 118.5cm (SD 13.9) Weight: 27.1kg (SD 12.2) BMI: 18.5 (SD:4.4) Tr: GC at baseline (n = 25)	Longitudinal (prospective): follow-up of 5y with 6mo interval	Motor: - StepWatch Activity Monitor - 10MWalk/Run	StepWatch Activity - Significant decrease in % low frequency strides (-5%) and significant increase in % high frequency strides (+4%) for the younger age group - Average strides/day: 5352 (SD 1899) - Mean 10MWalk/Run speed: 1.8 (SD 0.63 m/s)
Brogna et al. (2018)	**70**	**DMD** (n = 31): Age: 5-29y	Cross-sectional	Motor: - PUL 2.0	There were only two boys in the age range of this review PUL 2.0: - Ambulant - Total PUL score: 41 & 39 - PUL shoulder score: 11 & 10 - PUL midlevel score: 17 - PUL distal score: 13 & 12
Lee et al. (2018)	**71**	**DMD** (n = 39): Age: 5-34y	Longitudinal (retrospective) & cross-sectional: data from 2012-2017	Behaviour: - Medical record	There were only three boys having symptoms in the age range of this review Medical record: - Initial symptoms: Stuck on various topics, repeating questions/ phrases, objects must be placed a certain way, overly organised, checking behaviours, difficulty with changes to routine, excessive hand washing, repetitive behaviours

Brogna et al. (2019)	**7**	**DMD** (n = 92): Age: <7y (n = 35) >7y (n = 57) Tr: - No Steroid (n = 16) - AC (n = 42) - CS (n = 34) Mutations: - Deletions skipping exon 44 (n = 24) - Deletions skipping exon 45 (n = 27) - Deletions skipping exon 51 (n = 18) - Deletions skipping exon 53 (n = 28) - Single deletion exon 52, skipping 51 and 53 (n = 5)	Longitudinal (prospective): Follow-up at 12, 24 and 36mo	Motor: - 6MWT - TRF	6MWT: - Significant difference between the age groups at 24mo and 36mo ($p < 0.05$) - Significant difference between the two groups below and above 350m at 12mo, 24mo and at 36mo ($p \leq 0.001$) - No difference between the three steroid groups - Significant correlation between 6MWT and the groups below and above 6s on the TRF at baseline, 12mo, 24mo and at 36mo ($p \leq 0.0001$) - Significant difference between deletions amenable to skip exons 44, 45, 51 or 53 at 24mo ($p \leq 0.05$) and 36mo ($p \leq 0.01$) but not at 12mo ($p = 0.17$) TRF - 65 had TRF <6s - 31 had TRF >6s

Muntoni et al. (2019)	**72**	**DMD** (n = 395): Age: 1.8-16.7y Tr: - GS (n = 348) - No GS at first assessment (n = 127) Mutations: - Mutation skipping exons 44, 45, 51, or 53 (n = 138) - Nonsense mutations (n = 10) - Other mutations (n = 247)	Longitudinal (retrospective): Data from 2004 to 2015	Motor: - NSAA	NSAA: - Mean NSAA total score increased at a rate of 3 units per year followed by a peak at 6.3y - Largest probability of improvement in the age group <7y

Thangarajh et al. (2019)	**73**	**DMD** (n = 196): Age: 4.1-8y Tr: All boys were steroid-naïve Mutations: - Mutations upstream of DMD exon 45 (n = 88) - Mutations downstream of DMD exon 45 (n = 105) - Deletions (n = 137) - Point mutations (n = 34) - Duplications (n = 22)	Cross-sectional + Longitudinal (retrospective parental review)	Behaviour: - ICS Social emotional/behaviour: - PARS-III Language/cognitive/behaviour: - Parental review	Parental review: - Significant more learning difficulties in boys with downstream mutations of DMD exon 45 (p = 0.03) - A diagnosis of ASD reported in 3 boys, all of whom had DMD mutations downstream of DMD exon 45 - ADHD frequency higher in boys with DMD mutations downstream of DMD exon 45, but not significantly (p = 0.06) - Significant more language delays in boys with mutations downstream of DMD exon 45 (48%) (p = 0.005) - Boys with mutations downstream of DMD exon 45 talked significantly later (p = 0.03) - No differences among DMD mutations subtypes in language delays and learning difficulties PARS-III (Social emotional + behaviour): - No differences in total and sub scores between boys with downstream or upstream mutations of DMD exon 45 - No differences between mutation subtypes ICS: - 8% met criteria for IO behaviour - 5% met criteria for OD behaviour, including 8% of those with mutations downstream of DMD exon 45 and only 1% of those with mutations upstream of DMD exon 45 (All deletions) (p = 0.04)
Pereira et al. (2020)	**8**	**DMD** (n = 128): Age: 2-12y **Control** (n = 344): Age: 2-12y	Longitudinal: - Data from 1998-2015 (retrospective) - Data from 2015-2018 (prospective)	Motor: - 10MWT - TRF - 10MRT	TRF: - Significant higher mean and median values in DMD group in all age groups (p < 0.001) 10MWT: - Mean and median values at 6y show gradual increase with subsequent gait loss compared to controls 10MRT: - Progressive pattern of worsening of times from the age of 4 in DMD boys

Dommelen et al. (2020)	**74**	**DMD** (n = 76): Age: <26y Birthweight: 3400g (SD: 760) Mutation: - Deletion in DMD gene (n = 25) - Insertion in DMD gene (n = 8) - Small or other mutation (n = 7) **Control** (n = 12414): Age: <9y Birthweight: 3399g (SD 582)	Longitudinal (retrospective): Data from 1 to 48mo of age	Motor/Behaviour/social emotional: - DDI	DDI (Motor + behaviour + social emotional): - 2 to 3mo: Boys with DMD achieve milestones of gross and fine motor activity, adaptive behaviour, personal/social behaviour, and communication in DMD group later ($p < 0.01$) - 12 to 36mo: differences between controls and DMD group in the attainment of milestones concerning gross motor activity increased with age ($p < 0.001$) - 12 to 48mo: differences in milestone attainment concerning fine motor activity, adaptive behaviour, personal/social behaviour, and communication ($p < 0.01$) - Not being able to walk well at 24mo predicted an increased risk or DMD to approximately 1 in 100 boys (ppv = 0.01) - Not being able to walk smoothly at 36 months predicted an increased risk of approximately 1 in 16 boys (ppv = 0.06)
Norcia et al. (2021)	**4**	**DMD** (n = 134) Age: 1-32y Mutations: - Before exon 44 (n = 45) - Between exon 44 and 50 (n = 43) - After exon 51 (n = 40) - Beyond exon 63 (n = 6) **Control** (n = 150) Similar age range	Cross-sectional (Retrospective parental interview)	Gross motor milestones: Parental interview - Sitting independently: ability to sit independently without any support - Walking: ability to walk for more than a few steps without holding to furniture or people	Sitting independently: - **DMD:** mean age 7.04mo → only 2.98 % of them achieved sitting by 5.9mo (= WHO 50th percentile); 10% did not achieve sitting by 9.4mo (= outside of WHO 95% confidence interval) No significant difference between mutation subgroups - **TD:** mean age 7.07mo → no significant difference between DMD and TD Walking: - **DMD:** mean age 16.35mo → 23.88 % of them achieved walking by 12mo (= WHO 50th percentile); 17% did not achieve walking by 18mo (= outside of WHO 95% confidence interval) No significant difference between mutation subgroups - **TD:** mean age 12.26mo → significant difference between DMD and TD

Thangarajh et al. (2021)	**75**	**DMD** (n = 154) Age: - <7y (n = 49) - >7y (n = 71) Mutations: - 5'-before exon 44 (n = 53) - Exon 44-3' (n = 101)	Longitudinal (prospective)	Motor function: - 6MWT	- Faster decline in 6MWD in boys >7y compared to <7y + decline is unrelated to pathogenic variant location (no distinction in age groups for other results)
Donovan et al. (2021)	**76**	**DMD** (n = 70) **Control** (n = 10) **Age:** 5-12.9y - **5-6.9y (n = 18)** - 7-8.9y (n = 20) - 9-10.9y (n = 20) - 11-12.9y (n = 12)	Cross-sectional (prospective)	Motor function: - Step activity: steps per day - Functional abilities: 6MWT, supine up, 10m walk/run, 4 stairs - Strength	- 5-6.9y-olds: mean step count/day: 7033 (SD 1957) - within 1SD range of the control group - Decline in daily step count with increasing age → 3 older age groups significantly different from 5-6.9y-olds - Significant relation between step activity and functional abilities + strength
Brogna et al. (2021)	**77**	**DMD** (n = 27) Age: 5-30y Ambulant (n = 10) Non-ambulant (n = 17) Tr: all on GC	Longitudinal (Prospective): Follow up of 1y	Motor: - PUL 2.0 - MRI	Group of 5y-olds MRI score total - Baseline/Follow up: 14.5 MRI score shoulder - Baseline/Follow up: 11 MRI score arm level - Baseline/Follow up: / MRI score forearm level - Baseline/Follow up: 3.5 PUL total score - Baseline/Follow up: 39 PUL shoulder - Baseline/Follow up: 10 PUL mid level - Baseline/Follow up: 17 PUL distal level - Baseline/Follow up: 12

Mayhew et al. (2022)	**80**	**DMD** (n = 196) Age: 4.1-8.1y Height: 110 (SD 7.2) Weight: 20 (SD 3.6) BMI: 16.4 (SD 1.6)	Cross-sectional	Motor - TRF - 10m walk/run - NSAA - 6MWT	Following group comparisons were statistically significant TRF - 7y vs 4y (p = 0.049), 7y vs 5y (p < 0.0001), 7y vs 6y (p = 0.0005) 10m walk/run - 5y vs 4y (p = 0.04), 6y vs 4y (p = 0.03), 6y vs 5y (p = 0.004), 7y vs 6y (p = 0.004) 6MWT - 6y vs 4y (p = 0.006) NSAA - Total score – 6y vs 4y (p = 0.02) and 7y vs 6y (p = 0.045) Functional outcomes per group 4.0-4.9y - NSAA Total score: 19.7 (SD 4.7) - TRF: 0.17 (SD 0.06) - 10m walk/run: 0.16 (SD 0.03) - 6MWT: 311.8 (SD 51.6) 5.0-5.9y - NSAA Total score: 22.0 (SD 5.0) - TRF: 0.21 (SD 0.08) - 10m walk/run: 0.18 (SD 0.04) - 6MWT: 330.0 (SD 65.3)
Yan-Li Ma et al. (2022)	**79**	**DMD** (n = 152) Mutations: - Deletions (n = 136) - Duplications (n = 16) **BMD** (n = 17) - Deletions (n = 17)	Longitudinal (retrospective): Data from 2014-2021	Motor - Walking alone milestone	Walking alone milestone - DMD: 18.03mo (SD 7.12; range: 14-30mo) ☒ 61.18% independent walking delay - BMD: 12.88mo (SD 0.61, range:12-14) ☒ no walking delay - Significant differences between groups (p < 0.05)

Chieffo et al. (2022)	**78**	**DMD** (n = 20): Age: 48-72mo Mutations: - upstream exon 44 (n = 9) - Between exon 44-51 (n = 5) - Between 51-63 (n = 4) - Beyond exon 63 (n = 2) **Control** (n = 20) Age-matched	Cross-sectional	Language - BVL 4-12 Cognition - Bell test - ACPT -VAUMeLF	BVL 4-12 - Oral comprehension skills: Abnormal scores (−2SD) on lexical and syntactic comprehension 10% (mutations beyond exon 63) - Language production/oral production skills: abnormal scores (−2SD) on denomination found in 5% (mutation between exons 51 and 62). Abnormal scores (−2SD) on articulation 80% (mutations upstream of exon 44 (n = 5) and mutations after exon 44 (n = 11)) - Speech sound articulation test: 30% did not present the voiced vibrant liquid sound, 25% did not produce unvoiced palatoalveolar fricative phoneme, 20% did not present alveolar, labiodental, and alveolar affricate phonemes. - Oral repetition skills: Abnormal scores (−2SD) on word repetition found 20% (mutations after exon 51 (n = 2) and mutations beyond exon 63 (n = 2)). Abnormal scores (−2SD) on sentence repetition found 80%, mutations upstream exon 44 (n = 5) and mutations after exon 44 (n = 11) - The profile in Duchenne boys was different form the one observed in SLI with no cognitive impairment - Significant differences in performance according to the four brain dystrophin subgroups for the following administered tests: lexical complexity (p = 0.005) (deletions above exon 62) and word repetition (p = 0.002) (deletions above exon 51 and above exon 62)

DMD: Duchenne Muscular Dystrophy; N°= reference number; y: Year; TMRSB: Terman-Merrill revision of the Stanford- Binet test; MM: Motor milestones; mo: Month(s); WISC: Wechsler Intelligence Scale for Children; WPPSI: Wechsler Pre-School and Primary Scale of Intelligence; RBQ-A: The Rutter Behaviour Questionnaires A; SBIS: Stanford-Binet Intelligence Scales; RBQ-B: The Rutter Behaviour Questionnaires B; SD: Standard Deviation; MRC: Medical Research Council Scale for Muscle Strength; TWT: Timed Walking tests; %MRC: total muscle strength; MIF: Maximum isometric force; KE: Knee Extensors; KF: Knee Flexors; HF: Hip flexors, HE: Hip Extensors, HA: Hip Abductors; FD: Foot Dorsiflexors; SA: Shoulder Abductors; WE: Wrist Extensors; AM: Anthropometric measurements; CELI: Carrow Elicited Language Inventory; VABS: Vineland Adaptive Behavior Scales; REEMS: Receptive- Expressive Emergent Language Scale; PPVT: Peabody Picture Vocabulary Test; GMDS: Griffiths Mental Development Scales; RDLS: Reynell Developmental Language Scales; VBPVS: British Picture Vocabulary Scales; HOME: Home Observation for Measurement of the Environment; BSQ: Behavior screening questionnaire; AH4: Alice Heim Group Ability Test; HMAS: Hammersmith Motor Ability Score; CMS: Composite Muscle Score; MA: Motor Ability scale; TGM: Timed Gowers Manoeuvre; HHD: hand-held dynamometer; CBCL: Child Behavior Checklist; RCPM: Raven's Colored Progressive Matrices; DDST: Denver Developmental Screening Test; CELF-P: Clinical evaluation of Language Fundamentals-Preschool; EVT: Expressive Vocabulary Test; WRAVMA: Wide Range Assessment of Visual Motor Abilities; NEPSY: Developmental NEuroPSYchological Assessment; VIQ: Verbal Intelligence Quotient; PIQ: Performance intelligence quotient; PTC: Premature Termination Codon; GC: Glucocorticoids; 6MWT: Six-minute walk test; 6MWD: Six-minute walking distance; PIPA: The Preschool and Primary Inventory of Phonological Awareness; REY figure: Rey-Osterrieth Complex Figure; RWT: Regensburger Word Fluency Test; RAVLT: Rey Auditory Verbal Learning Test; RVDLT: Rey Visual Design Learning Test; CORSI: Corsi Block Tapping Test; TAP: Test Battery of Attentional Performance; BLS: Brunet-Lezine Scale; K-ABC: Kaufman Assessment Battery for Children; SON-R: Snijders–Oomen Non-verbal Intelligence Test for Children; CPRS-R:L: long version of the Conners Parents Rating Scales-Revised; CTRS-R:L: Long version of the Conners Teachers Rating Scales-Revised; DSM IV-TR: Diagnostic Statistical Manual, Fourth Edition, Text Revision; QMT: Quantitative muscle strength testing; MMT: Modified Medical Research Council (MRC) manual muscle test;

BFS: Brooke Functional Scale; VFS: Vignos Functional Scale; TFT: Timed Function Tests; HMFSE: Expanded Hammersmith Functional Motor Scales; Int St: Intermittent steroids; FSIQ: full scale intelligence quotient; VDS: Vineland-Doll Scale; ABS: Adaptive behavior subtest; Bayley-III: Bayley-III Scales of Infant and Toddler Development, third edition ; TI: Timed items; DQ: Developmental quotient; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence, Third edition; MMN: Mismatch negativity; EEG: Electroencephalography; TMT: timed motor tests; GMFM-88: Gross Motor Function Measure; SCDC: Social and Communication Disorders Checklist; 10MWalk/Run: 10-metre Walk/Run test; 100MTT: 100-meter timed test; QOL-Questionnaire: Quality of life questionnaire; PedsQL: Pediatric Quality of Life inventory, version 4; BKS: Binet-Kamat scale; PUL: Performance of the Upper Limb, second edition; NSAA: North Star Ambulatory Assessment; TRS: Timed rise from supine; ICS: IOWA Conners scale; OD: Oppositional-defiant; IO: Inattentive-overactive; PARS-III: Personal Adjustment and Role Skills Scale, 3rd edition; ASD: Autism spectrum disorder; ADHD: attention deficit hyperactivity disorder; 10MWT: 10 Meter Walk Test; TRF: Time to rise from the floor; 10MRT: 10 Meter Run Test; DDI: Dutch Development Instrument; ppv: percent predicted values; ACPT: auditory continuous performance test; BVL 4-12: Batteria per la Valutazione del Linguaggio in Bambini dai 4 ai 12 anni; VAUMeLF: Batteria per la Valutazione dell'Attenzione Uditiva e della Memoria di Lavoro Fonologica nell'Età Evolutiva