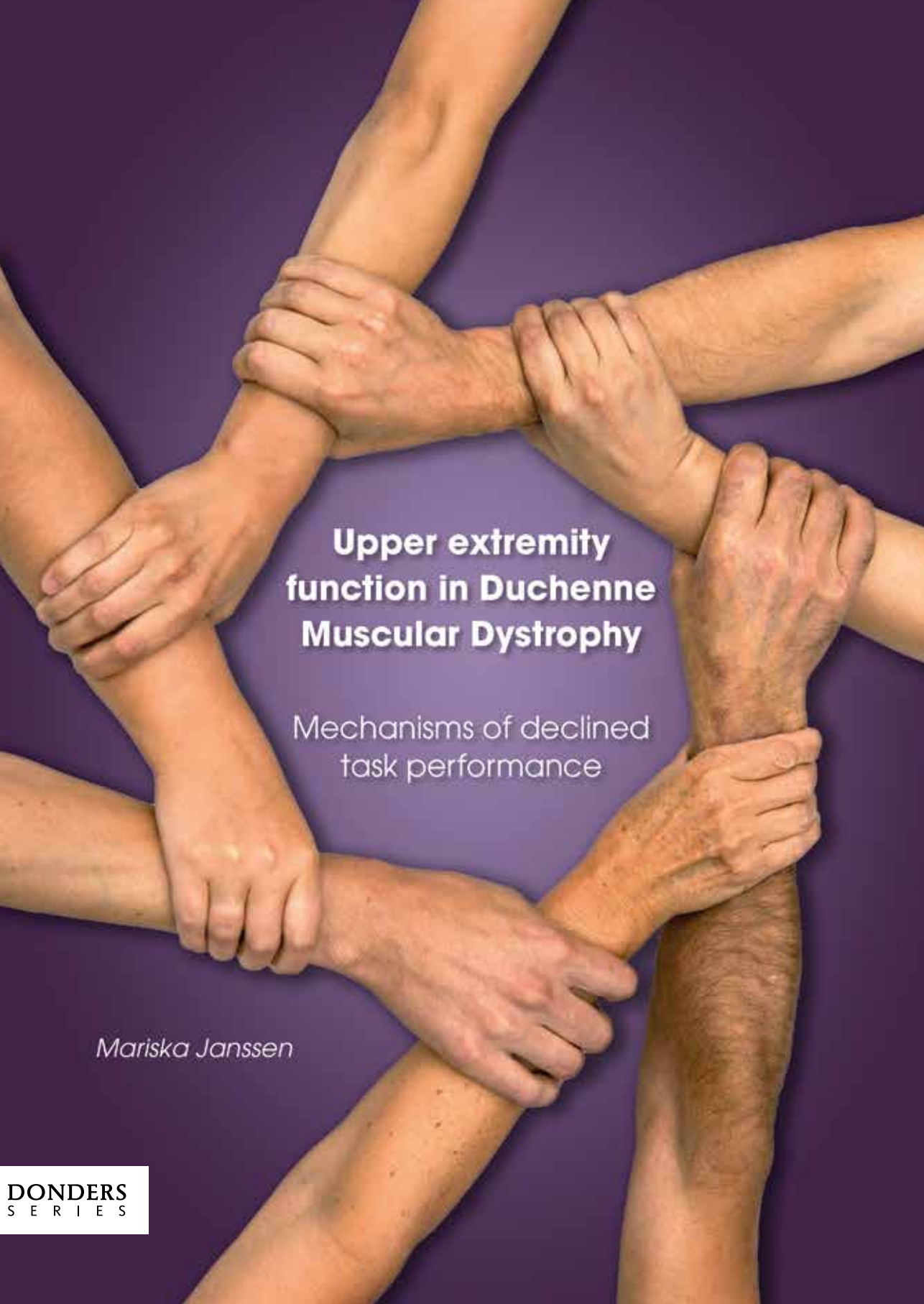

Upper extremity function in Duchenne Muscular Dystrophy

Mechanisms of declined task performance

Mariska Janssen

DONDERS SERIES

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The research described in this thesis was supported by the Toegepaste en Technische Wetenschappen (which is part of the Netherlands Organization for Scientific Research (NWO), and which is partly funded by the Ministry of Economic Affairs), United Parent Projects Muscular Dystrophy, Prinses Beatrix Spierfonds, Spieren voor Spieren, Johanna Kinderfonds, Kinderrevalidatiefonds Adriaanstichting, Focal Meditech, OIM Orthopedie, Ambroise, and Flextension.

Printing this thesis was financially supported by the Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Focal Meditech BV, Ambroise, Hankamp Rehab, TMSi and Leavo.

ISBN	978-94-6284-127-7
Cover design	Dorette Gerrits
Cover photo	Hans Franken
Layout	Mariska Janssen
Print	Ipskamp printing

Upper extremity function in Duchenne Muscular Dystrophy

Mechanisms of declined task performance

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen op donderdag 2 november 2017
om 10.30 uur precies

door

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geboren op 18 september 1986
te Boxmeer

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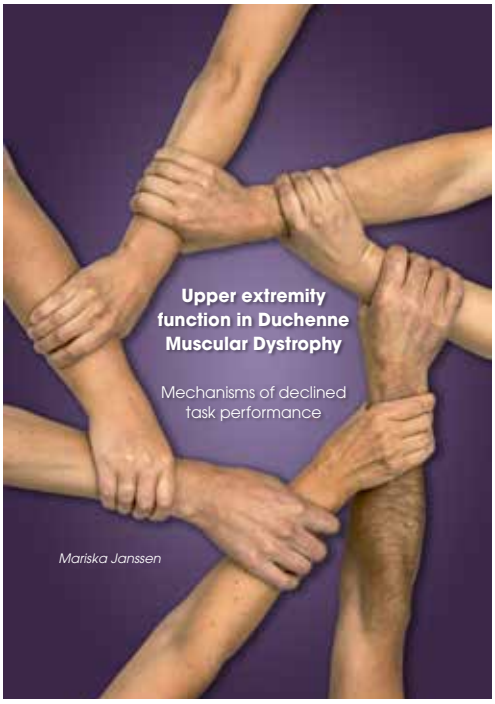
ABOUT THE COVER

The cover of this thesis represents multiple personal and career related aspects that are important to me. The circle of hands that are interlocked represent the main subject of my thesis, arm function. Arm function is very important in daily life and in interaction with others. Patients that participated in my studies often reminded me of this importance, which was one of the main motivators during my PhD. The circle also represents collaboration. Working as a member of the Flextension A-Gear team has shown me the importance of collaborating with multiple disciplines. Without close collaboration between scientists, clinicians, engineers, companies and of course patients this project would not have been as successful. Finally, the hands displayed on the cover photo are of family members that are very important to me. The success of this thesis is largely dependent on their indefinite support. Thank you!



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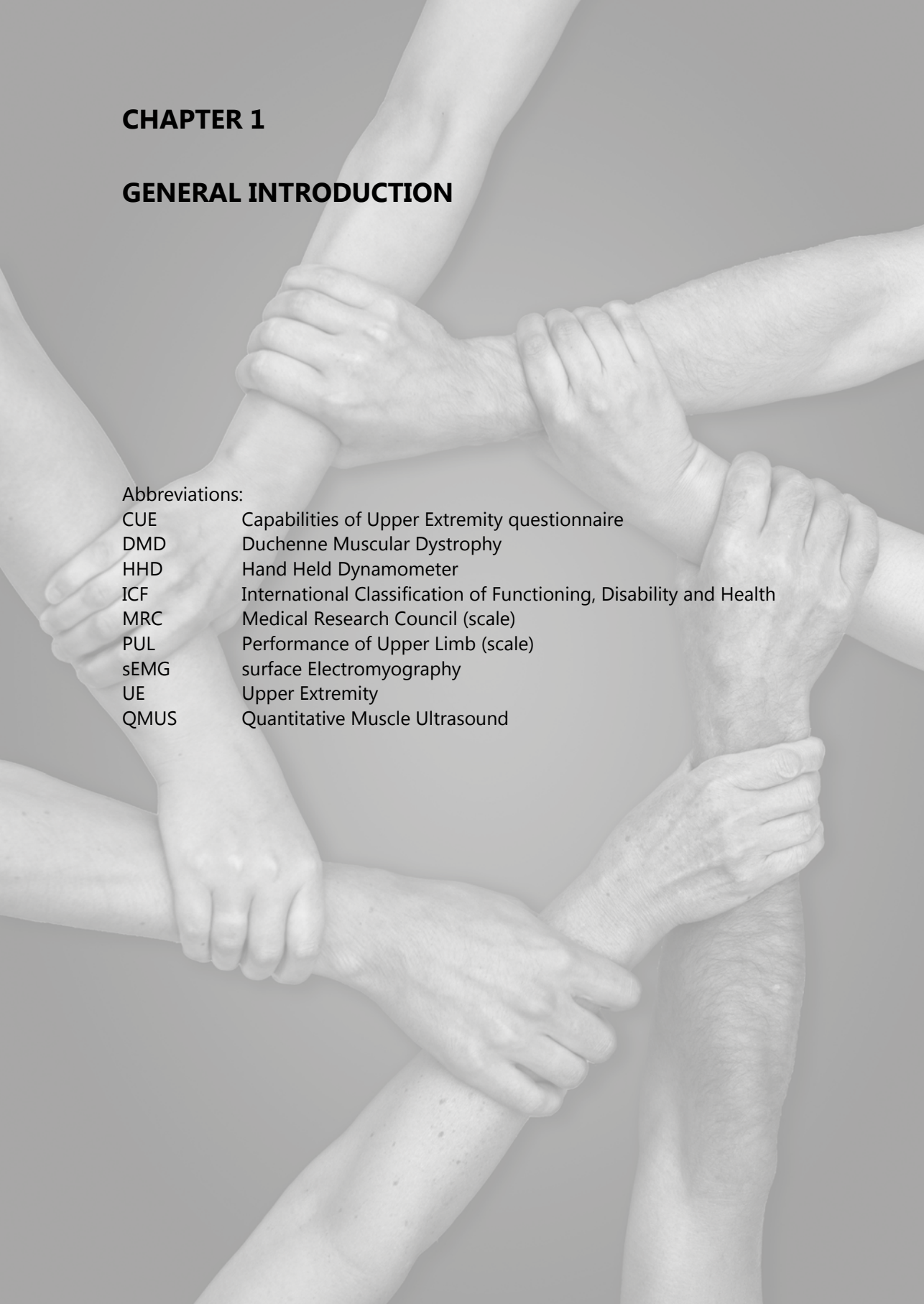
CHAPTER 1

GENERAL INTRODUCTION



Abbreviations:

CUE	Capabilities of Upper Extremity questionnaire
DMD	Duchenne Muscular Dystrophy
HHD	Hand Held Dynamometer
ICF	International Classification of Functioning, Disability and Health
MRC	Medical Research Council (scale)
PUL	Performance of Upper Limb (scale)
sEMG	surface Electromyography
UE	Upper Extremity
QMUS	Quantitative Muscle Ultrasound

Box 1: Virtual case

Imagine you are a twelve year old boy with Duchenne muscular dystrophy. You just started high school and you are trying to make new friends. This is quite challenging, because you are in a wheelchair, which makes you different from your classmates. In high school you need a lot of books and your schoolbag is really heavy. When you are trying to lift your bag, you notice that your arms are too weak and that you need to ask people for help to lift your schoolbag onto your wheelchair. When you discuss this problem with your physician, he recommends you to try one of the commercially available arm supports. The available options look much less fancy than the cool exoskeletons you have seen on television, but if they can help you to be more independent you are willing to try them. Unfortunately, the arm supports can only help you with certain activities. You still are not able to lift your schoolbag, but you can eat independently which is really nice. So you start using the arm support at school, until one of your classmates makes fun of your arm support. As a result, you do not want to use the arm support anymore and you have to ask for help again. On Facebook you have seen amazing solutions for very complicated technical problems. Should not one of these engineers be able to make an assistive device that can help you with all activities you want to do and that makes you look cool in front of your friends? That would really make you happy!

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder with an approximate prevalence of 1:5000 males[1]. X-linked mutations cause a phenotype in which 50 percent of the sons of gene mutation carriers are affected and 50 percent of the daughters of carriers become carriers of the gene mutation themselves (figure 1). DMD occurs as a result of mutations in the dystrophin gene, which leads to an absence of (or defect in) the dystrophin protein. Dystrophin is located on the muscle sarcolemma as part of a membrane-spanning protein complex that connects the inner cytoskeleton (F-actin) to the extra-cellular matrix (basal lamina) [2] (figure 2). The precise function of dystrophin is still unknown. It is assumed that the primary function of dystrophin is to provide mechanical reinforcement to the sarcolemma and, thereby, protect it from the membrane stresses that occur during muscle contractions[3, 4]. As a result, the muscle cells of people with DMD, which lack the dystrophin protein, are highly vulnerable.

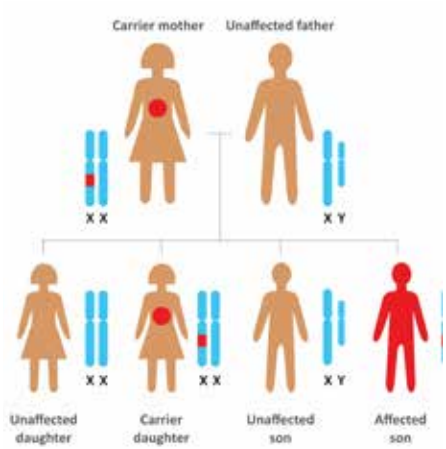


Figure 1. DMD genetics
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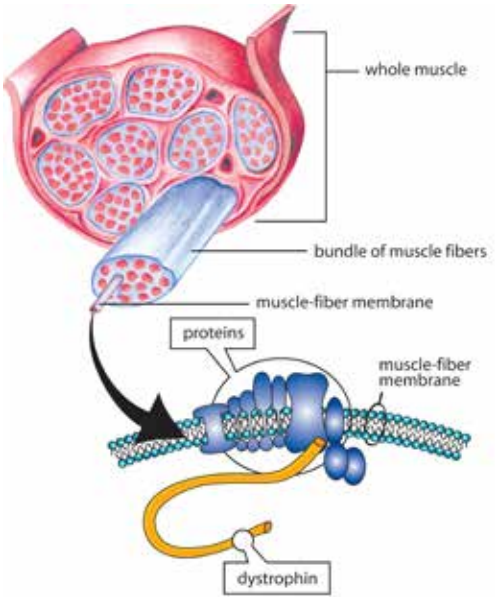

Figure 2. Location of dystrophin in muscle cell
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DMD is a progressive neuromuscular disorder, which means that the muscles of boys and men with DMD degenerate over time. Consequently they become weaker as they get older. Although DMD exists from birth, the diagnosis in patients without a family history is usually not made before the age of 4 years[5, 6]. At that age their physical abilities differ clearly from their healthy peers. DMD patients reach functional milestones with (mild) delays and most are unable to ever run and jump properly due to muscle weakness[5]. Later in life basic walking difficulties occur, which, if untreated, eventually results in wheelchair confinement around the age of 10[7-9]. At that age upper extremity (UE) function also starts to deteriorate, however, muscle weakness in the arms and hands is already present before the age of 10[10-12]. Although DMD is often studied in the context of skeletal muscle dysfunction, it actually is a multisystem disorder as dystrophin is also expressed in cardiac and smooth muscles, endocrine glands and neurons[13]. As a result many DMD patients also suffer from cardiomyopathy, which is usually diagnosed around the age of 14 years[14]. In addition, spinal deformities[8, 15] and respiratory insufficiency[16] are often seen and DMD patients are more prone to suffer from cognitive dysfunction as indicated by lower intelligence scores[17, 18]. Due to the absence of dystrophin in the brain, malformed and dysfunctional synapses are formed and alternations in the cellular metabolism can be seen. These mechanisms alter the formation and storage of new memories in the hippocampus, which add to cognitive dysfunction[13]. In addition, the chronically elevated inflammatory mediators may also affect hippocampal function and reduce cognitive function[13].

Currently, treatment of DMD patients is primarily aimed at symptom management. Corticosteroid treatment aims to slow disease progression, cardiomyopathy is treated by afterload reduction, cough assist devices and nocturnal ventilation are used to treat pulmonary problems, and other medical issues such as osteoporosis, scoliosis, gastrointestinal and urinary symptoms are addressed[19]. Unfortunately none of these treatments address the cause of the disease, and thus there is the need for a therapy that addresses both cardiac and skeletal muscle deterioration[20]. The relatively well-defined genetic cause of DMD makes it a possible candidate for gene therapy, in which one tries to shift the DMD phenotype to a more Becker like

phenotype by restoring the expression of gene harbouring initial deletions[21]. This can be achieved by editing the DMD gene through genome editing or exon skipping[21]. Genome editing tries to replace faulty DNA with healthy DNA by delivering healthy dystrophin cDNA to muscle cells[21]. However, this method is limited by the delivery mechanism of DNA to the cells. In addition, genome editing only has proven to be effective ex-vivo and in mdx mouse models, and clinical trials are relatively far away. Exon skipping aims to restore the disrupted open reading frame for DMD dystrophin mRNA transcripts by skipping the faulty genetic code, which results in the transcription of a partly effective dystrophin protein[22, 23]. Exon skipping appears to slow disease progression and is under consideration for regulatory approval. However, thus far exon skipping therapies only slow disease progression and is not curative. These new insights in gene therapy may in the future lead to a cure for DMD, however, much research still has to be done in this field.

UPPER EXTREMITY FUNCTION IN DUCHENNE MUSCULAR DYSTROPY

As no cure for DMD has been found yet, treatment is still mainly focused on delaying disease progression and preserving functional abilities. Nowadays, the median survival is above 30 years[7, 24], which implies that DMD patients are in a wheelchair and have limited UE function for the largest part of their lives. As illustrated by the virtual case in box 1, especially restrictions in UE function have a huge impact on their quality of life and functional independence. For this reason, knowledge of UE function and its decline is very important. The research that has been done until now has indicated that muscle force in DMD patients is already limited at a young age and that arm function starts to deteriorate when they become confined to a wheelchair[10]. Muscle weakness is more or less symmetrical, but extensor groups are weaker than flexor groups, and proximal muscle groups are weaker than distal muscle groups[25]. In addition, joint contractures, which occur most often at the level of the elbow, wrist and fingers, are seen in many patients[8, 26, 27]. Bartels et al. indicated that UE strength and UE range of motion are strongly associated with UE function[28]. Corticosteroid treatment and physical exercise programs have been proven beneficial for preserving UE function[9, 29-34]. Due to these interventions, which address the neuromuscular functions, functional decline can be decelerated by a few years, but not stopped[9, 31, 35]. Consequently, there is a need for other interventions that compensate for the loss of arm function. One solution could be the use of dynamic arm supports (either passive or active) that reduce the effort that is needed to perform functional activities with the arms. For this reason the Flextension A-Gear project (Box 2) was started.

OBJECTIVES

For the development and evaluation of new interventions, such as supportive aids and physical training programs, detailed insight in UE function is needed. Especially knowledge of the rate of functional deterioration, the specific movements and muscles that are affected, and the impact on social participation is important. Therefore, this thesis aims to gain more insight in UE function of boys and men with

Box 2: Flextension A-Gear project

Flextension was founded by an initiative of the Dutch Duchenne Parent Project in 2007. The project has the goal to improve the quality of life of boys and men with Duchenne Muscular Dystrophy (DMD) by developing new assistive devices. In 2011, Flextension received a STW grant for a first research project, the A(bility)-Gear project. In the A-Gear project various Dutch universities collaborate, i.e. University of Twente, VU Medical Centre, Delft University of Technology, and Radboud University Medical Center. The goal of the A-Gear project is to develop a natural arm support that can support the growing needs of boys and men with Duchenne muscular dystrophy.

The strategy of the project is to develop a passive and an active arm support, able to support the arm during activities of daily living. The passive arm support (Passive A-Gear) consists of a close to the body exoskeleton with a slender spring system that eliminates the effects of gravity and, therefore, makes it easier to move the arms. The active arm support (Active A-Gear) has the same mechanical basis as the passive A-Gear, but actuators and control strategies are added to give additional support to the users that need it.

In each of the collaborating institutes a PhD candidate has been working on the A-Gear project. At the Radboud University Medical Center research is directed at the clinical aspects of the project. An exploratory study to gain more insight into arm function of boys and men with DMD is conducted and the clinical effects of the prototypes are evaluated. Research at the Delft University of Technology focuses on the mechanical design of the Passive A-Gear and the development of slender spring systems for a close-to-body arm support. At the VU Medical Centre the focus is on the design of the Passive and Active A-Gear, with a special emphasis on the actuation of the Active A-Gear. The University of Twente is expert in bio-signaling and biomechanics and focuses on the sensory interface and control strategies that are needed to control the Active A-Gear.

This project is funded by the Technology Foundation STW (project 11832). Special thanks goes to the sponsors of the project: United Parent Projects Muscular Dystrophy, Prinses Beatrix Spierfonds, Spieren voor Spieren, Johanna Kinderfonds, Kinderrevalidatiefonds Adriaanstichting, Focal Meditech, OIM Orthopedie, Ambroise, and Intespring.

DMD by answering the following research questions:

1) How does UE function of DMD patients compare to healthy controls?
2) How does UE function of DMD patients differ between disease stages?
3) Which (new) outcome measures are feasible and valid for measuring UE

function in DMD patients?

4) What variables can be associated with UE function in DMD patients and how can knowledge of these variables lead to better management of UE limitations?

Next to the development of new interventions, the knowledge gained in this thesis can be used in clinical decision making (selection and timing of interventions) and it can be used as the basis for new randomized controlled trials into the effects of UE interventions, such as new medication, physical exercise training and supportive aids.

OUTCOME MEASURES OF UPPER EXTREMITY FUNCTION IN DUCHENNE MUSCULAR DYSTROPHY

In order to achieve the above mentioned goals, different research methods, i.e. web-based questionnaires, functional scales and physiologic outcome measures, were used. The web-based questionnaire quantified UE function subjectively, while the functional scales and physiologic outcome measures quantified UE function objectively. The aim was to include outcome measures on all levels of the International Classification of Functioning, Disability and Health (ICF). Figure 3 contains the ICF scheme of the main UE outcome measures used for each IFC level.

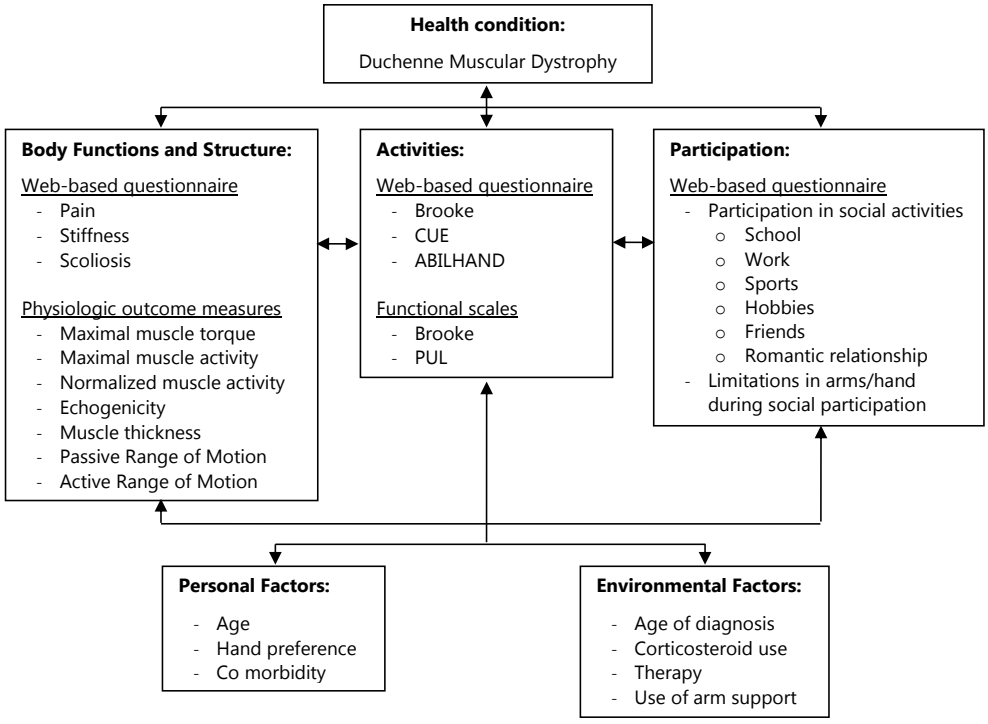

Figure 3. Main outcome measures at the different ICF levels

Web-based questionnaire

Although questionnaires give a subjective insight in UE function, questionnaires have some advantages over objective measurement instruments. Questionnaires are a relatively quick method for getting large amounts of information and they can be used to examine large populations. Especially web-based questionnaires can reach a large population while minimizing the effort to obtain information for both examiner and participant.

In this thesis an extensive web-based questionnaire regarding UE function, pain and stiffness in boys and men with DMD is used. In order to reach a large part of the DMD community, the questionnaire is translated into Dutch, Italian, Spanish, German, and French (Tekom, Hoofddorp, The Netherlands) and distributed through patient organizations in the different countries. The questionnaire contains questions related to all ICF domains (figure 3), and outcome measures are grouped in 4 categories: participant characteristics, UE pain and stiffness, UE activity level and participation restrictions due to UE limitations. Most questions are based on existing questionnaires, such as the University of Michigan Upper Extremity Questionnaire[37], the Capabilities of Upper Extremity (CUE) questionnaire[38] and the ABILHAND questionnaire[39].

Functional scales

Several scales to measure UE function in DMD have been developed over the years. The most commonly used functional UE scale in DMD is the Brooke Upper Extremity Rating Scale[40]. This scale quantifies UE function based on one single question with 6 answer options, which makes this scale not very sensitive for monitoring changes in UE function. Other UE functional scales have the disadvantage that they are not able to assess all different levels (proximal and distal) of functional abilities of DMD patients in different disease stages[41]. As a solution for this problem, the Performance of Upper Limb (PUL) scale has been developed. The PUL scale has specifically been designed for DMD patients with the aim of gaining insight in the progression of weakness and natural history of functional UE decline. In addition, the PUL scale aims to relate individual PUL items to activities of daily living[42]. The PUL is a reliable scale for both ambulant and non-ambulant DMD patients[43]. In this thesis, the Brooke scale is used as a gold standard for quantifying UE function and the PUL scale is used to gain a more thorough insight in the functional abilities of DMD patients.

Physiologic outcome measures

In the search for valid physiologic outcome measures we took the commonly used 'clinical gait analysis' as an example. In clinical gait analysis, 3D-motion analysis of the lower limbs and body is performed in combination with surface electromyography (sEMG) measurements of the muscles. This gives an objective and reliable insight in movement deficits of the lower extremities and is also useful to evaluate interventions aimed at improving lower limb function during gait[44]. Against this background,

it was considered that the combination of 3D-motion analysis and sEMG might also be a promising tool for evaluating UE function in DMD. In addition, muscle force measurements and muscle ultrasound were performed to gain insight in the disease progression at a muscular level.

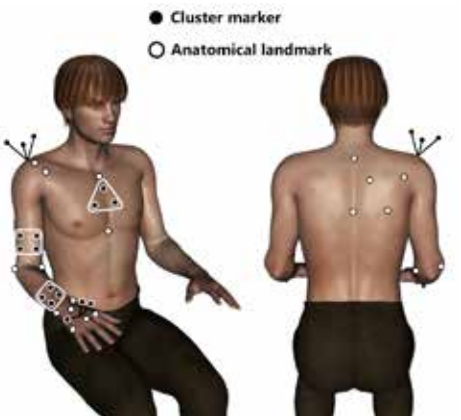

Figure 4. Kinematic upper extremity model

3D-motion analysis

In 3D-motion analysis, the motions of body segments are recorded and from that, joint kinematics are calculated. There are two different types of 3D-motion analysis, i.e. sensor based and camera based. In this thesis the Vicon motion analysis system (Oxford Metrics, Oxford, UK), which is a camera-based system, is used. For the analysis of UE kinematics a model consisting of 5 technical coordinate systems (marker clusters) is used to determine the segment positions and virtual markers on the anatomical landmarks are used for the calculation of the joint kinematics (figure 4). This method was found reliable in children[45]. Joint kinematics of single joint movements of the shoulder, elbow and wrist are calculated.

Surface electromyography

Muscle cells have semi-permeable membranes, meaning that ions can enter and exit the muscle cells through the membrane. When a muscle cell is at rest, there is an ionic equilibrium between the inner and outer spaces of the muscle cell. However, when muscle cells (a motor unit) are activated by the nervous system, the membrane is depolarized and a brief Na+ influx takes place. Immediately after this depolarization, the ionic balance in the muscle cell is restored by the active ion pump in the muscle membrane; this phase is called repolarization. When during the depolarization a certain Na+ threshold is reached, an action potential follows. During the action potential, the negative charge of the muscle cell changes briefly to a positive charge. The action potential spreads along and inside the muscle fiber, resulting in a release of Ca2+ ions inside the muscle cell. Next, Ca2+ binds to the receptors on actin filaments, which cause actin and myosin to bind and will eventually result in muscle contraction. The action potentials along the muscle fibers can be recorded through the skin using bipolar sEMG electrodes. These electrodes can measure small changes in the muscles electrical activity[46].

From the detected sEMG signals numerous outcome measures can be determined, such as amplitude, frequency and other time-related parameters. In this thesis the focus is only on the sEMG amplitude, which is a measure of the amount and size of the motor units that are activated. sEMG amplitude is related to muscle force, however, this relationship is complicated by both the character of the measured EMG and the

mechanics of force production in skeletal muscles[47]. sEMG measurements give insight in the activation patterns of muscles when performing activities. In addition, sEMG signals can potentially tell more about the magnitude of the muscle damage and the muscle capacity in DMD patients. They may also be used as a control signal in an active arm support.

Muscle force

Muscle strength assessments have been used for decades as a measure of disease severity in DMD. The most often used method for muscle strength testing is the Medical Research Council (MRC) scale[48]. This scale, however, assesses muscle strength on a 5-point scale and, therefore, it is not very sensitive or reliable[12, 49-51]. An alternative method to measure muscle strength is the use of a force sensor. Hand held dynamometers (HHDs) are most commonly used to perform such measurements. HHDs are much more sensitive than muscle strength testing with the MRC scale, however, they have the disadvantage that the results are influenced by the examiner's strength[52]. In addition, HHDs have a restricted range in which they can measure, which makes it impossible to reliably assess muscle strength in very weak patients, although this is of great clinical importance[53, 54]. To overcome the disadvantages of HHDs, a fixed-frame dynamometer is used to measure muscle strength in this thesis. This frame allows to measure smaller forces than with HHDs, and the measurements are not dependent on the force of the examiner as participants push against the frame. The position of the force sensor is adjustable, which makes it possible to standardize the muscle force measurements for each individual participant.

Quantitative muscle ultrasound

Quantitative muscle ultrasound (QMUS) is a non invasive imaging technique that is feasible for DMD patients[55]. QMUS is able to distinguish between healthy subjects and DMD patients. It can quantify disease progression, detect longitudinal changes in muscles, and can be related to physical functioning[55-57]. Using QMUS, muscle thickness and echogenicity (i.e. grayscale; the whiter the muscle the more it is affected by the disease) can be determined. In this thesis Z-scores are used to compare muscle thickness and echogenicity to specific reference values of healthy subjects in order to gain insight in the extent to which muscles are affected by DMD and in the pattern of muscle affliction.

OUTLINE OF THIS THESIS

Part 1 of this thesis addresses UE function based on a web-based questionnaire, whereas **part 2** deals with UE function based on functional scales and physiologic outcome measures.

Part 1: Upper extremity function based on the results of an international web-based survey

Part 1 contains three chapters that are based on the data resulting from an internationally distributed web-based questionnaire. In total, 213 DMD patients were included in this database focusing on all ICF domains. **Chapter 2** aims to provide insight into the changing patterns of UE function during the course of DMD, thereby providing an extensive description of UE function in DMD patients at different clinical disease stages. **Chapter 3** presents the results of factor analyses performed on UE function, pain and stiffness. The aim of this chapter is to gain insight into the underlying dimensions of the questionnaires, in order to develop a short questionnaire that clinicians can use for stepwise assessment of UE function, pain and stiffness in patients with DMD. In addition, this chapter aims to investigate the construct validity of the identified factors. The aim of **chapter 4** is to identify predictors of UE function in boys and men with DMD. This is done by performing multivariable linear regression analyses, where the factors resulting from chapter 3 are used as dependent variables.

Part 2: Upper extremity function explored by means of functional scales and physiologic outcome measures

Part 2 of this thesis contains three chapters that address UE function in DMD patients using functional scales and physiologic outcome measures. In all chapters, healthy subjects are used as a control group. **Chapter 5** presents the results of a pilot study aiming to determine the clinical feasibility of sEMG in boys with DMD, and to evaluate the construct validity of sEMG by determining if it is able to discriminate between healthy subjects and boys with DMD. **Chapter 6** aims to give a quantitative description of UE functioning during a variety of meaningful UE tasks in boys and men with DMD in different stages of the disease, in comparison to their healthy peers. In addition, this chapter aims to evaluate the relation between physiologic and structural UE functions and functional UE scales. This chapter presents the results of 20 healthy subjects and 23 boys and men with DMD in different disease stages. In **Chapter 7,** critical physiologic outcome variables leading to reduced UE task performance in DMD are identified and used to construct a biophysical model of the UE working mechanism in DMD.

Chapter 8 summarizes and discusses the work described in this thesis. Furthermore, it elaborates on how the knowledge on UE function in DMD patients can be translated into recommendations for interventions, such as dynamic arm supports. Finally, recommendations for future studies are made.

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PART 1

UPPER EXTREMITY FUNCTION BASED ON THE RESULTS OF AN INTERNATIONAL WEB-BASED SURVEY

CHAPTER 2

PATTERNS OF DECLINE IN UPPER LIMB FUNCTION OF BOYS AND MEN WITH DMD: AN INTERNATIONAL SURVEY

Published as:
Janssen MM, Bergsma A, Geurts AC, de Groot IJ. Patterns of decline in upper limb function of boys and men with DMD: an international survey. J Neurol. 2014;261(7):1269-88.

Abbreviations:

CUE	Capabilities of Upper Extremity questionnaire
DMD	Duchenne Muscular Dystrophy
ICF	International Classification of Functioning, Disability and Health
UE	Upper Extremity

ABSTRACT

AIM With increasing life expectancy, upper extremity (UE) function becomes more and more important in boys with Duchenne Muscular Dystrophy (DMD). Knowledge of UE function in these children is, however, limited. The aim of this study was to gain insight in the changing patterns of UE function during the course of DMD.

METHODS A web-based questionnaire on UE function, covering all domains of the International Classification of Functioning Disability and Health, was distributed worldwide. Primary domains of the questionnaire were: participant characteristics, UE pain and stiffness, UE activities, and social participation. Data were described per disease stage and analyzed using descriptive analysis.

RESULTS A total of 213 boys/men with DMD (1-35 years) were included in this study. UE pain, stiffness and activity limitations increased with disease stage. UE activity limitations already occurred in the early ambulatory stage. Compared to the healthy population, social participation was restricted in DMD patients and about 70% of the respondents experienced UE limitations when performing social activities. Despite the existence of UE impairments, only 9% of the respondents used supportive aids.

DISCUSSION Functional capacities and activities of the UE are limited already in the early ambulatory stage of patients with DMD affecting their social participation. Therefore, clinicians should pay attention to UE limitations before DMD patients lose their capacity to walk. Effective and adequate aids as well as attention for pain and stiffness in the therapeutic management could help to reduce UE activity limitations and related restrictions in social participation.

INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is the most common form of muscular dystrophy in children, with an incidence of one in 6000 male live births[22]. DMD is an X-linked recessive disorder characterized by progressive muscle wasting and weakness. Up to this point there is no cure for DMD, and treatment is mainly aimed at delaying disease progression and preserving functional abilities. Due to these treatments (including nocturnal ventilation), life expectancy in boys with DMD has increased from 14 years of age in the 1960s to 25 years of age in the 1990s. Currently, the median survival of boys with DMD is estimated to be over 30 years[8, 16].

To improve care for DMD patients and to develop tailored training and new supportive aids, it is important to gain more insight into the course of the disease and the factors affecting its course. The current literature on disease progression is mostly aimed at the level of muscle or cell structures, and hardly at the level of function or activity[12, 23, 32]. The maintenance of function and activity, however, is highly related to the level of independence and quality of life[24]. Therefore, it is relevant to investigate disease progression from the levels of function and activity as well.

The little knowledge that there is on function and activity in boys with DMD is mainly focused on the lower extremity. Loss of lower extremity function can be compensated fairly well by using a wheelchair; in contrast, upper extremity (UE) function is much harder to support. There are only few supporting devices for the arms available, and these devices do not cover the full range of function and activity[19]. With the current life expectancy, boys with DMD will live with impaired UE function for more than 15 years. If left unsupported, they may be seriously limited in UE activities and restricted in social participation for the same period of time.

In the literature, little is known about UE function in the course of DMD, especially regarding the execution of complex activities[30]. Understanding the execution of complex activities, e.g. during self-care and domestic life, is essential for the development of therapeutic interventions and supportive aids.

The International Classification of Function, Disability and Health (ICF) presents a framework to describe human functioning at three different levels: the level of body functions and structures, the level of activities and the level of social participation[26]. The latter two are highly interrelated. The relation between these levels, however, is not linear. Therefore, it is necessary to study upper limb function in a broad perspective, taking all domains of the ICF into account.

The aim of this study was to gain insight into the changing patterns of UE function in the course of DMD by means of an internationally distributed web-based questionnaire focusing on all levels of the ICF.

METHODS

Procedures

A web-based questionnaire, containing questions on all ICF domains (function, activity, participation), was translated into five languages (English, Dutch, German, Italian, Spanish). This questionnaire was subsequently distributed around the world by contacting Duchenne patients' organizations worldwide and asking them to send the internet address of the questionnaire to their members. The full questionnaire can be found in appendix 1. This procedure was approved by the medical ethical committee in the Arnhem-Nijmegen region (the Netherlands) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Participants

The questionnaire could be filled in by patients with DMD or their parents or caregivers. Because an anonymous web-based questionnaire was used in this study, the diagnosis of DMD could not be confirmed by DNA diagnosis. However, to make sure that respondents fitted the clinical Duchenne phenotype, the diagnostic criteria of Emery were used[9]. Based on these criteria respondents were excluded if the diagnosis was made after the age of 10 and if wheelchair confinement occurred after the age of 13 (when the respondents did not use corticosteroids). In addition female DMD patients and respondents with the diagnosis of Becker Muscular Dystrophy or any other muscular dystrophy were excluded. Respondents were also excluded if the stage of the disease could not be determined based on their answers.

Outcome measures

Outcomes were categorized in four different categories. Participant characteristics were shown to give insight in the population. Pain and stiffness give insight in the ICF function level, UE activity gives insight in the ICF activity level and social participation gives insight in the ICF participation level.

Participant characteristics

To see if the population is comparable to the DMD population reported in literature, the following participant characteristics were assessed: age, age of diagnosis, age of wheelchair confinement, corticosteroid use, presence of scoliosis (based on the respondents knowledge, not confirmed by a physician) and the use of assistive devices for the arms.

Pain and stiffness

Questions concerning pain and stiffness were modified from the University of Michigan Upper Extremity Questionnaire[28]. Three different aspects of pain and stiffness were assessed: frequency (range: 0-6), severity (range: 0-10) and limitations due to pain and stiffness (range: 0-10). Pain and stiffness combination scores were calculated by taking the sum of the frequency, severity and limitation scores for

pain and stiffness, respectively (range: 0-26). The percentage of respondents that experienced pain was set at a combination score larger than 1.

UE activity

Items at the level of activities were chosen from existing measures used in clinical practice and were based on the study by van Beek et al.(submitted)[30]. They concluded that the Capabilities of Upper Extremity questionnaire (CUE)[18] and the ABILHAND questionnaire[31] are the most applicable self-report instruments to investigate the upper extremity activity level in teenage boys with DMD. The CUE examines basic UE mobility activities. In addition, the ABILHAND examines complex UE activities. Next to the 22 ABILHAND items described by Vandervelde et al.[31], four more items were added (i.e., eat with a spoon, use fork and knife, drink a glass of water without straw, and use the keyboard of a computer) because these activities were indicated as very important by boys with DMD[30]. This adapted scale will be referred to as ABILHAND-plus. Furthermore, the Brooke scale[3] was selected as the golden standard for assessing basis UE activity in patients with DMD. Lastly, participants were asked for the three activities that cause the most problems due to UE impairments.

Social participation

Concerning social participation, participants were asked whether they went to school, had a job, practiced sports, had hobbies, performed activities with friends and/or were involved in a romantic relationship. In addition, the respondents were asked if they experienced UE limitations while performing social activities (5 point scale).

Analysis

For all outcome measures, the total group score was determined as well as the score per disease stage. Four different disease stages were defined based on the guidelines of Bushby et al.[4]: in the early ambulatory stage, walking difficulties are experienced, however, the person is still able to climb stairs; in the late ambulatory stage, the person is still able to walk, but not able to climb stairs; in the early non-ambulatory stage, persons are no longer able to walk, but their UE function is not very limited (Brooke scale 1-2[3]); and in the late non-ambulatory stage, UE function is increasingly limited (Brooke ≥ 3).

Descriptive analysis of the data was performed: mean, median, standard deviation and frequency tables were calculated if applicable. When the participants did not fully complete the questionnaire, all available items were included in the analysis. Wilcoxon rank sum tests for independent groups were used to compare differences in pain and stiffness between the preferred and non-preferred side. All statistical analyses were done using IBM SPSS Statistics version 20 for windows (IBM®, Somers, USA).

RESULTS

Participant characteristics

In total, 344 participants from 14 different countries (Italy, the Netherlands, England, Spain, USA, Germany, Belgium, Switzerland, Canada, Ireland, Australia, Nepal, Peru and India) answered the questionnaire, of which 131 were excluded based on the exclusion criteria. From the 213 remaining participants, 198 filled in the complete questionnaire, whereas 15 participants filled in the questionnaire partially. Table 1 shows the participant characteristics.

Table 1. Participant characteristics.

	Total	Early ambulatory stage	Late ambulatory stage	Early non-ambulatory stage	Late non-ambulatory stage
Age (median (range))	13.1 (1.5-35.2)	7.2 (1.5-16.7)	11.6 (7.1-21.7)	13.5 (8.4-19.5)	19.9 (9.2-35.2)
N	213	66	29	24	94
Age of diagnosis (median (range))	4 (0-10)	3 (0-8)	4 (0-10)	4 (0-9)	4 (0-10)
N	213	66	29	24	94
Age wheelchair confined	10 (1-20)	-	-	12 (6-17)	10 (1-20)
N	112	-	-	23	89
Corticosteroid use (%)*	54.7 / 11.3 / 34.0	71.2/ 1.5 / 25.8	96.6 / 3.4 / 0.0	79.2 / 8.3 / 12.5	23.4 / 21.3 / 55.3
N	212	65	29	24	94
Scoliosis (%)**	17.8 / 31.0 / 51.2	3.0 / 13.6 / 83.3	0.0 / 37.9 / 62.1	4.2 / 33.3 / 62.5	37.2 / 40.4 / 22.3
N	213	66	29	24	94
Percentage wearing arm splints (%)	9.4	6.1	0.0	0.0	17.0
N	213	66	29	24	94
Percentage using arm support (%)	8.5	0.0	3.4	4.2	17.0
N	213	66	29	24	94

* First number = currently uses corticosteroids, second number = did use corticosteroids in the past, third number = does not use corticosteroids. ** First number = severe scoliosis, second number = mild scoliosis, third number = no scoliosis.

Pain and stiffness

The pain and stiffness combination scores ranged between 0 and 26 (26 = maximum possible score). No differences were found between the preferred and non preferred side. Pain was most frequently present the shoulders, while stiffness was most frequently present in the fingers. Pain levels gradually increased with disease stage, while stiffness levels increased most in the late non-ambulatory stage (figure 1, table 2). In table 2 the pain and stiffness levels of the preferred and non preferred side are combined.

UE activity

Forty-four percent of the respondents in the early ambulatory stage reported limitations while performing the basic activities of the CUE. In addition, 25% of the respondents in the early ambulatory stage reported that it was difficult or impossible to perform some of the daily activities from the ABILHAND-plus. These percentages increase to respectively 95% and 90% in the late non-ambulatory stage (table 3).

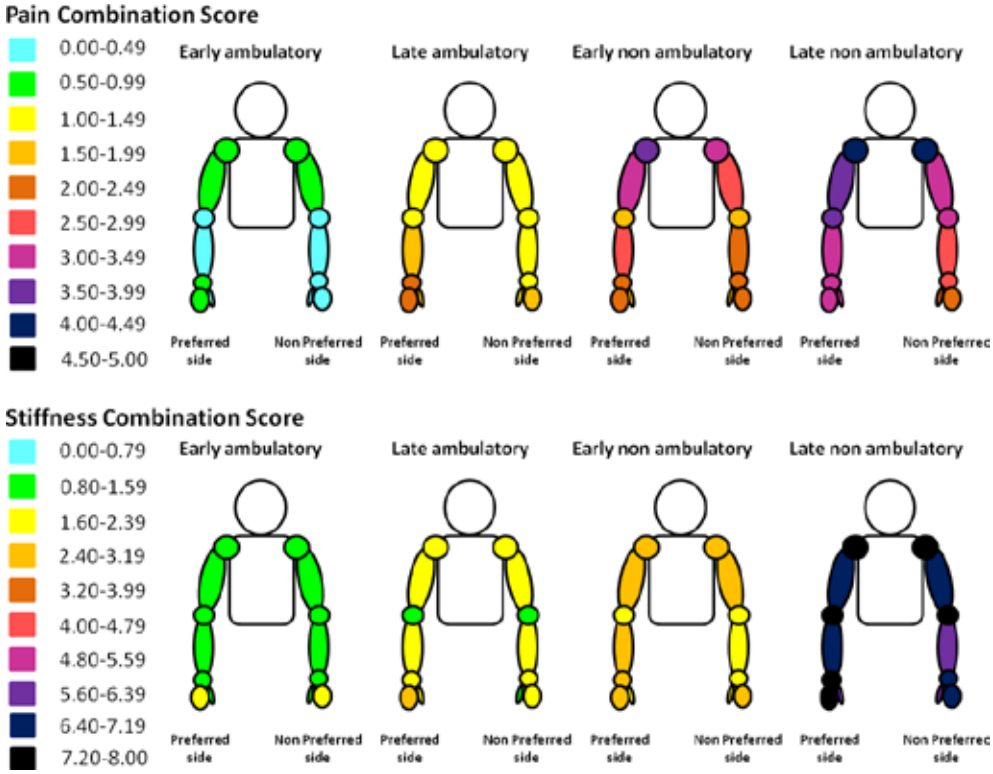

Figure 1. Average pain and stiffness combination scores per body segment
Maximal possible score = 26

Table 2. Pain and Stiffness

	Total	Early ambulatory stage	Late ambulatory stage	Early non-ambulatory stage	Late non-ambulatory stage
Percentage of respondents that experienced pain (%) (pain combination score > 1)					
Shoulders	39.4	13.6	24.1	45.8	60.6
Upper arms	35.0	17.4	24.1	43.8	48.4
Elbows	33.3	9.1	22.4	29.2	54.8
Forearms	32.9	13.6	27.6	39.6	46.3
Wrists	31.2	11.4	29.3	35.4	44.7
Thumbs	25.8	7.6	24.1	29.2	38.3
Fingers	29.3	11.4	27.6	33.3	41.5
N	213	66	29	24	94
Percentage of respondents that experienced stiffness (%) (stiffness combination score > 1)					
Shoulders	42.7	25.0	32.8	39.1	59.0
Upper arms	39.6	25.8	32.8	34.8	52.7
Elbows	40.1	22.7	29.3	28.3	58.5
Forearms	38.9	24.2	31.0	32.6	53.2
Wrists	41.3	25.0	34.5	28.3	58.0
Thumbs	38.4	25.0	31.0	30.4	52.1
Fingers	45.3	30.3	39.7	34.8	60.1
N	213	66	29	24	94

Table 3. Activity limitations (Brooke, CUE, ABILHAND-plus) per disease stage.

	Total	Early ambulatory stage	Late ambulatory stage	Early non-ambulatory stage	Late non-ambulatory stage
Brooke scale (median (range))	2 (1-6)	1 (1-2)	2 (1-4)	2 (1-2)	5 (3-6)
N	213	66	29	24	94
CUE* (% / %)					
Reach forward, shoulder level	23 / 42	16 / 0	52 / 11	60 / 4	9 / 90
Arms over head	20 / 48	23 / 0	46 / 16	52 / 21	2 / 98
Reach to the floor	28 / 55	48 / 11	52 / 30	46 / 42	3 / 96
Raise a 5 pound object over the head	29 / 60	61 / 13	29 / 50	58 / 42	0 / 100
Slide a light object towards you	34 / 29	17 / 0	52 / 2	54 / 0	35 / 63
Slide a 10 pound object towards you	36 / 54	69 / 9	57 / 32	50 / 42	4 / 94
Slide a light object away from you	32 / 28	17 / 0	48 / 2	38 / 4	37 / 61
Slide a 10 pound object away from you	35 / 53	63 / 9	57 / 7	46 / 46	7 / 90
Push up in chair	25 / 68	53 / 23	36 / 64	29 / 71	1 / 99
Curl wrist upward	40 / 31	44 / 0	57 / 7	44 / 15	32 / 63
Supination	39 / 36	42 / 2	59 / 11	65 / 15	25 / 72
Hold a hammer					
Pick up a small object with thumb and first two fingers	33 / 20	20 / 0	46 / 0	21 / 4	42 / 43
Hold a small object between thumb and index finger	36 / 19	27 / 2	48 / 0	17 / 8	44 / 40
Hold/open a 2 pound object with the tips of the fingers	35 / 51	59 / 5	63 / 29	52 / 40	6 / 91
Manipulate a small object with the fingers	42 / 27	45 / 8	32 / 21	44 / 8	42 / 47
Push a button with tip of the index finger	34 / 20	23 / 0	36 / 0	33 / 0	40 / 44
Average	33 / 40	39 / 5	48 / 19	44 / 23	21 / 74
ABILHAND-plus** (%)	a	a	a	a	a
Take the cap off a bottle †	74	49	48	63	98
Cut nails †	88	81	83	77	96
Button up a shirt	77	56	55	68	97
Fasten the zipper of a jacket	63	22	32	41	100
Turn a key in a keyhole	67	34	52	38	99
Fasten a snap e.g. from jacket or bag	67	34	40	43	100
Open a pack of chips ‡	73	57	38	59	95
Open a pack of biscuits	69	49	38	52	93
Insert a key in keyhole †	54	11	23	33	94
Turn off a tap	52	16	19	18	90
Turn on a tap	52	18	19	18	90
Fill a glass with water	62	13	60	45	96
Sharpen a pencil ‡	52	25	27	25	82
Open a lunch box	56	21	27	32	91
Squeeze toothpaste onto a toothbrush	57	26	31	21	92
Spread butter on a slice of bread	60	30	28	35	92
Open a toothpaste tube	56	30	19	21	92
Count banknotes †	46	12	14	25	74
Deal cards ‡	54	16	33	24	87
Unwrap a chocolate bar ‡	45	7	15	21	82
Dry hands	43	5	0	13	87
Wash hands	40	2	8	4	84
Eat with a spoon	38	2	4	13	76
Use fork and knife	56	19	27	43	89
Drink a glass of water without straw	45	0	8	13	92
Use keyboard of a computer	31	4	4	4	63
Average	57	25	29	33	90

* CUE: first number = percentage of respondents that answered the activity to be moderately, somewhat or a little limited; second number = percentage of respondents that answered the activity to be very, extremely or totally limited. The rest percentage is the percentage of respondents that answered that the activity was not limited (percentage not shown in table). ** ABILHAND-plus: percentage of respondents that answered the activity to be difficult or impossible. The rest percentage is the percentage of respondents that answered the activity to be easy (percentage not shown in table). † Items that were specific to adults. ‡ Items that were specific to children.

Overall the activity 'eat and preparing food' was experienced most problematic. However in the ambulatory stages the activities 'get dressed', 'reach to objects / lift objects' and 'write' were mentioned more often, while in the non-ambulatory stages 'personal hygiene', 'drink' and 'use the computer' were mentioned most next to the activity 'eat and preparing food' (table 4).

Table 4. Activities that cause the most problems in daily life due to UE impairments.

	Total	Early ambulatory stage	Late ambulatory stage	Early non-ambulatory stage	Late non-ambulatory stage
Eat and prepare food (%)	13	6	4	10	18
Get dressed (%)	12	19	20	16	7
Reach to objects / lift objects (%)	11	15	24	18	6
Write (%)	9	15	14	10	7
Personal hygiene (%)	9	6	6	4	12
Drink (%)	8	2	4	2	12
Using the computer (%)	7	0	0	6	11
Play / crafts (%)	4	11	6	2	2
Use the toilet (%)	4	2	6	4	4
Playing video games / control television / use telephone (%)	3	0	0	4	5
Touch / scratch the face (%)	3	0	0	0	5
Open packaging (%)	3	5	6	4	1
Open doors / unlock locks (%)	3	5	4	4	2
Control the wheelchair (%)	3	0	4	0	4
Use books / schoolbags (%)	2	2	0	6	2
Practice sports (%)	2	8	0	4	0
Interaction with other humans (%)	1	0	0	2	1
Other (%)	3	5	2	2	4
N	213	66	29	24	94

The numbers in this table represents the percentage of respondents that mentioned the activity when asking for the activities that cause the most problems in daily life due to UE impairments.

Social participation

Restrictions in social participation increased with increased disease stage. The percentage of respondents that experience UE limitations when performing social activities increases with the stage of the disease (table 5).

DISCUSSION

This study showed that activity limitations of the upper extremity in Duchenne Muscular Dystrophy (DMD) already occur in the early ambulatory phase, and increase with more advanced stages of the disease. In addition pain and stiffness increase with more advanced disease stages and restrictions in participation are more frequently present in more advanced disease stages.

Participant characteristics

The respondents in this study were between 1 and 37 years old and comprised DMD patients in all stages of the disease. Age of diagnosis, age of being wheelchair confined, prevalence of scoliosis and corticosteroid use were comparable to the results reported in literature[5, 16, 20, 21].

Table 5. Social participation per disease stage

	Total	Early ambulatory stage	Late ambulatory stage	Early non-ambulatory stage	Late non-ambulatory stage
Participants					
going to school (%)	78	91	96	96	59
N	200	58	27	24	91
working (%)	11	2	4	4	20
N	198	56	27	24	91
playing sports (%)	38	50	30	33	35
N	198	56	27	24	91
having a hobby (%)	83	66	89	92	89
N	198	56	27	24	91
in a romantic relationship (%)	3	0	0	0	7
N	197	55	27	24	91
Participation restrictions					
experiencing limitations of the arms and/or hands during school activities (%)*	68 / 14	63 / 2	85 / 0	78 / 4	59 / 35
N	154	51	26	23	54
experiencing limitations of the arms and/or hands during work activities (%)*	62 / 14	100 / 0	100 / 0	100 / 0	56 / 17
N	21	1	1	1	18
experiencing limitations of the arms and/or hands playing sports (%)*	66 / 16	75 / 0	88 / 0	50 / 25	56 / 31
N	76	28	8	8	32
experiencing limitations of the arms and/or hands during hobbies (%)*	60 / 7	46 / 0	58 / 0	45 / 0	70 / 15
N	164	37	24	22	81
experiencing limitations of the arms and/or hands in a romantic relationship (%)*	33 / 33	.	.	.	33 / 33
N	6	0	0	0	6

* Participation: first number = percentage of respondents that experienced mild participation restrictions due to UE limitations; second number = percentage of respondents that experienced severe participation restrictions due UE limitations. The rest percentage is the percentage of respondents that answered to experience no limitations in the arms and/or hands (percentage not shown in table).

The use of splints and supportive devices for the arms was around 9%. However, the percentage of participants that reported having difficulties using their UE was much larger. A Brooke scale of 1 was reported by merely 34% of the respondents, indicating that 66% of the boys already experienced some activity limitations, even in an early stage of the disease. Only a small percentage of the participants that experienced upper extremity limitations used an arm support. This finding is in contrast with the lower extremity, where splints are highly recommended and used. The non frequent use of arm supports could be caused by the fact that arm supports do not give natural support or that the arm supports are too prominent. Both invisibility and the ability to give natural support are important for orthotics to be worn in daily life[27].

Pain and stiffness

In total, 35.6% of the respondents experienced pain in their UE more than a few times a month; in adults this percentage was 55.4%. These numbers are comparable with the literature, where percentages between 4.3 and 54% have been reported[10, 29, 33].

Pain combination scores gradually increased in the more advanced disease stages. The average pain and stiffness combination scores are relatively low (figure 1). This is probably due to the large number of respondents that do not experience pain or stiffness. The pain combination scores of the respondents that did experience pain ranged from 1 to 21 and the stiffness combination scores ranged from 1 to 26. No other studies on the relation between pain and disease progression in DMD were found. Stiffness also appeared to increase with the stage of the disease, which is in correspondence with Cornu et al.[7]. They, however, measured the stiffness in the joint, whereas we assessed the subjective experience of joint stiffness.

Overall, pain was most severe in the shoulders. This is in accordance with the results of Engel et al.[10] and Tifferau et al.[29]. Stiffness was most severe in the fingers. One explanation for this could be that the participants were still able to use their fingers in a relatively late stage of the disease, while the shoulder and elbow could not be moved anymore, making patients probably less aware of the stiffness in their shoulders.

UE activity

The Brooke scale is the most commonly used instrument to evaluate the upper limb activity level in boys with DMD. The CUE has never been used in boys with DMD. The ABILHAND has been validated in boys with DMD[31]; and van Opstal et all. used the ABILHAND to measure the capacity to manage daily activities that require the use of the upper limb[25]. They also divided the results for the different disease stages ('ambulant', 'nonambulant, relatively good arm abilities' and 'nonambulant, decreased arm abilities'). The scores per items were not shown in this study, however the total score indicated that arm function decreases with disease stage. This is comparable to the results of this study.

The ABILHAND has been validated in children older than 6 years, the CUE has only been used in adult subject. Since 23 participants were under the age of 6 years and 175 participants were under the age of 18 years, it could be that some activities in the CUE and ABILHAND are not valid for the participants. The CUE however consists of basic activities which were considered as not very age specific, therefore age was not expected to be a limiting factor to perform the CUE activities. The ABILHAND consists of more complex activities which could be more difficult to perform by very young children. For example, the activities 'cut nails', 'open a pack of chips' and 'open a pack of biscuits' are pointed out more difficult in the early ambulatory stage compared to the late ambulatory stage. This is probably due to the fact that the children in the early ambulatory stage (median age 7.2 years) are too young to be able to perform the item without difficulties.

Regarding the CUE, item 12 (Holding an object like a hammer with your hand) was erroneously not included in the questionnaire. This, however, did not influence the remaining results of the CUE, since we looked at the separate items and not at the total score.

The scores on the reported Brooke scale increased with age. The median age at which UE activity level started to deteriorate (Brooke 2) was 11.4 years. This result is comparable to the results of Jung et al. who found that the median age of Brooke scale 2 was around 10 years[15], and to Lord et al. who found a median age around 11 years[17].

The Brooke scale gives a stepwise insight into UE activity, whereas CUE and ABILHAND-plus provide us with a more detailed description of the activity limitations related to the UE. Items from the CUE as well as the ABILHAND-plus are already difficult in the early ambulatory stage. This indicates that difficulties performing upper extremity tasks occur already long before boys with DMD lose the ability to walk. These early activity limitations related to UE impairments have not been reported before.

Social participation

Restricted social participation is a huge problem in boys with DMD[13]. This can result in reduced engagement in social activities, social withdrawal or even social isolation[4]. The results of this study show that 95.1% of the respondents between 5 and 20 years went to school or attended other classes, which is comparable to the worldwide population in developed countries where 95.9% of children attend school[1]. Of the respondents over 20 years of age, 34.8% worked and 26.1% of the respondents over 20 years of age still attended school. In the healthy population of the same age, over 80% of the people are employed or have education[6].

Of all the boys with DMD, 37% participated in sports and 7.4% of the adults reported having a romantic relationship. These percentages are lower than in the healthy (adult) population worldwide[11, 14]. In comparison, Bendixen et al. stated that boys with DMD showed less participation in the physical domain, but not in the recreational and social domains[2]. The results of the current study, however, showed that participation in boys with DMD was also restricted in these other domains. This difference can be explained by the applied measurement instruments. Bendixen et al.[2] used the Children's Assessment of Participation and Enjoyment, while we used open questions. In addition, the participants of the study by Bendixen et al.[2] were between 5 and 15 years of age, whereas the population also included boys older than 15 years. Older boys are expected to have more participation restrictions, since they have more UE impairments. This is confirmed by the results in table 5, where about 70% of the respondents report experiencing mild or severe UE limitations when performing social activities and these percentages tend to increase with disease stage.

CONCLUSION

Pain, stiffness, activity limitations and social participation restrictions are higher in more advanced disease stages. However, they are already present in the early ambulatory stage. About 70% of the respondents state that they experience UE

limitations when performing social activities. Therefore clinicians should already pay attention to upper limb activity limitation before the DMD patients lose their capacity to walk. Effective and adequate aids as well as attention for pain and stiffness in the therapeutic management could help to reduce UE activity limitations and related restrictions in social participation.

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SUPPLEMENTARY MATERIAL

Table S.1. Full questionnaire

Nr.	Questions	Answer options
1	Respons ID	Given by the computer
2	What is your age?	Open question
3	Who filled out the questionnaire?	1 = myself 2 = mother 3 = father 4 = caregiver 5 = other (open question)
4	In which country do you live?	Open question
5	Were you born in this country?	1 = yes 2 = no
6	Since when have you lived in this country? (if question 5 = 2)	Open question
7	In which country were you born? (if question 5 = 2)	Open question
8	How tall are in cm?	Open question
9	What is your weight in kg?	Open question
10	What is your preferred hand?	1 = right 2 = left 3 = first right now left 4 = first left now right 5 = no preference
11	When was the diagnosis Duchenne muscular dystrophy made for you?	Open question
12	Who made the diagnosis?	1 = general practitioner 2= pediatrician 3 = pediatric neurologist 4 = neurologist 5 = I don't know 6 = other (open question)
13	Do you know which gene deviation you have?	1 = no 2 = yes
14	Which gene deviation you have? (if question 13 = 2)	Open question
15	Do you have other chronic diseases?	1 = no 2 = yes
16	What chronic disease do you have? (if question 15 = 2)	Open question
17	Have you ever seriously injured e.g. a bone fracture one of your arms or hands?	1 = no 2 = left arm 3 = right arm 4 = left hand 5 = right hand (more than one answers possible)
18	Have you ever had surgery of one of your arms or hands?	1 = no 2 = left arm 3 = right arm 4 = left hand 5 = right hand (more than one answers possible)
19	Do you have spinal deformities e.g. scoliosis?	1 = no 2 = yes mild 3 = yes severe
20	Was surgery performed to correct for spinal deformities? (if question 19 = 2 or 3)	1 = no 2 = yes
21	In what year was surgery performed? (if question 20 = 2)	Open question
22	Do you use corticosteroids prednisone/prednisol or deflazacort at this moment?	1 = no 2 = not anymore 3 = yes
23	Which type of medication did you use? (if question 22 = 2)	1 = prednisolon/prednisone 2 = deflazacort
24	Did you use it continuously or with intervals? (if question 22 = 2)	1 = continuously 2 = 10 days on 10 days off 3 = other (open question)

Nr.	Questions	Answer options
25	Which dose did you use? (if question 22 = 2)	Open question
26	When did you start using this medication? (if question 22 = 2)	Open question
27	When did you stop using this medication? (if question 22 = 2)	Open question
28	Why did you stop using this medication? (if question 22 = 2)	Open question
29	When did you start using this medication? (if question 22 = 3)	Open question
30	Which type of medication do you use? (if question 22 = 3)	1 = prednisolon/prednisone 2 = deflazacort
31	Do you use it continuously or with intervals? (if question 22 = 3)	1 = continuously 2 = 10 days on 10 days off 3 = other (open question)
32	Which dose did you use? (if question 22 = 3)	Open question
33	Do you use other medication which can possibly affect the course of Duchenne muscular dystrophy?	1 = no 2 = yes
34	What medication that can possibly affect the course of Duchenne muscular dystrophy do you use? (if question 33 = 2)	Open question
35	Do you use supplements like vitamins or homeopathic remedies?	1 = no 2 = yes
36	What supplements do you use? (if question 35 = 2)	Open question
37	Did you ever had physiotherapy?	1 = never 2 = yes, but not anymore 3 = yes, with periods of no therapy 4 = yes, continuously
38	How often do you have physiotherapy now? (if question 37 = 3 or 4)	Open question
39	For how long are your arms/hands treated by the physiotherapist each week? (if question 37 = 3 or 4)	1 = none 2 = ⋯ minutes a week (open question)
40	What kind of physiotherapy do you receive for your arms/hands? (if question 39 = 2)	1 = stretching 2 = supported active movements 3 = passive movements 4 = other movements, namely (open question) (more than one answer possible)
41	Do you exercises your arms/hands yourself or with your parents/caregivers?	1 = no 2 = yes, on average once a week 3 = yes, on average once a day 4 = yes, more than once a day
42	What kind of exercises do you do by yourself or with your parents/caregivers? (if question 41 = 2, 3 or 4)	1 = stretching 2 = supported active movements 3 = passive movements 4 = other movements, namely (open question) (more than one answer possible)
43	Do you swim or do you get hydrotherapy?	1 = no 2 = yes
45	Did you ever receive occupational therapy e.g. practicing daily activities or use of assistive devices?	1 = never 2 = yes, but not anymore 3 = yes, with periods of no therapy 4 = yes, continuously
46	How often do you receive occupational therapy currently? (if question 45 = 3 or 4)	Open question
47	For how long are your arms/hands treated by the occupational therapist each week? (if question 45 = 3 or 4)	1 = none 2 = ⋯ minutes a week (open question)
48	What kind of occupational therapy do you receive for the arms/hands? (if question 47 = 2)	1 = practice use of devices 2 = practice use of arm support 3 = fitting of splints 4 = different, namely⋯ (open question)
49	Which devices do you use for walking, transfers, or in therapy?	1 = Standing frame 2 = Long leg braces 3 = Wheelchair, pushed by somebody else 4 = Manual wheelchair (independent travelling) 5 = Manual wheelchair with electrical supported wheels 6 = Electrical wheelchair (independent travelling) 7 = Scooter

Nr.	Questions	Answer options
		8 = Other motorized vehicle (e.g. Segway)
		9 = 2- wheeled-bicycle
		10 = 2- wheeled-bicycle with electrical support
		11 = 3- wheeled-bicycle
		12 = 3- wheeled-bicycle with electrical suppor
50	How often do you use these devices? (asked for the separate devices)	1 = never
		2 = few times a year
		3 = few times a month
		4 = few times a week
		5 = almost every day
		6 = Daily for a significant part of the day
50	Are you completely wheelchair confined?	1 = no
		2 = yes, since (open question)
51	Do you use splints for your arms and/or hands?	1 = no
		2 = yes, namely (open question)
52	How often do you wear these splints?	1 = few times a year
		2 = few times a month
		3 = few times a week
		4 = almost every day
		5= Daily for a significant part of the day
		6 = during the night
53	Do you use some kind of arm support other than splints?	1 = no
		2 = yes, namely (open question)
54	How often do you use this arm support?	1 = few times a year
		2 = few times a month
		3 = few times a week
		4 = almost every day
		5= Daily for a significant part of the day
55	For which activities do you use the arm support?	Open question
56	How often do you have pain in your right shoulder?	0 = never
		1 = few times a year
		2 = few times a month
		3 = few times a week
		4 = almost every day
		5= Daily for a significant part of the day
		6 = always
57	How often do you have pain in your right upper arm?	Same as question 56
58	How often do you have pain in your right elbow?	Same as question 56
59	How often do you have pain in your right forearm?	Same as question 56
60	How often do you have pain in your right wrist?	Same as question 56
61	How often do you have pain in your right thumb?	Same as question 56
62	How often do you have pain in the fingers of your right hand?	Same as question 56
63	How often do you have pain in your left shoulder?	Same as question 56
64	How often do you have pain in your left upper arm?	Same as question 56
65	How often do you have pain in your left elbow?	Same as question 56
66	How often do you have pain in your left forearm?	Same as question 56
67	How often do you have pain in your left wrist?	Same as question 56
68	How often do you have pain in your left thumb?	Same as question 56
69	How often do you have pain in the fingers of your left hand?	Same as question 56
70	How severe is the pain in your right shoulder?	0 = No pain
		10 = Worst pain imaginable
71	How severe is the pain in your right upper arm?	Same as question 70
72	How severe is the pain in your right elbow?	Same as question 70
73	How severe is the pain in your right forearm?	Same as question 70
74	How severe is the pain in your right wrist?	Same as question 70
75	How severe is the pain in your right thumb?	Same as question 70
76	How severe is the pain in the fingers of your right hand?	Same as question 70
77	How severe is the pain in your left shoulder?	Same as question 70
78	How severe is the pain in your left upper arm?	Same as question 70
79	How severe is the pain in your left elbow?	Same as question 70
80	How severe is the pain in your left forearm?	Same as question 70
81	How severe is the pain in your left wrist?	Same as question 70

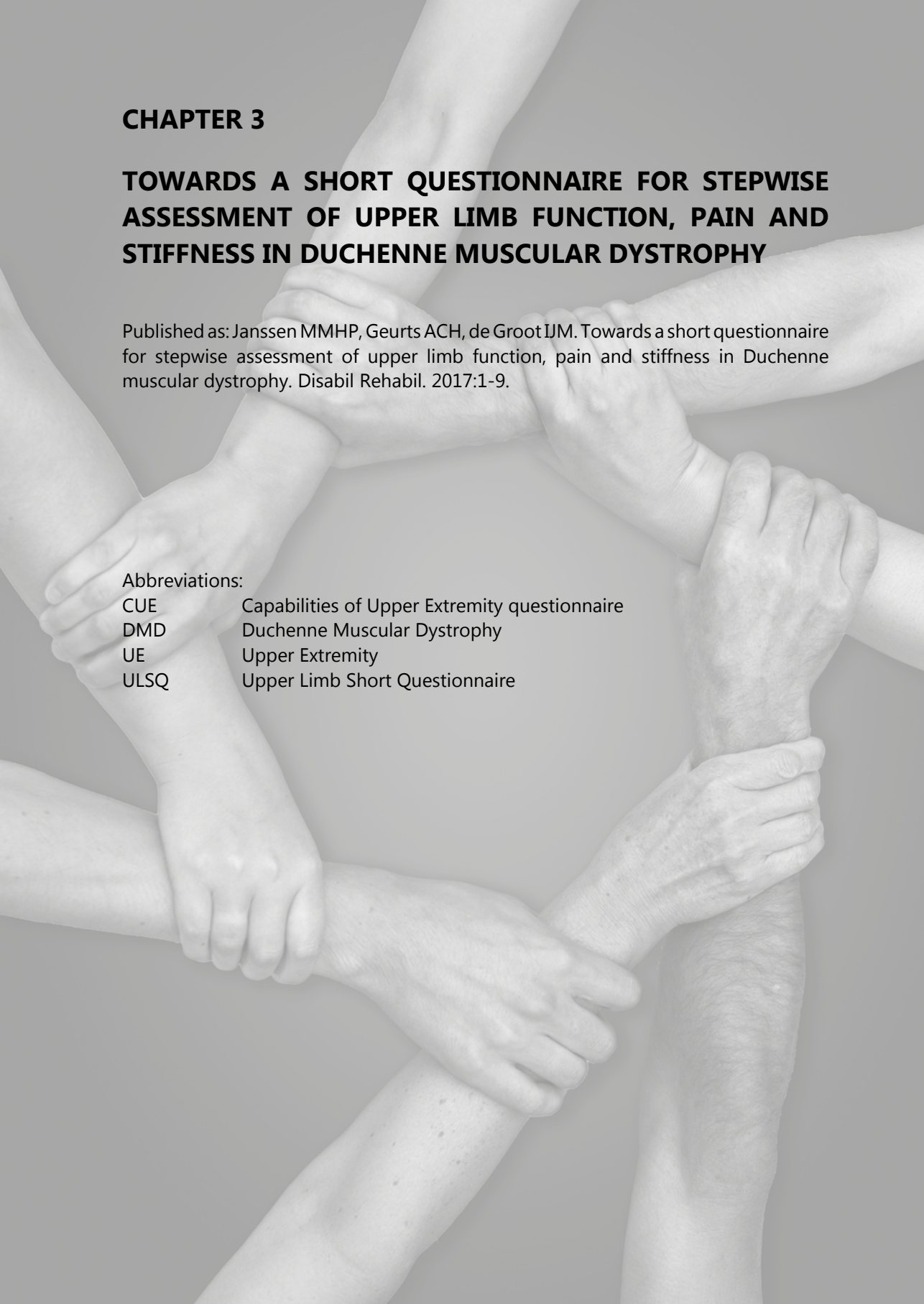
Nr.	Questions	Answer options
82	How severe is the pain in your left thumb?	Same as question 70
83	How severe is the pain in the fingers of your left hand?	0 = No limitations 10 = Fully limited
84	How limited are you due to the pain in your right shoulder?	Same as question 83
85	How limited are you due to the pain in your right upper arm?	Same as question 83
86	How limited are you due to the pain in your right elbow?	Same as question 83
87	How limited are you due to the pain in your right forearm?	Same as question 83
88	How limited are you due to the pain in your right wrist?	Same as question 83
89	How limited are you due to the pain in your right thumb?	Same as question 83
90	How limited are you due to the pain in the fingers of your right hand?	Same as question 83
91	How limited are you due to the pain in your left shoulder?	Same as question 83
92	How limited are you due to the pain in your left upper arm?	Same as question 83
93	How limited are you due to the pain in your left elbow?	Same as question 83
94	How limited are you due to the pain in your left forearm?	Same as question 83
95	How limited are you due to the pain in your left wrist?	Same as question 83
96	How limited are you due to the pain in your left thumb?	Same as question 83
97	How limited are you due to the pain in the fingers of your left hand?	Same as question 83
98	How often do you experience stiffness in your right shoulder?	0 = never 1 = few times a year 2 = few times a month 3 = few times a week 4 = almost every day 5= Daily for a significant part of the day 6 = always
99	How often do you experience stiffness in your right upper arm?	Same as question 98
100	How often do you experience stiffness in your right elbow?	Same as question 98
101	How often do you experience stiffness in your right forearm?	Same as question 98
102	How often do you experience stiffness in your right wrist?	Same as question 98
103	How often do you experience stiffness in your right thumb?	Same as question 98
104	How often do you experience stiffness in the fingers of your right hand?	Same as question 98
105	How often do you experience stiffness in your left shoulder?	Same as question 98
106	How often do you experience stiffness in your left upper arm?	Same as question 98
107	How often do you experience stiffness in your left elbow?	Same as question 98
108	How often do you experience stiffness in your left forearm?	Same as question 98
109	How often do you experience stiffness in your left wrist?	Same as question 98
110	How often do you experience stiffness in your left thumb?	Same as question 98
111	How often do you experience stiffness in the fingers of your left hand?	Same as question 98
112	How severe is the stiffness in your right shoulder?	0 = No stiffness 10 = Worst stiffness imaginable
113	How severe is the stiffness in your right upper arm?	Same as question 112
114	How severe is the stiffness in your right elbow?	Same as question 112
115	How severe is the stiffness in your right forearm?	Same as question 112
116	How severe is the stiffness in your right wrist?	Same as question 112
117	How severe is the stiffness in your right thumb?	Same as question 112
118	How severe is the stiffness in the fingers of your right hand?	Same as question 112
119	How severe is the stiffness in your left shoulder?	Same as question 112
120	How severe is the stiffness in your left upper arm?	Same as question 112
121	How severe is the stiffness in your left elbow?	Same as question 112
122	How severe is the stiffness in your left forearm?	Same as question 112
123	How severe is the stiffness in your left wrist?	Same as question 112
124	How severe is the stiffness in your left thumb?	Same as question 112
125	How severe is the stiffness in the fingers of your left hand?	Same as question 112
126	How limited are you due to the stiffness in your right shoulder?	0 = No limitations 10 = Fully limited
127	How limited are you due to the stiffness in your right upper arm?	Same as question 126
128	How limited are you due to the stiffness in your right elbow?	Same as question 126
129	How limited are you due to the stiffness in your right forearm?	Same as question 126
130	How limited are you due to the stiffness in your right wrist?	Same as question 126
131	How limited are you due to the stiffness in your right thumb?	Same as question 126
132	How limited are you due to the stiffness in the fingers of your right hand?	Same as question 126
133	How limited are you due to the stiffness in your left shoulder?	Same as question 126

Nr.	Questions	Answer options
134	How limited are you due to the stiffness in your left upper arm?	Same as question 126
135	How limited are you due to the stiffness in your left elbow?	Same as question 126
136	How limited are you due to the stiffness in your left forearm?	Same as question 126
137	How limited are you due to the stiffness in your left wrist?	Same as question 126
138	How limited are you due to the stiffness in your left thumb?	Same as question 126
139	How limited are you due to the stiffness in the fingers of your left hand?	Same as question 126
140	Which description is most suitable for you? (Brooke scale)	1 = Starting with my arms at my sides, I can lift both arms sideways in a full circle until they touch above my head 2 = I can raise both of my arms above my head only by flexing my elbow (i.e. shortening the circumference of the movement) or using trick movements 3 = I cannot raise my hands above my head but I can raise an 8oz (250 ml) glass of water to my mouth (by using one or both hands) 4 = I can raise my hands to my mouth (I can raise each hand separately) but I cannot raise an 8oz (250 ml) glass of water to my mouth 5 = I cannot raise my hand to my mouth but I can use my hands to hold a pen or pick up coins from the table 6 = I cannot raise my hands to my mouth and I have no useful function of my hands
141	Which description is most suitable for you? (Vignos scale)	1 = I walk and climb stairs without assistance 2 = I walk and climb stairs with aid of railing 3 = I walk and climb stairs slowly with aid of railing (over 12 seconds for 4 standard stairs) 4 = I walk unassisted and rise from chair but I cannot climb stairs 5 = I walk unassisted but I cannot arise from chair or climb stairs 6 = I walk only with assistance or I walk independently with long leg braces 7 = I walk in long leg braces but I require assistance for balance 8 = I stand in long leg braces but I am unable to walk even with assistance 9 = I am confined to a wheelchair 10 =I am Confined to bed
142	Think about reaching out with your arm to touch something directly in front of you that is at shoulder level. How limited are you doing this using your right arm	1 = totally limited 2 = extremely limited 3 = very limited 4 = moderately limited 5 = some limitation 6 = a little limited 7 = not at all limited
143	Think about reaching out with your arm to touch something directly in front of you that is at shoulder level. How limited are you doing this using your left arm	Same as question 142
144	Think about raising your arm directly over your head, with your arm straight. How limited are you doing this using your right arm	Same as question 142
145	Think about raising your arm directly over your head, with your arm straight. How limited are you doing this using your left arm	Same as question 142
146	Think about reaching down to touch the floor and sitting back up straight, without hooking with your other arm or using it to pull yourself up. How limited are you doing this using your right arm?	Same as question 142
147	Think about reaching down to touch the floor and sitting back up straight, without hooking with your other arm or using it to pull yourself up. How limited are you doing this using your left arm?	Same as question 142
148	Think about raising a 5-pound object like a heavy blanket over your head using both arms. (Don't worry about whether you could grab it with your hands, just if you could raise something that heavy over your head.). How limited are you doing this using both arms?	Same as question 142
149	Think about pulling or sliding (without grasping) a light object such as a	Same as question 142

Nr.	Questions	Answer options
	can of soda, that is on a table, towards you. How limited are you doing this using your right arm?	
150	Think about pulling or sliding (without grasping) a light object such as a can of soda, that is on a table, towards you. How limited are you doing this using your left arm?	Same as question 142
151	Think about pulling or sliding (without grasping) a heavy object (up to 10 pounds), that is on a table, towards you. How limited are you doing this using your right arm?	Same as question 142
152	Think about pulling or sliding (without grasping) a heavy object (up to 10 pounds), that is on a table, towards you. How limited are you doing this using your left arm?	Same as question 142
153	Think about pushing a light object such as a can of soda on a table, away from you. How limited are you doing this using your right arm?	Same as question 142
154	Think about pushing a light object such as a can of soda on a table, away from you. How limited are you doing this using your left arm?	Same as question 142
155	Think about pushing a heavy object (up to 10 pounds) on a table, away from you. How limited are you doing this using your right arm?	Same as question 142
156	Think about pushing a heavy object (up to 10 pounds) on a table, away from you. How limited are you doing this using your left arm?	Same as question 142
157	Think about pushing down with both arms into your chair enough to lift your buttocks (both sides) off the seat (do a push-up weight shift). How limited are you doing this?	Same as question 142
158	With your hand on your lap palm down, think about curling your wrist upwards, keeping your arm on your lap. How limited are you doing this using your right arm?	Same as question 142
159	With your hand on your lap palm down, think about curling your wrist upwards, keeping your arm on your lap. How limited are you doing this using your left arm?	Same as question 142
160	Think about turning your hand over, keeping your elbow bent at your side (like turning a doorknob or a dial). How limited are you doing this using your right arm?	Same as question 142
161	Think about turning your hand over, keeping your elbow bent at your side (like turning a doorknob or a dial). How limited are you doing this using your left arm?	Same as question 142
162	Think about picking up a small object such as a paper clip or the cap of a tube of toothpaste with the tips of your thumb and first two fingers. How limited are you doing this using your right arm?	Same as question 142
163	Think about picking up a small object such as a paper clip or the cap of a tube of toothpaste with the tips of your thumb and first two fingers. How limited are you doing this using your left arm?	Same as question 142
164	Think about pinching and holding an object between your thumb and the side of your index finger, such as holding a key. How limited are you doing this using your right arm?	Same as question 142
165	Think about pinching and holding an object between your thumb and the side of your index finger, such as holding a key. How limited are you doing this using your left arm?	Same as question 142
166	Think about grasping a large object like the lid of a 2 pound jar of mayonnaise with the tips of the fingers hard enough to pick the jar up or open the lid. How limited are you doing this using your right arm?	Same as question 142
167	Think about grasping a large object like the lid of a 2 pound jar of mayonnaise with the tips of the fingers hard enough to pick the jar up or open the lid. How limited are you doing this using your left arm?	Same as question 142
168	Think about using your fingers to manipulate objects, such as holding a coin and turning it over and over with your fingers. How limited are you doing this using your right arm?	Same as question 142
169	Think about using your fingers to manipulate objects, such as holding a coin and turning it over and over with your fingers. How limited are you doing this using your left arm?	Same as question 142
170	Think about pressing something with the tip of your index finger (not knuckle) such as dialing a touch-tone phone or ringing a doorbell. How limited are you doing this using your right arm?	Same as question 142
171	Think about pressing something with the tip of your index finger (not knuckle) such as dialing a touch-tone phone or ringing a doorbell. How limited are you doing this using your left arm?	Same as question 142
	(ABILHAND) Describe for the following activities how well you have been able to implement these in the past 3 months, WITHOUT support of other people or assistive devices.	
172	Taking the cap off a bottle	1 = impossible

Nr.	Questions	Answer options
		2 = difficult
		3 = easy
		4 = I don't know
173	Cutting my nails	Same as question 172
174	Buttoning up a shirt	Same as question 172
175	Fastening the zipper of a jacket	Same as question 172
176	Turning a key in a keyhole	Same as question 172
177	Fastening a snap (e.g. from jacket or bag)	Same as question 172
178	Opening a pack of chips	Same as question 172
179	Opening a pack of biscuits	Same as question 172
180	Inserting a key in keyhole	Same as question 172
181	Turning off a tap	Same as question 172
182	Turning on a tap	Same as question 172
183	Filling a glass with water	Same as question 172
184	Sharpening a pencil	Same as question 172
185	Opening a lunch box	Same as question 172
186	Squeezing toothpaste onto a toothbrush	Same as question 172
187	Spreading butter on a slice of bread	Same as question 172
188	Opening a toothpaste tube	Same as question 172
189	Counting banknotes	Same as question 172
190	Dealing cards	Same as question 172
191	Unwrapping a chocolate bar	Same as question 172
192	Drying my hands	Same as question 172
193	Washing my hands	Same as question 172
194	Eat with a spoon	Same as question 172
195	Use fork and knife	Same as question 172
196	Drink a glass of water (without straw)	Same as question 172
197	Use keyboard of computer	Same as question 172
198	Which 5 ABILHAND items (question 172-197) are most important to you?	
199	What are the most important problems you encounter in daily life due to limitations in arms and or hands in order of importance?	Open question
200	Do you go to school or attend other classes?	1 = no
		2 = yes
201	Do you encounter limitations in the arms and/or hands during school or study? (if question 200 = 2)	1 = no
		2 = a little inconvenience
		3 = regular inconvenience
		4 = severe inconvenience
		5 = Proper participation of the education is impossible due to limitations in arms/hands
202	Which activities at school are limited? (if question 201 = 2-6)	Open question
203	What is the highest education you have finished until now?	1 = primary school
		2 = secondary school
		3 = college
		4 = university
		5 = special education
204	Do you work internships and volunteering work included?	1 = no
		2 = yes
205	What kind of work do you do more than one is possible? (if question 204 = 2)	Open question
206	Do you suffer from limitations in your arms and/or hands in carrying out your work? (if question 204 = 2)	1 = no
		2 = a little inconvenience
		3 = regular inconvenience
		4 = severe inconvenience
		5 = Proper participation of the education is impossible due to limitations in arms/hands
207	Which activities are limited? (if question 206 = 2-6)	Open question
208	Are you participating in sport?	1 = no
		2 = yes
209	What kind of sports? (if question 208 = 2)	Open question
210	Do you suffer from limitations in your arms and/or hands in doing your sport? (if question 208 = 2)	1 = no
		2 = a little inconvenience

Nr.	Questions	Answer options
		3 = regular inconvenience 4 = severe inconvenience 5 = Proper participation of the education is impossible due to limitations in arms/hands
211	Which activities are limited? (if question 210 = 2-6)	Open question
212	Do you have a hobby or leisure time activity?	1 = no 2 = yes
213	What are your hobbies or leisure time activities? (if question 212 = 2)	Open question
214	Do you suffer from limitations in your arms and/or hands when performing these activities? (if question 212 = 2)	1 = no 2 = a little inconvenience 3 = regular inconvenience 4 = severe inconvenience 5 = Proper participation of the education is impossible due to limitations in arms/hands
215	Which activities are limited? (if question 214 = 2-6)	Open question
216	How many friends do you have?	1 = none 2 = 1-5 3 = 6-10 4 = more than 10
217	What kind of activities do you do with them?	Open question
218	Do you suffer from limitations in your arms and/or hands during these activities?	1 = no 2 = a little inconvenience 3 = regular inconvenience 4 = severe inconvenience 5 = Proper participation of the education is impossible due to limitations in arms/hands
219	Which activities are limited? (if question 218 = 2-6)	Open question
220	Do you have a romantic relationship?	1 = no 2 = yes
221	Which activities do you like to do together more than one is possible? (if question 220 = 2)	Open question
222	Do you suffer from limitations in your arms and/or hands during these activities? (if question 220 = 2)	1 = no 2 = a little inconvenience 3 = regular inconvenience 4 = severe inconvenience 5 = Proper participation of the education is impossible due to limitations in arms/hands
223	Which activities are limited? (if question 222 = 2-6)	Open question
224	Comments	Open question



CHAPTER 3

TOWARDS A SHORT QUESTIONNAIRE FOR STEPWISE ASSESSMENT OF UPPER LIMB FUNCTION, PAIN AND STIFFNESS IN DUCHENNE MUSCULAR DYSTROPHY

Published as: Janssen MMHP, Geurts ACH, de Groot IJM. Towards a short questionnaire for stepwise assessment of upper limb function, pain and stiffness in Duchenne muscular dystrophy. Disabil Rehabil. 2017:1-9.

Abbreviations:

CUE	Capabilities of Upper Extremity questionnaire
DMD	Duchenne Muscular Dystrophy
UE	Upper Extremity
ULSQ	Upper Limb Short Questionnaire

ABSTRACT

PURPOSE Duchenne muscular dystrophy can lead to upper extremity limitations, pain and stiffness. In a previous study, these domains have been investigated using extensive questionnaires, which are too time consuming for clinical practice. This study aimed at gaining insight in the underlying dimensions of these questionnaires, and to construct a short questionnaire that can be used for clinical assessment.

METHODS Exploratory factor analysis was performed on the responses of 213 participants to a web-based survey to find the underlying dimensions in the Capabilities of Upper Extremity questionnaire, the ABILHAND questionnaire, and questionnaires regarding pain and stiffness. Based on these underlying dimensions a stepwise approach was formulated. In addition, construct validity of the factors was investigated.

RESULTS In total, 14 factors were identified. All had high internal consistency (Cronbach's alpha > 0.89) and explained 80-88% of the variance of the original questionnaires. Construct validity was supported, because participants in the early ambulatory stage performed significantly better ($p < 0.001$) than participants in the late non-ambulatory stage.

CONCLUSION The factors identified from the set of questionnaires provide a valid representation of upper extremity function, pain and stiffness in Duchenne muscular dystrophy. Based on the factor commonalities, the Upper Limb Short Questionnaire was formulated.

INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is the most common type of muscular dystrophy. DMD is caused by a defect in the dystrophin gene, which is located on the X-chromosome. This defect leads to a shortage or absence of the dystrophin protein, which results in progressive muscle degeneration[1]. As a consequence, boys with DMD experience muscular weakness already in early childhood. Boys with DMD lose the ability to walk around the age of 10[2] and, without corticosteroid treatment, arm function starts to decrease in the early ambulatory phase[3].

Until now no cure has been found for DMD, however life expectancy is increasing due to disease retarding treatments like corticosteroids and supportive techniques such as nocturnal ventilation[4]. Currently, median survival of boys with DMD is estimated to be over 30 years[2,4], which means that men with DMD experience functional limitations for the largest part of their lives. Functional limitations in the lower extremities can be compensated fairly well by using a wheelchair. In contrast, limitations in the upper extremities (UE) are much harder to compensate. This is unfortunate, since arm function is important to maintain independence in daily life. We previously investigated arm function in boys with DMD during the course of their disease using a web-based questionnaire[3]. We concluded that arm function started to decrease already in the early ambulatory phase and that, despite this loss of arm function, arm supports were rarely used.

In this previous study, UE function was measured using three existing questionnaires: the Capabilities of Upper Extremity Questionnaire (CUE)[5], the ABILHAND questionnaire (including few additional questions[6]), and the Brooke scale[7]. These scales were chosen based on unpublished data from our own research group, in which we concluded that these scales are the most appropriate self-report instruments to investigate upper extremity function in teenage boys with DMD. Taken together, these UE questionnaires consist of more than 60 questions. In addition, questions concerning pain and stiffness were modified from the University of Michigan Upper Extremity Questionnaire[8]. In total, 42 questions about pain and 42 questions about stiffness in the upper extremities were asked.

This large number of questions gives an extensive insight into arm function and experienced pain and stiffness, but it also has disadvantages. The large number of questions can lead to low patient compliance. In addition, using all questions would be too time consuming for diagnostic purposes in a clinical context. For clinical practice a short questionnaire would be needed to identify what aspects of arm function the rehabilitation should focus on. Therefore, the primary aim of this study was to gain insight in the underlying dimensions of the above-mentioned set of questionnaires in order to formulate a short questionnaire that clinicians can use for stepwise assessment of UE function, pain and stiffness in patients with DMD. The secondary aim of this study was to investigate the construct validity of the identified factors in boys and men with DMD.

METHODS

Participants

This study was part of a larger study in which a total of 344 participants from 14 different countries responded to a web-based questionnaire[3]. The originally English questionnaire was translated into Dutch, Italian, Spanish, German, and French (Tekom, Hoofddorp, The Netherlands) and distributed through patient organizations in the different countries. We excluded respondents that did not agree with the clinical Duchenne phenotype, based on the diagnostic criteria of Emery[9]. Participants were also excluded if the diagnosis was made after the age of 10 years, or when participants who did not use corticosteroids and who were 14 years or older were not wheelchair confined[9]. In total 213 participants were included. The questionnaires used for data collection were approved by the medical-ethical committee in the Arnhem-Nijmegen region (the Netherlands).

Questionnaires

Arm function was assessed with the Capabilities of Upper Extremity Questionnaire (CUE)[5] and the ABILHAND questionnaire[6]. These questionnaires were chosen based on unpublished data of our own research group, in which we concluded that the above mentioned self reported questionnaires were most suitable for examining UE function in DMD patients, since no specific UE questionnaires for DMD were available at the time of that study. The chosen questionnaires were widely used for several diagnostic groups. The CUE consists of 17 items (of which 15 items are asked for either hand, yielding a total of 32 items) that examine basic functional activities of the upper extremities. The ABILHAND questionnaire consists of 22 items that assess more complex activities of the upper extremities. Next to the 22 ABILHAND items described by Vandervelde et al.[6], four more items were added (i.e., "eat with a spoon", "use fork and knife", "drink a glass of water without straw", and "use the keyboard of a computer"), because these activities were indicated as very important by boys with DMD (unpublished data from our own research group). This adapted scale will be referred to as ABILHAND-plus.

Pain and stiffness in the segments and joints of the upper limbs were assessed with a scale that was adapted from the University of Michigan Upper Extremity Questionnaire[8]. Pain and stiffness were assessed on three different aspects: frequency, severity, and activity limitations due to pain and stiffness. Frequency was measured on a 7-point scale (range 0-6), whereas severity and activity limitations were measured on an 11-point scale (range 0-10).

Detailed information on the questionnaires used in this study is presented in supplementary tables S1-4.

Statistical methods

For the ABILHAND-plus there were 4 answer options, including the option "I don't

know". Since, 28.5% of the respondents filled in "I don't know" for at least one of the items, we chose to replace this value with the average of the remaining items, so the results of these respondents could still be included in the factor analysis. However, when more that 1/3rd of the items was scored as "I don't know" (which was the case for 2.5% of the respondents) we interpreted these as missing values, because taking the average of the remaining items was considered unreliable.

Exploratory factor analysis was performed to test the underlying dimensions in the questionnaires used. Principal component analysis was applied as the extraction method. Orthogonal rotation (varimax) with Kaiser's criterion, Eigenvalues > 1.0, was used to determine the final number of extracted factors. The Kaiser-Meyer-Olkin measure was used to verify the sampling adequacy for the analysis. In addition, Bartlett's test of sphericity was applied to test if correlations between items were sufficiently large for principal component analysis.

Cronbach's alpha was calculated as a measure of internal consistency of each constructed factor. The percentage of variance explained by each factor is also presented.

To test the construct validity of the factors, the hypothesis was formulated that participants in the early ambulatory disease stage performed significantly better than participants in the late non ambulatory disease stage. Student t-tests were used to test for statistical differences between the groups defined. The mean group differences with 95% confidence intervals of the factor sum scores are presented.
All statistical analysis were performed using IBM SPSS statistics 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Participant characteristics

Questionnaires were filled in by patients themselves (20%) or by their parents/ legal guardians (80%). Of the 213 included participants, 198 filled in the complete questionnaire, whereas 15 participants ended the questionnaire prematurely. Participants were on average 13 years (range: 1-35 years) and 55% of the participants were wheelchair confined (median age of wheelchair confinement: 10 years, range 1-20 years). The median age of diagnosis was 4 years (range 0-10 years) and 66% of the participants used corticosteroids (currently or in the past). In addition, 49% of the participants had a mild or severe scoliosis. A more detailed description of the participants can be found in Janssen et al. 2014[3].

Factors

Sample adequacy of the factor analysis was good for all questionnaires (Kaiser Meyer Olkin > 0.9). In addition, Bartlett's tests of sphericity indicated that correlations between items were sufficiently large for principal component analysis (p-value <

0.001). Table 1 represents the descriptive values for the factors identified in the CUE, ABILHAND-plus, pain and stiffness questionnaires.

Table 1. The factors and their characteristics resulting from factor analysis on each questionnaire (CUE, ABILHAND-plus, PAIN and STIFFNESS)

Factors	N	Eigenvalues	% of explained variance	% of explained variance (total)	Cronbach' s Alpha	Kaiser Meyer Olkin	Bartlett' s tests of sphericity (P-value)
CUE				86.6		0.91	0.001
Basic hand function	8	22.4	74.7		0.98		
Heavy lifting	10	2.5	8.3		0.98		
Light or no lifting	12	1.1	3.6		0.99		
ABILHAND-plus				80.4		0.97	0.001
Gross hand function	16	19.7	75.7		0.97		
Fine hand function	10	1.2	4.7		0.98		
PAIN				86.3		0.86	0.001
Pain limitations	14	21.4	50.9		0.98		
Pain severity (not shoulder)	12	6.1	14.5		0.97		
Distal pain frequency	6	3.2	7.7		0.93		
Shoulder pain	4	2.0	4.7		0.89		
Proximal pain frequency (not shoulder)	4	1.5	3.5		0.93		
Elbow pain frequency	2	1.1	2.6		0.90		
STIFFNESS				87.9		0.98	0.001
Stiffness frequency	14	27.8	66.1		0.98		
Stiffness limitations	14	4.3	10.3		0.99		
Stiffness severity	14	2.1	5.1		0.98		

N = the number of items in the factor. KMO = Kaiser-Myer-Olkin measure of sampling adequacy. CUE = Capabilities of Upper Extremity questionnaire[5], ABILHAND-plus[6], PAIN and STIFFENESS questionnaires[9].

In total 14 factors were identified in the CUE, ABILHAND-plus, and the questionnaires regarding pain and stiffness. The CUE resulted in 3 factors, of which the corresponding items were related to "basic hand function", "heavy lifting" and "light or no lifting". The internal consistency of each factor was high (Cronbachs' alpha: 0.98 - 0.99). With respect to the ABILHAND-plus two factors were identified, of which the corresponding items were related to "gross hand function" and "fine hand function". For both factors the internal consistency was high (Cronbachs' alpha: 0.97 - 0.98). Factor analysis on the pain questionnaire resulted in six factors: "pain limitations", "pain severity (not shoulder)", "distal pain", "shoulder pain", "proximal pain frequency (not shoulder)", and "elbow pain frequency". The internal consistency for all factors was high (Cronbachs' alpha: 0.89 - 0.98). Within the stiffness questionnaire three factors were identified: "stiffness frequency", "stiffness limitations", and "stiffness severity", all having a high internal consistency (Cronbachs' alpha: 0.98 - 0.99). The total percentage of explained variance for the factors identified in each questionnaire ranged from 80-88%. All items had large rotated factor loadings and we were able to interpret the commonality in each of the factors. Detailed descriptions of the items and their rotated factor loadings are presented in supplementary table S.5.

Table 2 represents the correlation coefficients between the different factors. Most of the correlations were below 0.80, which indicated that the factors had unique identities. As expected, some of the CUE and ABILHAND-plus factors showed high correlations (R: 0.71 – 0.91).

Table 2. The Pearson correlation between each pair of two factors

	CUE			ABILHAND		PAIN						STIFFNESS		
	Basic hand function	Heavy lifting	Light or no lifting	Gross hand function	Fine hand function	Pain limitations	Pain severity (not shoulder)	Distal pain frequency	Shoulder pain	Proximal pain frequency (not shoulder)	Elbow pain frequency	Stiffness frequency	Stiffness limitations	Stiffness severity
CUE														
Basic hand function	1.00													
Heavy lifting	**0.71**	1.00												
Light or no lifting	**0.81**	**0.88**	1.00											
ABILHAND-plus														
Gross hand function	**0.85**	**0.81**	**0.91**	1.00										
Fine hand function	**0.75**	**0.86**	**0.88**	**0.91**	1.00									
PAIN														
Pain limitations	-0.27	-0.32	-0.34	-0.31	-0.29	1.00								
Pain severity (not shoulder)	-0.18	-0.30	-0.28	-0.25	-0.25	**0.46**	1.00							
Distal pain frequency	-0.21	-0.24	-0.23	-0.19	-0.19	**0.40**	**0.58**	1.00						
Shoulder pain	-0.33	-0.40	-0.38	-0.39	-0.35	**0.44**	**0.70**	**0.60**	1.00					
Proximal pain frequency (not shoulder)	-0.15	-0.24	-0.21	-0.16	-0.17	**0.40**	**0.56**	**0.74**	**0.64**	1.00				
Elbow pain frequency	-0.39	-0.40	**-0.42**	-0.37	-0.36	**0.41**	**0.55**	**0.61**	**0.61**	**0.69**	1.00			
STIFFNESS														
Stiffness frequency	**-0.41**	**-0.42**	**-0.47**	**-0.46**	**-0.40**	**0.47**	0.37	0.33	**0.44**	0.32	0.38	1.00		
Stiffness limitations	**-0.44**	**-0.43**	**-0.50**	**-0.50**	**-0.45**	**0.54**	0.26	0.28	0.34	0.25	0.30	**0.68**	1.00	
Stiffness severity	-0.34	-0.32	-0.38	-0.37	-0.31	**0.57**	0.23	0.23	0.28	0.22	0.24	**0.64**	**0.82**	1.00

Values with a Pearson correlation coefficient above 0.4 are printed in bold.

Construct validity

In table 3, the means and 95% confidence intervals of the factor sum scores for patients in the early ambulatory stage and those in the late non ambulatory stage are presented. We hypothesized that participants in the early ambulatory disease stage would perform significantly better than participants in the late non ambulatory disease stage. All factors confirmed this hypothesis, reflecting a good construct validity.

Table 3. Mean with 95% confidence intervals (CI) of the factor sum scores for patient groups in different disease stages and of the differences between these two groups

	Early ambulatory stage			Late non ambulatory stage			Difference compared to late-non- ambulatory stage		
Factors (min-max)*	N	Mean	[95% CI]	N	Mean	[95% CI]	Mean	[95% CI]	P-value
CUE									
Basic hand function (8-56)	64	51.9	[50.6, 53.3]	94	31.0	[27.8, 34.2]	21.0	[16.9, 25.0]	<0.001
Heavy lifting (10-70)	64	55.1	[52.4, 57.8]	94	14.8	[13.1, 16.4]	40.3	[37.3, 43.4]	<0.001
Light or no lifting (12-84)	64	79.0	[77.3, 80.7]	94	27.4	[24.4, 30.3]	51.7	[47.8, 55.5]	<0.001
ABILHAND-plus									
Gross hand function (16-48)	53	45.2	[44.3, 46.0]	88	24.9	[22.9, 26.9]	20.3	[17.6, 23.0]	<0.001
Fine hand function (10-30)	52	25.8	[24.6, 26.9]	91	12.5	[11.7, 13.4]	13.2	[11.8, 14.6]	<0.001
PAIN									
Pain limitations (0-140)	66	1.1	[0.1, 2.1]	94	20.2	[13.7, 26.8]	-19.1	[-27.1, -11.2]	<0.001
Pain severity (not shoulder) (0-120)	66	2.7	[1.1, 4.3]	94	13.9	[9.4, 18.3]	-11.2	[-16.7, -5.7]	<0.001
Distal pain frequency (0-36)	66	0.6	[0.2, 1.0]	94	3.6	[2.4, 4.8]	-3.0	[-4.4, -1.5]	<0.001
Shoulder pain (0-32)	66	1.0	[0.3, 1.7]	94	5.7	[4.5, 7.0]	-4.7	[-6.3, -3.1]	<0.001
Proximal pain frequency (not shoulder) (0-24)	66	0.7	[0.3, 1.2]	94	2.7	[1.8, 3.6]	-1.9	[-3.1, -0.8]	<0.001
Elbow pain frequency (0-12)	66	0.2	[0.0, 0.3]	94	2.0	[1.5, 2.5]	-1.8	[-2.4, -1.2]	<0.001
STIFFNESS									
Stiffness frequency (0-84)	66	3.4	[1.9, 4.9]	94	23.2	[17.8, 28.7]	-19.8	[-26.5, -13.2]	<0.001
Stiffness limitations (0-140)	66	4.6	[-0.2, 9.4]	94	40.6	[31.3, 50.0]	-36.0	[-48.0, -24.1]	<0.001
Stiffness severity (0-140)	66	9.9	[2.5, 17.2]	94	34.9	[27.0, 42.7]	-25.0	[-36.3, -13.7]	<0.001

* (min-max) = minimal and maximal possible score per factor

Upper Limb Short Questionnaire (ULSQ)

Table 4 gives a proposal for the Upper Limb Short Questionnaire , which can be used for stepwise assessment of upper limb function, pain and stiffness in clinical practice. Based on the factors identified in this study (see table 3), 14 new initial questions were formulated. Depending on the intended use of the Upper Limb Short Questionnaire , a specific set of follow-up questions can be asked. These follow-up questions correspond with the items of the original questionnaires clustering under the same factor.

DISCUSSION

We found 14 different underlying dimensions (factors) in a set of 4 questionnaires regarding UE function, pain and stiffness in boys and men with DMD. Each factor showed good internal consistency and good construct validity, with respect to discriminating patients in the early ambulatory from those in the late non ambulatory disease stage. These results allowed us to propose a short questionnaire for stepwise assessment of UE function, pain and stiffness for clinical use based on the existing questionnaires: the Upper Limb Short Questionnaire.

Table 4. The proposed Upper Limb Short Questionnaire (ULSQ) to assess upper limb function, pain and stiffness in patients with DMD based on the factor communalities that can be used as a stepwise approach in clinical practice.

Factor	Initial questions	Score options*
Heavy lifting	Do you experience problems in your arms when lifting heavy objects (> 5 pounds)?	0: No 1: Yes
Light or no lifting	Do you experience problems in your arms when you reach for or lift light objects such as an empty can?	0: No 1: Yes
Basic hand function	Do you experience problems using your hands for basic functions like manipulating small objects or holding a key?	0: No 1: Yes
Gross hand function	Do you experience problems using your hands when performing daily activities that require gross hand function like washing your hands or eating with a spoon?	0: No 1: Yes
Fine hand function	Do you experience problems using your hands when performing daily activities that require fine hand function like buttoning up your shirt?	0: No 1: Yes
Pain limitations	Do you experience limitations performing daily activities due to pain in your upper limb?	0: No 1: Yes
Pain severity (not shoulder)	How severe is the pain you experience in your upper limb when performing daily activities?	0: No pain 1: Mild or severe pain
Distal pain frequency	How frequently do you have pain in your hands or fingers?	0: Not more than once a month 1: More than once a month
Shoulder pain	Do you experience pain in your shoulder(s)?	0: No 1: Yes
Proximal pain frequency (not shoulder)	How frequently do you experience pain in your upper or lower arm?	0: Not more than once a month 1: More than once a month
Elbow pain frequency	How frequently do you experience pain in your elbows?	0: Not more than once a month 1: More than once a month
Stiffness frequency	How frequently do you experience stiffness in your arms?	0: Not more than once a month 1: More than once a month
Stiffness limitations	Do you experience limitations performing daily activities due to stiffness in your upper limb?	0: No 1: Yes
Stiffness severity	How severe is the stiffness you experience in your upper limb when performing daily activities?	0: No stiffness 1: Mild or severe stiffness

* If the answer to an initial question is 1, no follow-up questions are necessary. Otherwise, follow-up questions should consist of the items that group under the factor corresponding with the initial question (see also appendix A and B).

UE function was originally measured using the CUE and ABILHAND-plus questionnaires. Although the CUE consists of 32 items, one item ("holding an object like a hammer with your hand (left and right)") was erroneously not included in the questionnaire, so that 30 items remained. From the CUE and ABILHAND-plus questionnaires a total of five factors were extracted. Internal consistency of the items within these factors was high, but also the correlation between the factors related to CUE and ABILHAND-plus was high. As a result it might be questioned if these factors can be considered to be independent factors. Additional research is needed to see if all the newly formulated questions in the short questionnaire, which are based on the factors, independently contribute to the insight in arm function.

The factors on UE function as identified in this study appear to be coherent with the clinical representation of DMD patients. It is well known that proximal muscles and extensor groups are affected earlier and more severely than distal muscles and flexor groups in DMD patients [10–12]. When looking at the CUE, we indeed saw that the factor "heavy lifting", which mainly depends on proximal muscle function, was most severely affected, in comparison to "light or no lifting" and "basic hand function", which are more dependent on distal muscle function. In addition, the ABILHAND-

plus factors are roughly in line with the literature. Vandervelde et al. described the difficulty of the ABILHAND items in patients with neuromuscular disorders using a Rasch model, where positive difficulty scores indicate a higher level of item difficulty[6]. It becomes clear that the items that represented "gross hand function" in our study were generally less difficult than those representing "fine hand function". Only two items within the factor "fine hand function" had negative difficulty scores, and also two items within the factor "gross hand function" had a positive difficulty score. As Vandervelde et al.[6] examined patients with neuromuscular disorders, of whom more than 20% were patients with DMD, comparable outcomes are in the line of expectation.

The 42 items about pain resulted in six factors. Internal consistency of the items within each factor was high and the correlation between the factors was moderate, indicating that each factor described a unique aspect of pain. When looking at the different segments that are represented in each factor, it can be seen that for pain limitations and pain severity almost all segments grouped in one factor, whereas for pain frequency segments were divided over four different factors. This might imply that questions regarding pain frequency are more prone to discriminate between the effect of pain in different body segments than questions regarding pain severity or limitations due to pain. When looking at the factors that discriminated between segments we found that the shoulder, elbow, more proximal aspects of the arm and more distal aspects of the arm loaded on separate factors. Pain was most frequently present in the shoulder, followed by the elbow, proximal aspects of the arm (upper and lower arm) and distal aspects of the arm (wrist, fingers, and thumb). This is generally in line with literature, as Engel et al.[13] and Tiffereau et al.[14] reported that pain was more frequent in the shoulder compared to other parts of the UE, while Pangalila et al.[15] reported equal occurrence of pain in the shoulder and arm.

Factor analysis on the stiffness questionnaire resulted in three unique factors. In contrast with pain, stiffness complaints in the different body segments all grouped together in one factor. However, frequency, severity and limitations due to stiffness represented different dimensions, which implies that it is important to ask for all these aspects of stiffness. Therefore, three questions regarding stiffness were formulated in the short questionnaire.

The factors found in this study explained more than 80% of the variance of the original questionnaires. In addition, the factors could be interpreted well, as the rotated factor loadings were moderate to high and showed clear commonalities between the items within the factors. Moreover, the construct validity of the factors was good, as all factors showed that participants in the early ambulatory stage scored significantly better than participants in the late non ambulatory stage. For the above-mentioned reasons, we believe that the applied factor analysis is a valid tool to formulate a short questionnaire for the stepwise assessment of UE function, pain and stiffness in DMD patients.

We believe that the Upper Limb Short Questionnaire is suitable to be further developed into an outcome measure for research purposes as well as into a tool for clinical assessment of UE function, pain and stiffness. Based on the intended use, the administration and scoring of the Upper Limb Short Questionnaire differs. When used as an outcome measure in research, we propose to assess each of the 14 Upper Limb Short Questionnaire items, without follow-up questions, scoring either 0 (no restrictions) or 1 (restrictions), yielding a minimal sum score of 0 (no UE limitations, pain or stiffness) and a maximal score of 14 (severe UE function limitations, pain and stiffness). However, before the Upper Limb Short Questionnaire can be used as an outcome measure, it should be further tested. Future studies should particularly investigate its discriminative capacity in patients with different disease stages as well as its internal consistency, item hierarchy and test-retest reliability. When the Upper Limb Short Questionnaire is used for clinical assessment of UE function, pain and stiffness, a similar sum score (0-14) can be used, but the follow-up questions related to the initial questions can additionally be used to gain detailed insight in the specific problems experienced by an individual patient and to tailor clinical management.

A limitation of this study is that the results are based on subjective answers, as no clinical tests were performed to verify UE function, pain or stiffness levels of the respondents. In addition, the use of a questionnaire could lead to interpretation errors, as no researcher could be contacted in the case of uncertainties experienced by respondents. Therefore the results of this study should be interpreted with care.

The results of this study only apply to patients with DMD and cannot be translated to other populations. The method used in this study, however, is applicable in other populations, but could result in different factors. Marino et al. 1998[5], for example, performed exploratory factor analysis on the CUE in patients with tetraplegia and found four subscales that were only partly in line with our research. Nevertheless, we think that the factors and short questionnaire as formulated in this study could be similar for patients with a similar clinical representation, such as patients with other neuromuscular disorders characterized by proximal muscular weakness. The Upper Limb Short Questionnaire can be used as an identifier of arm-hand limitations and the start of more thorough clinical investigation.

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SUPPLEMENTARY MATERIAL

Supplementary Table S.1. ABILHAND-plus questionnaire

Describe for the following activities how well you have been able to implement these in the past 3 months, WITHOUT support of other people or assistive devices.		
Item Number	**Full description**	**Score**
1	Taking the cap off a bottle	1-4
2	Cutting my nails	1-4
3	Buttoning up a shirt	1-4
4	Fastening the zipper of a jacket	1-4
5	Turning a key in a keyhole	1-4
6	Fastening a snap e.g. from jacket or bag	1-4
7	Opening a pack of chips	1-4
8	Opening a pack of biscuits	1-4
9	Inserting a key in keyhole	1-4
10	Turning off a tap	1-4
11	Turning on a tap	1-4
12	Filling a glass with water	1-4
13	Sharpening a pencil	1-4
14	Opening a lunch box	1-4
15	Squeezing toothpaste onto a toothbrush	1-4
16	Spreading butter on a slice of bread	1-4
17	Opening a toothpaste tube	1-4
18	Counting banknotes	1-4
19	Dealing cards	1-4
20	Unwrapping a chocolate bar	1-4
21	Drying my hands	1-4
22	Washing my hands	1-4
23	Eat with a spoon	1-4
24	Use fork and knife	1-4
25	Drink a glass of water without straw	1-4
26	Use keyboard of computer	1-4

ABILHAND-plus questionnaire[6]. Score 1-4: 1 = impossible, 2 = difficult, 3 = easy, 4 = I don' t know.

Supplementary Table S.2. Capabilities of upper extremity questionnaire (CUE)

Item number	Full question	Short name*	Score
1a	Think about reaching out with your arm to touch something directly in front of you that is at shoulder level. How limited are you doing this using your right arm	Reach forward - Preferred	1-7
1b	Think about reaching out with your arm to touch something directly in front of you that is at shoulder level. How limited are you doing this using your left arm	Reach forward - Non Preferred	1-7
2a	Think about raising your arm directly over your head, with your arm straight. How limited are you doing this using your right arm	Reach upward - Preferred	1-7
2b	Think about raising your arm directly over your head, with your arm straight. How limited are you doing this using your left arm	Reach upward - Non Preferred	1-7
3a	Think about reaching down to touch the floor and sitting back up straight, without hooking with your other arm or using it to pull yourself up. How limited are you doing this using your right arm?	Reach downward - Preferred	1-7
3b	Think about reaching down to touch the floor and sitting back up straight, without hooking with your other arm or using it to pull yourself up. How limited are you doing this using your left arm?	Reach downward - Non Preferred	1-7
4	Think about raising a 5-pound object like a heavy blanket over your head using both arms. (Don' t worry about whether you could grab it with your hands, just if you could raise something that heavy over your head.). How limited are you doing this using both arms?	Lift heavy object - Both	1-7
5a	Think about pulling or sliding (without grasping) a light object such as a can of soda, that is on a table, towards you. How limited are you doing this using your right arm?	Pull light object - Preferred	1-7
5b	Think about pulling or sliding (without grasping) a light object such as a can of soda, that is on a table, towards you. How limited are you doing this using your left arm?	Pull light object - Non Preferred	1-7
6a	Think about pulling or sliding (without grasping) a heavy object (up to 10 pounds), that is on a table, towards you. How limited are you doing this using your right arm?	Pull heavy object - Preferred	1-7
6b	Think about pulling or sliding (without grasping) a heavy object (up to 10 pounds), that is on a table, towards you. How limited are you doing this using your left arm?	Pull heavy object - Non Preferred	1-7
7a	Think about pushing a light object such as a can of soda on a table, away from you. How limited are you doing this using your right arm?	Push light object - Preferred	1-7
7b	Think about pushing a light object such as a can of soda on a table, away from you. How limited are you doing this using your left arm?	Push light object - Non Preferred	1-7
8a	Think about pushing a heavy object (up to 10 pounds) on a table, away from you. How limited are you doing this using your right arm?	Push heavy object - Preferred	1-7
8b	Think about pushing a heavy object (up to 10 pounds) on a table, away from you. How limited are you doing this using your left arm?	Push heavy object - Non Preferred	1-7
9	Think about pushing down with both arms into your chair enough to lift your buttocks (both sides) off the seat (do a push-up weight shift). How limited are you doing this?	Push yourself up - Both	1-7
10a	With your hand on your lap palm down, think about curling your wrist upwards, keeping your arm on your lap. How limited are you doing this using your right arm?	Wrist curl - Preferred	1-7
10b	With your hand on your lap palm down, think about curling your wrist upwards, keeping your arm on your lap. How limited are you doing this using your left arm?	Wrist curl - Non Preferred	1-7

Item number	Full question	Short name*	Score
11a	Think about turning your hand over, keeping your elbow bent at your side (like turning a doorknob or a dial). How limited are you doing this using your right arm?	Supination - Preferred	1-7
11b	Think about turning your hand over, keeping your elbow bent at your side (like turning a doorknob or a dial). How limited are you doing this using your left arm?	Supination - Non Preferred	1-7
12a	Think about grasping and holding an object like a hammer with your hand. How limited are you doing this kind of thing using your right hand?	Grasp and hold – Preferred	1-7
12b	Think about grasping and holding an object like a hammer with your hand. How limited are you doing this kind of thing using your left hand?	Grasp and hold – Non Preferred	1-7
13a	Think about picking up a small object such as a paper clip or the cap of a tube of toothpaste with the tips of your thumb and first two fingers. How limited are you doing this using your right arm?	Small object 3 fingers - Preferred	1-7
13b	Think about picking up a small object such as a paper clip or the cap of a tube of toothpaste with the tips of your thumb and first two fingers. How limited are you doing this using your left arm?	Small object 3 fingers - Non Preferred	1-7
14a	Think about pinching and holding an object between your thumb and the side of your index finger, such as holding a key. How limited are you doing this using your right arm?	Key grip - Preferred	1-7
14b	Think about pinching and holding an object between your thumb and the side of your index finger, such as holding a key. How limited are you doing this using your left arm?	Key grip - Non Preferred	1-7
15a	Think about grasping a large object like the lid of a 2 pound jar of mayonnaise with the tips of the fingers hard enough to pick the jar up or open the lid. How limited are you doing this using your right arm?	Wide grip - Preferred	1-7
15b	Think about grasping a large object like the lid of a 2 pound jar of mayonnaise with the tips of the fingers hard enough to pick the jar up or open the lid. How limited are you doing this using your left arm?	Wide grip - Non Preferred	1-7
16a	Think about using your fingers to manipulate objects, such as holding a coin and turning it over and over with your fingers. How limited are you doing this using your right arm?	Manipulate - Preferred	1-7
16b	Think about using your fingers to manipulate objects, such as holding a coin and turning it over and over with your fingers. How limited are you doing this using your left arm?	Manipulate - Non Preferred	1-7
17a	Think about pressing something with the tip of your index finger (not knuckle) such as dialing a touch-tone phone or ringing a doorbell. How limited are you doing this using your right arm?	Push button - Preferred	1-7
17b	Think about pressing something with the tip of your index finger (not knuckle) such as dialing a touch-tone phone or ringing a doorbell. How limited are you doing this using your left arm?	Push button - Non Preferred	1-7

Capabilities of upper extremity questionnaire[5]. * Item performed with the left and right hand were converted to the preferred and non-preferred hand based on the hand preference subjects indicated. 1-7: 1 = totally limited, 2 = extremely limited, 3 = very limited, 4 = moderately limited, 5 = some limitation, 6 = a little limited, 7 = not at all limited.

Supplementary Table S.3. Pain questionnaire

Item Number	Full description	Short description*	Score
1	How often do you have pain in your right shoulder?	Pain freq preferred shoulder	0-6
2	How often do you have pain in your right upper arm?	Pain freq preferred upper arm	0-6
3	How often do you have pain in your right elbow?	Pain freq preferred elbow	0-6
4	How often do you have pain in your right forearm?	Pain freq preferred forearm	0-6
5	How often do you have pain in your right wrist?	Pain freq preferred wrist	0-6
6	How often do you have pain in your right thumb?	Pain freq preferred thumb	0-6
7	How often do you have pain in the fingers of your right hand?	Pain freq preferred fingers	0-6
8	How often do you have pain in your left shoulder?	Pain freq non-preferred shoulder	0-6
9	How often do you have pain in your left upper arm?	Pain freq non-preferred upper arm	0-6
10	How often do you have pain in your left elbow?	Pain freq non-preferred elbow	0-6
11	How often do you have pain in your left forearm?	Pain freq non-preferred forearm	0-6
12	How often do you have pain in your left wrist?	Pain freq non-preferred wrist	0-6
13	How often do you have pain in your left thumb?	Pain freq non-preferred thumb	0-6
14	How often do you have pain in the fingers of your left hand?	Pain freq non-preferred fingers	0-6
15	How severe is the pain in your right shoulder?	Pain sev preferred shoulder	0-10 †
16	How severe is the pain in your right upper arm?	Pain sev preferred upper arm	0-10 †
17	How severe is the pain in your right elbow?	Pain sev preferred elbow	0-10 †
18	How severe is the pain in your right forearm?	Pain sev preferred forearm	0-10 †
19	How severe is the pain in your right wrist?	Pain sev preferred wrist	0-10 †
20	How severe is the pain in your right thumb?	Pain sev preferred thumb	0-10 †
21	How severe is the pain in the fingers of your right hand?	Pain sev preferred fingers	0-10 †
22	How severe is the pain in your left shoulder?	Pain sev non-preferred shoulder	0-10 †
23	How severe is the pain in your left upper arm?	Pain sev non-preferred upper arm	0-10 †
24	How severe is the pain in your left elbow?	Pain sev non-preferred elbow	0-10 †
25	How severe is the pain in your left forearm?	Pain sev non-preferred forearm	0-10 †
26	How severe is the pain in your left wrist?	Pain sev non-preferred wrist	0-10 †
27	How severe is the pain in your left thumb?	Pain sev non-preferred thumb	0-10 †
28	How severe is the pain in the fingers of your left hand?	Pain sev non-preferred fingers	0-10 †
29	How limited are you due to the pain in your right shoulder?	Pain lim preferred shoulder	0-10 ‡
30	How limited are you due to the pain in your right upper arm?	Pain lim preferred upper arm	0-10 ‡
31	How limited are you due to the pain in your right elbow?	Pain lim preferred elbow	0-10 ‡
32	How limited are you due to the pain in your right forearm?	Pain lim preferred forearm	0-10 ‡
33	How limited are you due to the pain in your right wrist?	Pain lim preferred wrist	0-10 ‡
34	How limited are you due to the pain in your right thumb?	Pain lim preferred thumb	0-10 ‡
35	How limited are you due to the pain in the fingers of your right hand?	Pain lim preferred fingers	0-10 ‡
36	How limited are you due to the pain in your left shoulder?	Pain lim non-preferred shoulder	0-10 ‡
37	How limited are you due to the pain in your left upper arm?	Pain lim non-preferred upper arm	0-10 ‡
38	How limited are you due to the pain in your left elbow?	Pain lim non-preferred elbow	0-10 ‡
39	How limited are you due to the pain in your left forearm?	Pain lim non-preferred forearm	0-10 ‡
40	How limited are you due to the pain in your left wrist?	Pain lim non-preferred wrist	0-10 ‡
41	How limited are you due to the pain in your left thumb?	Pain lim non-preferred thumb	0-10 ‡
42	How limited are you due to the pain in the fingers of your left hand?	Pain lim non-preferred fingers	0-10 ‡

Pain questionnaire adapted from the University of Michigan Upper Extremity Questionnaire[8]. * Item performed with the left and right hand were converted to the preferred and non preferred hand based on the hand preference subjects indicated. 0-6: 0 = never, 1 = few times a year, 2 = few times a month, 3 = few times a week, 4 = almost every day, 5= Daily for a significant part of the day, 6 = always. †: 0 = No pain, 10 = Worst pain imaginable. ‡: 0 = No limitations, 10 = Fully limited.

Supplementary Table S.4. Stiffness questionnaire

Item Number	Full description	Short description*	Score
1	How often do you experience stiffness in your right shoulder?	Stiffness freq preferred shoulder	0-6
2	How often do you experience stiffness in your right upper arm?	Stiffness freq preferred upper arm	0-6
3	How often do you experience stiffness in your right elbow?	Stiffness freq preferred elbow	0-6
4	How often do you experience stiffness in your right forearm?	Stiffness freq preferred forearm	0-6
5	How often do you experience stiffness in your right wrist?	Stiffness freq preferred wrist	0-6
6	How often do you experience stiffness in your right thumb?	Stiffness freq preferred thumb	0-6
7	How often do you experience stiffness in the fingers of your right hand?	Stiffness freq preferred fingers	0-6
8	How often do you experience stiffness in your left shoulder?	Stiffness freq non-preferred shoulder	0-6
9	How often do you experience stiffness in your left upper arm?	Stiffness freq non-preferred upper arm	0-6
10	How often do you experience stiffness in your left elbow?	Stiffness freq non-preferred elbow	0-6
11	How often do you experience stiffness in your left forearm?	Stiffness freq non-preferred forearm	0-6
12	How often do you experience stiffness in your left wrist?	Stiffness freq non-preferred wrist	0-6
13	How often do you experience stiffness in your left thumb?	Stiffness freq non-preferred thumb	0-6
14	How often do you experience stiffness in the fingers of your left hand?	Stiffness freq non-preferred fingers	0-6
15	How severe is the stiffness in your right shoulder?	Stiffness sev preferred shoulder	0-10 †
16	How severe is the stiffness in your right upper arm?	Stiffness sev preferred upper arm	0-10 †
17	How severe is the stiffness in your right elbow?	Stiffness sev preferred elbow	0-10 †
18	How severe is the stiffness in your right forearm?	Stiffness sev preferred forearm	0-10 †
19	How severe is the stiffness in your right wrist?	Stiffness sev preferred wrist	0-10 †
20	How severe is the stiffness in your right thumb?	Stiffness sev preferred thumb	0-10 †
21	How severe is the stiffness in the fingers of your right hand?	Stiffness sev preferred fingers	0-10 †
22	How severe is the stiffness in your left shoulder?	Stiffness sev non-preferred shoulder	0-10 †
23	How severe is the stiffness in your left upper arm?	Stiffness sev non-preferred upper arm	0-10 †
24	How severe is the stiffness in your left elbow?	Stiffness sev non-preferred elbow	0-10 †
25	How severe is the stiffness in your left forearm?	Stiffness sev non-preferred forearm	0-10 †
26	How severe is the stiffness in your left wrist?	Stiffness sev non-preferred wrist	0-10 †
27	How severe is the stiffness in your left thumb?	Stiffness sev non-preferred thumb	0-10 †
28	How severe is the stiffness in the fingers of your left hand?	Stiffness sev non-preferred fingers	0-10 †
29	How limited are you due to the stiffness in your right shoulder?	Stiffness lim preferred shoulder	0-10 ‡
30	How limited are you due to the stiffness in your right upper arm?	Stiffness lim preferred upper arm	0-10 ‡
31	How limited are you due to the stiffness in your right elbow?	Stiffness lim preferred elbow	0-10 ‡
32	How limited are you due to the stiffness in your right forearm?	Stiffness lim preferred forearm	0-10 ‡
33	How limited are you due to the stiffness in your right wrist?	Stiffness lim preferred wrist	0-10 ‡
34	How limited are you due to the stiffness in your right thumb?	Stiffness lim preferred thumb	0-10 ‡
35	How limited are you due to the stiffness in the fingers of your right hand?	Stiffness lim preferred fingers	0-10 ‡
36	How limited are you due to the stiffness in your left shoulder?	Stiffness lim non-preferred shoulder	0-10 ‡
37	How limited are you due to the stiffness in your left upper arm?	Stiffness lim non-preferred upper arm	0-10 ‡
38	How limited are you due to the stiffness in your left elbow?	Stiffness lim non-preferred elbow	0-10 ‡
39	How limited are you due to the stiffness in your left forearm?	Stiffness lim non-preferred forearm	0-10 ‡
40	How limited are you due to the stiffness in your left wrist?	Stiffness lim non-preferred wrist	0-10 ‡
41	How limited are you due to the stiffness in your left thumb?	Stiffness lim non-preferred thumb	0-10 ‡
42	How limited are you due to the stiffness in the fingers of your left hand?	Stiffness lim non-preferred fingers	0-10 ‡

Stiffness questionnaire adapted from the University of Michigan Upper Extremity Questionnaire[8]. * Item performed with the left and right hand were converted to the preferred and non preferred hand based on the hand preference subjects indicated. 0-6: 0 = never, 1 = few times a year, 2 = few times a month, 3 = few times a week, 4 = almost every day, 5= Daily for a significant part of the day, 6 = always. †: 0 = No stiffness, 10 = Worst stiffness imaginable. ‡: 0 = No limitations, 10 = Fully limited.

Table B.1 Factors with the (suggested) label and the corresponding items with rotated factor loadings.

	Factor 1		Factor 2		Factor 3		Factor 4		Factor 5		Factor 6	
	Item	RFL	Item	RFL	Item	RFL	Item	RFL	Item	RFL	Item	RFL
CUE	**Basic hand function**		**Heavy lifting**		**Light or no lifting**							
	Key grip - Preferred	0.85	Pull heavy object - Non Preferred	0.84	Reach upward - Preferred	0.74						
	Key grip - Non Preferred	0.85	Pull heavy object - Preferred	0.84	Reach upward - Non Preferred	0.73						
	Small object 3 fingers - Non Preferred	0.85	Push heavy object - Preferred	0.83	Reach forward - Preferred	0.72						
	Small object 3 fingers - Preferred	0.84	Lift heavy object - Both	0.82	Reach forward - Non Preferred	0.72						
	Manipulate - Preferred	0.83	Push yourself up - Both	0.77	Pull light object - Preferred	0.69						
	Manipulate - Non Preferred	0.83	Push heavy object - Non Preferred	0.74	Pull light object - Non Preferred	0.68						
	Push button - Non Preferred	0.81	Reach downward - Non Preferred	0.68	Push light object - Non Preferred	0.64						
	Push button - Preferred	0.80	Reach downward - Preferred	0.67	Push light object - Preferred	0.64						
			Wide grip - Preferred	0.64	Wrist curl - Non Preferred	0.60						
			Wide grip - Non Preferred	0.63	Wrist curl - Preferred	0.59						
					Supination - Non Preferred	0.59						
					Supination – Preferred	0.57						
ABILHAND-plus	**Gross hand function**		**Fine hand function**									
	Use keyboard of computer	0,87	Cutting my nails	0,83								
	Washing my hands	0,83	Buttoning up a shirt	0,80								
	Eat with a spoon	0,83	Turning a key in a keyhole	0,79								
	Drying my hands	0,82	Fastening the zipper of a jacket	0,79								
	Counting banknotes	0,80	Fastening a snap e.g. from jacket or bag	0,78								
	Unwrapping a chocolate bar	0,79										
	Dealing cards	0,77	Taking the cap off a bottle	0,75								
	Drink a glass of water without straw	0,73	Filling a glass with water	0,74								
	Turning on a tap	0,71	Inserting a key in keyhole	0,72								
	Turning off a tap	0,71	Spreading butter on a slice of bread	0,66								
	Use fork and knife	0,71	Opening a pack of chips	0,63								
	Squeezing toothpaste onto a toothbrush	0,70										
	Sharpening a pencil	0,69										
	Opening a lunch box	0,67										
	Opening a toothpaste tube	0,66										
	Opening a pack of biscuits	0,61										
PAIN	**Pain limitations**		**Pain severity (not shoulder)**		**Distal pain frequency**		**Shoulder pain**		**Proximal pain frequency (not shoulder)**		**Elbow pain frequency**	
	Pain lim preferred elbow	0.90	Pain sev non-preferred thumb	0.88	Pain freq preferred thumb	0.81	Pain freq non-preferred shoulder	0.77			Pain freq preferred elbow	0.79
	Pain lim preferred wrist	0.89	Pain sev preferred thumb	0.83	Pain freq non-preferred thumb	0.80	Pain sev non-preferred shoulder	0.74			Pain freq non-preferred elbow	0.66
	Pain lim preferred forearm	0.89	Pain sev preferred forearm	0.82	Pain freq preferred fingers	0.79	Pain freq preferred shoulder	0.74	Pain freq preferred forearm	0.68		
	Pain lim non-preferred thumb	0.89	Pain sev non-preferred fingers	0.82	Pain freq non-preferred fingers	0.79	Pain sev preferred shoulder	0.63	Pain freq non-preferred forearm	0.68		
	Pain lim non-preferred elbow	0.89	Pain sev non-preferred wrist	0.82	Pain freq non-preferred wrist	0.72			Pain freq preferred upper arm	0.61		
	Pain lim non-preferred forearm	0.87	Pain sev non-preferred forearm	0.81	Pain freq preferred wrist	0.65			Pain freq non-preferred upper arm	0.60		
	Pain lim preferred upper arm	0.86	Pain sev preferred wrist	0.81								
	Pain lim non-preferred wrist	0.86	Pain sev preferred fingers	0.75								
	Pain lim non-preferred upper arm	0.85	Pain sev non-preferred upper arm	0.75								
	Pain lim preferred thumb	0.85	Pain sev preferred upper arm	0.72								
	Pain lim non-preferred fingers	0.85	Pain sev non-preferred elbow	0.69								
	Pain lim preferred shoulder	0.83	Pain sev preferred elbow	0.67								
	Pain lim preferred fingers	0.82										
	Pain lim non-preferred shoulder	0.82										
STIFFNESS	**Stiffness frequency**		**Stiffness limitations**		**Stiffness severity**							
	Stiffness freq non-preferred thumb	0,85	Stiffness lim non-preferred thumb	0,81	Stiffness sev non-preferred upper arm	0,84						
	Stiffness freq non-preferred forearm	0,82	Stiffness lim non-preferred forearm	0,79								
	Stiffness freq non-preferred wrist	0,82	Stiffness lim non-preferred wrist	0,79	Stiffness sev preferred upper arm	0,82						

Stiffness freq preferred thumb	0,82	Stiffness lim non-preferred elbow	0,78	Stiffness sev non-preferred shoulder	0,80
Stiffness freq non-preferred fingers	0,82	Stiffness lim preferred thumb	0,78		
Stiffness freq preferred wrist	0,81	Stiffness lim preferred forearm	0,78	Stiffness sev preferred forearm	0,79
Stiffness freq preferred upper arm	0,81	Stiffness lim preferred upper arm	0,77	Stiffness sev preferred shoulder	0,79
Stiffness freq non-preferred upper arm	0,80	Stiffness lim preferred elbow	0,77	Stiffness sev non-preferred forearm	0,78
		Stiffness lim non-preferred upper arm	0,76		
Stiffness freq preferred fingers	0,80			Stiffness sev non-preferred wrist	0,74
Stiffness freq preferred forearm	0,79	Stiffness lim preferred wrist	0,75	Stiffness sev non-preferred elbow	0,72
Stiffness freq non-preferred shoulder	0,76	Stiffness lim preferred shoulder	0,75	Stiffness sev preferred wrist	0,72
Stiffness freq preferred shoulder	0,75	Stiffness lim non-preferred fingers	0,75	Stiffness sev non-preferred thumb	0,71
Stiffness freq non-preferred elbow	0,74	Stiffness lim non-preferred shoulder	0,74	Stiffness sev preferred elbow	0,70
Stiffness freq preferred elbow	0,74	Stiffness lim preferred fingers	0,69	Stiffness sev preferred thumb	0,69
				Stiffness sev preferred fingers	0,63
				Stiffness sev non-preferred fingers	0,61

RFL = rotated factor loading. The item short names used in this table are fully explained in tables A.1-A.4.

CHAPTER 4

VARIABLES ASSOCIATED WITH UPPER EXTREMITY FUNCTION IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

Published as: Janssen MM, Hendriks JC, Geurts AC, de Groot IJ. Variables associated with upper extremity function in patients with Duchenne muscular dystrophy. J Neurol. 2016;263(9):1810-8.

Abbreviations:

CUE	Capabilities of Upper Extremity questionnaire
DMD	Duchenne Muscular Dystrophy
UE	Upper Extremity

ABSTRACT

INTRODUCTION Preserving upper extremity (UE) function in patients with Duchenne Muscular Dystrophy (DMD) is extremely important as it is related to independence and quality of life. For clinical decision making, knowledge of variables associated with UE function is necessary. This knowledge is, however, limited. Therefore, this study aims to gain more insight into the variables associated with UE function in DMD.

METHODS Data from an international web-based questionnaire on UE function, obtained from 213 DMD patients, were used. Six dependent variables regarding UE function were used in multivariable linear regression analyses. In addition, 26 independent variables regarding patient characteristics, medication, therapy, supportive aids, pain, stiffness and participation were used.

RESULTS Twelve independent variables showed a significant relation to UE function. Variables with a negative relation to UE function were: later disease stage, occurrence of scoliosis, higher age, use of UE splints, more frequent stiffness complaints, more limitations due to stiffness, more frequent elbow pain, and having physical therapy. A positive relation with UE function was seen for going to school or work, use of corticosteroids, higher BMI, and higher age at diagnosis. These variables explained 56-81% of the variation of the different measures of UE function.

DISCUSSION Knowledge of variables associated with UE function is very important in the clinical management of DMD patients. The results of this study suggest that corticosteroid use and participation in school and work related activities are positively related to UE function in DMD patients, as well as reducing pain and stiffness and preventing scoliosis.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is one of the most common neuromuscular disorders. DMD is an X-linked recessive disorder affecting about 1:5000 live born males[24]. The disease is characterized by progressive muscle weakening leading to functional disabilities. In an early stage boys with DMD have difficulties with walking, running and climbing stairs. Around the age of 12 they become wheelchair confined and from that age on, upper extremity (UE) function also starts to deteriorate[14, 23]. The loss of UE function leads to severe problems in the performance of daily activities and participation in society[14], ultimately affecting independence and quality of life[25].

Until now no cure has been found for DMD, however, life expectancy has rapidly increased over the last few decades. Currently life expectancy is about 30-40 years[8, 18, 19], which means that DMD patients are in a wheelchair for the largest part of their lives and that they are fully dependent on the use of their arms during this life span. As limitations in UE function have a huge impact on the lives of DMD patients, preservation of UE function is very important. To this end, effective interventions are necessary and variables associated with UE function should be taken into consideration when making clinical decisions. Our knowledge of effective interventions and variables associated with UE function is, however, limited.

Several studies have indicated that treatment with corticosteroids has beneficial effects on the preservation of UE function in DMD patients[1, 6, 12]. In addition, Wagner et al. 2007 recommended daily stretching exercises, particularly of the distal upper extremities, in these patients[32]. However, scientific evidence for the effects of UE stretching exercises in DMD is lacking. Furthermore, evidence for the effects of physical therapy and occupational therapy on the preservation of UE function is limited. Yet, there is preliminary evidence for the efficacy of stretching and the use of splints for the lower extremities [4, 28].

To our knowledge there are no observational studies that have investigated variables associated with UE function in DMD, such as 'participant characteristics', 'pain', 'stiffness' and 'participation'. However, this information could play an important role in clinical decision making with regard to the preservation (or perhaps even improvement) of UE function. Therefore, this study aimed to gain more insight into the variables associated with UE function in DMD using multivariable linear regression analysis of data obtained through a large international web-based survey[14].

METHODS

Participant characteristics

This study was part of a larger study in which 344 participants from 14 different countries responded to a web-based questionnaire[14]. We excluded respondents

that did not agree with the clinical Duchenne phenotype, based on the diagnostic criteria of Emery et. al. [9]. Participants were also excluded if the diagnosis was made after the age of 10 years, or when participants who did not use corticosteroids and who were 14 years or older, were not wheelchair confined [9]. In total 213 participants were included in this study. Participants were on average 13 years (range: 1-35 years) and 55 percent of the participants were wheelchair confined (median age: 10 years). Corticosteroid use was reported by 55% of the respondents, while 11% had stopped using corticosteroids and 34% had never used steroids. In addition, 49% of the participants had a mild or severe scoliosis. A detailed description of the participants characteristics has been reported in a previous study[14]. This study was approved by the medical-ethical committee in the Arnhem-Nijmegen region (the Netherlands) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The web-based questionnaire

The web-based questionnaire consisted of 224 items in total. Some items were extracted from existing questionnaires such as the Capabilities of Upper Extremity questionnaire (CUE)[21], the ABILHAND questionnaire[31] (including few additional questions), and questions concerning pain and stiffness that were modified from the University of Michigan Upper Extremity Questionnaire[27]. Besides these existing questionnaires, questions regarding 'patient characteristics, 'medication', 'therapy', 'supportive aids' and 'participation' were added to the web-based questionnaire.

For this study we used a subset of items from the total questionnaire (table 1). To find the underlying dimensions and reduce the number of items for regression analysis, exploratory factor analysis was performed on the subcategories 'pain', 'stiffness', and 'upper extremity function' [15]. Dependent variables were the Brooke scale and the factor sum scores of the CUE and ABILHAND. Factor analysis of the CUE resulted in 3 factors: 'basic hand function', 'heavy lifting' and 'light or no lifting'. 'Basic hand function' contains items regarding grasping and manipulating objects with the fingers. 'Heavy lifting' contains items regarding lifting and moving heavy objects and lifting one's own body weight, whereas 'light or no lifting' contains items that require arm movements with no or minimal additional weight, such as reaching for objects or sliding light objects over a tabletop. Factor analysis of the ABILHAND resulted in 2 factors: 'gross hand function' and 'fine hand function'. 'Gross hand function' contains items such as 'washing and drying one's hands', 'turning on and off a tap', and 'opening a lunchbox', whereas the factor 'fine hand function' contains items such as 'buttoning up a shirt', 'cutting nails' and 'inserting a key in a keyhole'. For the independent variables, factor analysis was performed on the pain and stiffness questions. Factor analysis performed on the pain questions resulted in 6 factors: 'pain limitations', 'pain severity (not shoulder)', 'distal pain frequency', 'shoulder pain', 'proximal pain frequency (not shoulder)' and 'elbow pain frequency'. Factor analysis performed on the stiffness questions resulted in 3 factors: 'stiffness frequency', 'stiffness limitations' and 'stiffness severity'. All descriptions were chosen

based on the communalities of the items within one factor. Ultimately, we used the sum scores of the items within each factor for further analysis[15]. In total 32 variables were included in this study.

Table 1. Overview of variables

Category	Variable	Description
Outcome measures (dependent variables)		
Upper extremity function	Brooke	Brooke scale [2]
	Basic hand function	Sum scores of the items regarding basic hand function from the capabilities of upper extremity questionnaire (CUE) [21]*
	Heavy lifting	Sum scores of the items regarding heavy lifting from the CUE*
	Light or no lifting	Sum scores of the items regarding light or no lifting from the CUE*
	Gross hand function	Sum scores of the items regarding gross hand function from the Abilhand questionnaire[31] *
	Fine hand function	Sum scores of the items regarding fine hand function from the Abilhand questionnaire*
Possible variables associated with UE function (independent variables)		
Patient characteristics	Age	Age when participant responded to questionnaire
	Disease stage	Stage of the disease according the criteria of Bushby et al. [3]
	BMI	Body Mass Index
	Age at diagnosis	Age when the diagnosis Duchenne was established
	Injuries	Occurrence of severe injuries (e.g. bone fracture) in the arms
	Scoliosis	Occurrence of spinal deformities (e.g. scoliosis)
Medication	Corticosteroids	Use of corticosteroids
	Homeopathic remedies	Use of homeopathic remedies
Therapy	Physical therapy	Participants that receive physical therapy
	Practice at home	Participants that practice at home
	Hydro therapy	Participants that receive hydro therapy
	Occupational therapy	Participants that receive occupational therapy
Supportive aids	Splints	Use of arm/hand splints
	Arm supports	Use of arm supports
Participation	School/Work	Participants that go to school or work
	Sport	Participants that participate in sports
	Hobby	Participants that practice a hobby
Pain	Pain limitations	Sum scores of the items regarding functional limitations due to pain in the arms and/or hands*
	Pain severity (not shoulder)	Sum scores of the items regarding pain severity in the arms and/or hands (except for the shoulder segment) *
	Distal pain frequency	Sum scores of the items regarding pain frequency in the wrist, fingers and thumb*
	Shoulder pain	Sum scores of the items regarding shoulder pain frequency and severity*
	Proximal pain frequency (not shoulder)	Sum scores of the items regarding pain frequency in the lower arm and upper arm*
	Elbow pain frequency	Sum scores of the items regarding pain frequency in the elbow*
Stiffness	Stiffness frequency	Sum scores of the items regarding stiffness frequency in the arms and/or hands*
	Stiffness limitations	Sum scores of the items regarding functional limitations due to stiffness in the arms and/or hands*
	Stiffness severity	Sum scores of the items regarding stiffness severity in the arms and/or hands*

* The sum scores resulted from an exploratory factor analysis that was performed on the Capabilities of upper extremity questionnaire[21], the Abilhand questionnaire[31] and pain and stiffness questionnaires adapted from the University of Michigan Upper Extremity Questionnaire[27]. The complete overview of the exploratory factor analysis is described in a different study[15].

Data analysis

Median values and ranges were used to describe the continuous variables. Valid percentages were used to describe categorical variables. Univariable regression analysis and stepwise multivariable linear regression analysis were performed to identify variables associated with the measures of UE function (dependent variables). Independent variables consisted of items from the sub categories 'patient characteristics', 'medication', 'therapy', 'supportive aids', 'participation', 'pain' and 'stiffness' (table 1). Data were analyzed using IBM SPSS Statistics version 20 for Windows (IBM, Somers, NY, USA).

RESULTS

Participant characteristics

In total, 213 participants were included in this study, of which 198 participants filled in the complete questionnaire and 15 participants filled in only a part of the questionnaire, as they ended the questionnaire prematurely. Table 2 describes the outcome measures that relate to UE function. Table 3 describes the possible associated variables in the subcategories: 'patient characteristics', 'medication', 'therapy', 'supportive aids', 'participation', 'pain' and 'stiffness'.

Table 2. Descriptives of outcome measures

Outcome measure (min-max possible score)	N	Median (min-max)	Category	N (Valid %)
Brooke	213		Brooke 1	7 (33.8)
			Brooke 2	43 (20.2)
			Brooke 3	17 (8.0)
			Brooke 4	14 (6.6)
			Brooke 5	40 (18.8)
			Brooke 6	27 (12.7)
Basic hand function (8-56)	210	48 (8-56)		
Heavy lifting (10-70)	210	31 (10-70)		
Light or no lifting (12-84)	210	57 (12-84)		
Gross hand function (15-45)	189	42 (16-48)		
Fine hand function (11-33)	191	19 (10-30)		

Univariable regression analysis

The results of univariable linear regression analyses of potential variables associated with UE function in patients with DMD are presented in table 4. For each dependent variable the independent variables that were associated with a p-value<0.2 were entered in the multivariable linear regression analysis.

Multivariable regression analysis

Multivariable stepwise linear regression analysis revealed a total of 12 different variables associated with one or more aspects of UE function (table 5). These associated variables explained 56-81% of the variation of the different measures of UE function. The variables that were positively related to UE function were: 'going to school or work', 'use of corticosteroids', 'higher BMI' and 'later age at diagnosis'. The variables that were negatively related to UE function were: 'later disease stage',

'occurrence of scoliosis', 'higher age', 'use of UE splints, 'more frequent stiffness complaints', 'more limitations due to stiffness', 'more frequent elbow pain' and 'having physical therapy'.

Table 3. Descriptives of possible associated variables

Predictors (min-max possible score)	N	Median (min-max)	Category	N (Valid %)
Age	213	13.1 (1.5-35.2)		
Disease stage	213		Early ambulatory	66 (31.0)
			Late ambulatory	29 (13.6)
			Early non ambulatory	24 (11.3)
			Late non ambulatory	94 (44.1)
BMI	209	20.1 (5.9-44.1)		
Age at diagnosis	213	4 (0-10)		
Injuries	213		No	186 (87.3)
			Yes	27 (12.7)
Scoliosis	213		No scoliosis	109 (51.2)
			Mild scoliosis	66 (31.0)
			Severe scoliosis	38 (17.8)
Corticosteroids	212		No	72 (34.0)
			Not anymore	24 (11.3)
			Yes	116 (54.7)
Homeopathic remedies	213		No	99 (46.5)
			Yes	114 (53.5)
Physical therapy	213		No	17 (8.0)
			Not anymore	19 (8.9)
			With periods of no therapy	31 (14.6)
			Yes continuously	146 (68.5)
Practice at home	213		No	123 (57.7)
			On average once a week	38 (17.8)
			On average once a day	40 (18.8)
			More than once a day	12 (5.6)
Hydro therapy	213		No	92 (43.2)
			Yes	121 (56.8)
Occupational therapy	213		No	123 (57.7)
			Not anymore	37 (17.4)
			With periods of no therapy	31 (14.6)
			Yes continuously	22 (10.3)
Splints	213		No	192 (90.6)
			Yes	20 (9.4)
Arm supports	213		No	195 (91.5)
			Yes	18 (8.5)
School/Work	200		No	34 (17.0)
			Yes	166 (83.0)
Sport	198		No	122 (61.6)
			Yes	76 (38.4)
Hobby	198		No	34 (17.2)
			Yes	164 (82.8)
Pain limitations (0-140)	213	0 (0-140)		
Pain severity (not shoulder) (0-120)	213	0 (0-120)		
Distal pain frequency (0-36)	213	0 (0-24)		
Shoulder pain (0-32)	213	0 (0-21)		
Proximal pain frequency (not shoulder) (0-24)	213	0 (0-22)		
Elbow pain frequency (0-12)	213	0 (0-11)		
Stiffness frequency (0-84)	212	2 (0-84)		
Stiffness limitations (0-140)	212	0 (0-140)		
Stiffness severity (0-140)	212	2 (0-140)		

Table 4. Univariable linear regression analysis

	Brooke		Basic hand function		Heavy lifting		Light or no lifting		Gross hand function		Fine hand function	
Associated variables	N	β (95% CI)	N	β (95% CI)	N	β (95% CI)	N	β (95% CI)	N	β (95% CI)	N	β (95% CI)
Age	213	**0.20 (0.18; 0.22)**	210	**-1.34 (-1.56; -1.12)**	210	**-2.06 (-2.33; -1.78)**	210	**-2.86 (-3.18; -2.54)**	189	**-1.23 (-1.40; -1.06)**	191	**-0.69 (-0.80; -0.57)**
Disease stage	213	**1.19 (1.08; 1.30)**	210	**-6.94 (-8.22; -5.67)**	210	**-13.39 (-14.56; -12.22)**	210	**-17.12 (-18.63; -15.60)**	189	**-6.95 (-7.86; -6.04)**	191	**-4.50 (-5.04; -3.96)**
BMI	209	**0.05 (0.00; 0.09)**	206	0.14 (-0.22; 0.49)	206	**-0.72 (-1.20; -0.23)**	206	**-0.76 (-1.38; -0.13)**	185	0.05 (-0.25; 0.36)	187	-0.09 (-0.28; 0.10)
Age at diagnosis	213	**0.09 (-0.04; 0.22)**	210	-0.17 (-1.25; 0.90)	210	**-1.69 (-3.14; -0.24)**	210	**-1.62 (-3.50; 0.26)**	189	0.07 (-0.87; 1.00)	191	0.08 (-0.50; 0.65)
Injuries	213	**0.79 (0.03; 1.54)**	210	**-5.16 (-11.34; 1.01)**	210	**-9.11 (-17.51; -0.71)**	210	**-13.87 (-24.60; -3.13)**	189	**-4.66 (-9.78; 0.47)**	191	**-2.33 (-5.52; 0.86)**
Scoliosis	213	**1.55 (1.29; 1.81)**	210	**-11.38 (-13.63; -9.14)**	210	**-16.20 (-19.20; -13.20)**	210	**-21.67 (-25.43; -17.91)**	189	**-9.60 (-11.41; -7.79)**	191	**-5.65 (-6.79; -4.50)**
Corticosteroids	212	**-1.02 (-1.26; -0.77)**	209	**6.26 (4.16; 8.36)**	209	**8.17 (5.28; 11.05)**	209	**13.83 (10.34; 17.32)**	188	**8.42 (6.91; 9.93)**	190	**5.02 (4.07; 5.98)**
Homeopathic remedies	213	**-0.39 (-0.90; 0.12)**	210	**3.38 (-0.76; 7.53)**	210	2.41 (-3.28; 8.09)	210	**5.90 (-1.37; 13.17)**	189	**2.84 (-0.64; 6.32)**	191	**1.42 (-0.74; 3.58)**
Physical therapy	213	-0.06 (-0.33; 0.21)	210	0.77 (-1.40; 2.95)	210	**-2.77 (-5.72; 0.18)**	210	-0.40 (-4.22; 3.42)	189	0.52 (-1.32; 2.36)	191	-0.07 (-1.22; 1.07)
Practice at home	213	0.08 (-0.19; 0.34)	210	-0.71 (-2.88; 1.46)	210	**-2.05 (-5.00; 0.90)**	210	-1.09 (-4.89; 2.71)	189	-0.48 (-2.29; 1.33)	191	-0.59 (-1.71; 0.52)
Hydro therapy	213	**-1.88 (-2.32; -1.43)**	210	**13.23 (9.44; 17.01)**	210	**17.94 (12.76; 23.11)**	210	**27.07 (20.72; 33.42)**	189	**13.34 (10.38; 16.31)**	191	**7.33 (5.42; 9.24)**
Occupational therapy	213	0.03 (-0.21; 0.28)	210	0.27 (-1.73; 2.27)	210	**-1.89 (-4.61; 0.82)**	210	-1.51 (-5.01; 1.98)	189	-0.06 (-1.75; 1.62)	191	-0.55 (-1.58; 0.48)
Splints	213	**1.55 (0.71; 2.40)**	210	**-8.42 (-15.42; -1.43)**	210	**-15.42 (-24.87; -5.97)**	210	**-21.95 (-34.01; -9.89)**	189	**-11.39 (-16.84; -5.94)**	191	**-6.32 (-9.73; -2.90)**
Arm supports	213	**1.76 (0.88; 2.64)**	210	-2.63 (-10.06; 4.79)	210	**-17.53 (-27.40; -7.67)**	210	**-23.14 (-35.78; -10.50)**	189	**-8.08 (-14.08; -2.07)**	191	**-5.68 (-9.39; -1.97)**
School/Work	200	**-2.10 (-2.74; -1.46)**	200	**18.63 (13.50; 23.75)**	200	**17.90 (10.64; 25.16)**	200	**29.62 (20.56; 38.69)**	189	**14.83 (10.69; 18.98)**	191	**7.73 (5.09; 10.37)**
Sport	198	**-0.49 (-1.03; 0.05)**	198	**5.76 (1.36; 10.17)**	198	**4.44 (-1.50; 10.37)**	198	**7.95 (0.29; 15.61)**	188	**3.59 (0.03; 7.16)**	190	**1.75 (-0.46; 3.95)**
Hobby	198	**0.90 (0.21; 1.59)**	198	**-4.38 (-10.12; 1.37)**	198	**-9.34 (-16.93; -1.76)**	198	**-10.51 (-20.39; -0.64)**	188	**-4.07 (-8.77; 0.63)**	190	-1.23 (-4.20; 1.75)
Pain limitations	213	**0.02 (0.01; 0.03)**	210	**-0.17 (-0.25; -0.08)**	210	**-0.27 (-0.38; -0.16)**	210	**-0.37 (-0.51; -0.23)**	189	**-0.15 (-0.22; -0.09)**	191	**-0.09 (-0.13; -0.05)**
Pain severity (not shoulder)	213	**0.02 (0.01; 0.04)**	210	**-0.16 (-0.27; -0.04)**	210	**-0.35 (-0.50; -0.20)**	210	**-0.42 (-0.61; -0.22)**	189	**-0.16 (-0.25; -0.07)**	191	**-0.10 (-0.16; -0.04)**
Distal pain frequency	213	**0.07 (0.02; 0.12)**	210	**-0.65 (-1.07; -0.23)**	210	**-1.04 (-1.61; -0.47)**	210	**-1.30 (-2.03; -0.56)**	189	**-0.45 (-0.80; -0.11)**	191	**-0.29 (-0.51; -0.08)**
Shoulder pain	213	**0.12 (0.08; 0.17)**	210	**-0.92 (-1.28; -0.56)**	210	**-1.50 (-1.98; -1.03)**	210	**-1.87 (-2.48; -1.25)**	189	**-0.86 (-1.16; -0.57)**	191	**-0.48 (-0.66; -0.30)**
Proximal pain frequency (not shoulder)	213	**0.09 (0.02; 0.16)**	210	**-0.64 (-1.21; -0.06)**	210	**-1.36 (-2.13; -0.59)**	210	**-1.53 (-2.52; -0.53)**	189	**-0.51 (-0.98; -0.04)**	191	**-0.34 (-0.63; -0.05)**
Elbow pain frequency	213	**0.35 (0.24; 0.47)**	210	**-2.85 (-3.78; -1.93)**	210	**-4.01 (-5.26; -2.75)**	210	**-5.42 (-7.02; -3.82)**	189	**-2.13 (-2.89; -1.36)**	191	**-1.25 (-1.73; -0.78)**
Stiffness frequency	212	**0.04 (0.03; 0.05)**	209	**-0.29 (-0.38; -0.20)**	209	**-0.42 (-0.54; -0.29)**	209	**-0.60 (-0.75; -0.45)**	188	**-0.26 (-0.33; -0.19)**	190	**-0.14 (-0.19; -0.09)**
Stiffness limitations	212	**0.02 (0.02; 0.03)**	209	**-0.17 (-0.22; -0.13)**	209	**-0.23 (-0.30; -0.16)**	209	**-0.35 (-0.43; -0.26)**	188	**-0.15 (-0.19; -0.11)**	190	**-0.09 (-0.11; -0.06)**
Stiffness severity	212	**0.02 (0.01; 0.03)**	209	**-0.15 (-0.20; -0.09)**	209	**-0.19 (-0.26; -0.11)**	209	**-0.29 (-0.39; -0.20)**	188	**-0.13 (-0.17; -0.08)**	190	**-0.07 (-0.09; -0.04)**

Variables with a P-value<0.2 are displayed bold. These variables were included in the multivariable regression analysis.

Table 5. Multivariable linear regression analysis

Associated variables	Brooke* (N = 207)	Basic hand function** (N = 199)	Heavy lifting** (N = 199)	Light or no lifting** (N = 208)	Gross hand function** (N = 187)	Fine hand function** (N = 189)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Age	0.07 (0.05; 0.10)	-0.47 (-0.82; -0.12)	- -	-0.99 (-1.35; -0.62)	-0.36 (-0.57; -0.15)	- -
Disease stage	0.69 (0.54; 0.84)	-1.84 (-3.69; 0.02)	-10.77 (-12.19; -9.35)	-9.15 (-11.24; -7.06)	-2.69 (-3.82; -1.55)	-3.04 (-3.64; -2.44)
BMI	-0.03 (-0.05; -0.01)	- -	- -	- -	- -	- -
Age_Diag	-0.07 (-0.13; 0.00)	- -	- -	- -	- -	- -
Scoliosis	0.31 (0.12; 0.50)	-4.79 (-7.17; -2.42)	-4.78 (-7.07; -2.49)	-4.36 (-7.11; -1.61)	-2.24 (-3.72; -0.75)	-1.30 (-2.27; -0.34)
Corticosteroids	-0.26 (-0.40; -0.12)	- -	- -	3.50 (1.50; 5.50)	2.76 (1.52; 3.99)	1.64 (0.82; 2.46)
Physical therapy	- -	- -	-2.11 (-3.66; -0.55)	- -	- -	- -
Splints	0.45 (0.05; 0.86)	- -	- -	-7.04 (-12.75; -1.33)	-5.63 (-8.59; -2.68)	-2.40 (-4.43; -0.37)
School/Work	- -	7.34 (2.81; 11.86)	4.78 (0.61; 8.95)	- -	4.04 (1.23; 6.85)	2.16 (0.44; 3.89)
Elbow pain frequency	- -	-0.71 (-1.48; 0.06)	- -	- -	- -	- -
Stiffness frequency	0.01 (0.00; 0.02)	- -	-0.08 (-0.16; -0.01)	-0.18 (-0.27; -0.10)	-0.09 (-0.14; -0.05)	- -
Stiffness limitations	- -	-0.07 (-0.11; -0.02)	- -	- -	- -	-0.02 (-0.04; 0.00)
R^2	0.81	0.56	0.75	0.81	0.75	0.70

* A lower score indicates better arm function. ** A lower score indicates worse arm function

DISCUSSION

The aim of our study was to gain insight into the variables associated with UE function in boys and men with DMD. Knowledge of these variables is essential for the clinical management of these patients. In this study we found 4 variables that were positively associated with UE function and 8 variables that had a negative association with UE function.

The finding that use of corticosteroids was positively related to UE function is not surprising, as it has been proven that this medication can retard disease progression[1, 6, 12, 26]. The positive relation between going to school or work and UE function may be attributed to the fact that people that go to school or work are often physically more active than people that do not. Indeed, physical activity is important to maintain functional independence[13, 22]. The finding that patients who were diagnosed at a later age have better UE function may be due to the fact these patients usually have a slower disease progression. Another positive determinant of UE function was a higher BMI, which seems to be counterintuitive because, on the one hand, it is associated with arms that weigh more, requiring more strength to lift the arms. On the other hand, a higher BMI is often related to a better nutritional status (even though protein loss may still occur when BMI is high[16, 17]) and malnutrition occurs more often in people with a low BMI, as it is associated with dysphagia, typically occurring in the later stages of DMD[7, 30]. Malnutrition can be related to a lack of energy, increased fatigability, reduced muscle strength, and muscle wasting leading to loss of functional capacity [7, 20]. Thus, a higher BMI may be associated with a reduced likelihood of malnutrition, which could explain the positive relationship with UE function independent of disease stage. Nevertheless, future studies should try to disentangle these interrelationships to optimize clinical management.
With regard to the variables that have a negative relationship with UE function, a

later disease stage and a higher age are well conceivable based on the progressive nature of DMD. Although we found no studies that related the occurrence of scoliosis to UE function, it can be expected that deformity of the spine has a negative effect on sitting balance and reduced sitting balance has a negative influence on UE function[5, 10, 11]. The negative relation of UE function with pain and stiffness is not surprising as pain and stiffness complaints are known to have a negative impact on general physical functioning[29]. However, based on our analysis, stiffness seems to have a stronger relation with UE function than pain, as only one pain variable (elbow pain frequency) was related to one dependent variable (Brooke scale), whereas stiffness variables were related to all measures of UE function. One possible explanation for the fact that stiffness seems to have a stronger relation with UE function is that DMD patients experience more stiffness-related than pain-related UE problems[14]. The fact that only elbow pain frequency relates to UE function could be because the elbow is often used as a hinge point on the arm rest or table to perform daily activities. Pain in the elbow could, therefore, be the key element in the restriction of the performance of UE activities. Remarkably, stiffness severity was not identified as a variable associated with UE function, which may indicate that stiffness severity is harder to score subjectively than stiffness frequency and stiffness limitations. Another explanation might be that the 3 stiffness variables were rather strongly correlated ($r>0.6$), as a result of which stiffness severity did not add to the explained variance of UE function in the multivariable model. The finding that use of splints and physical therapy showed a negative association with UE function is probably caused by the likelihood that these interventions are recommended more often to relatively severely affected patients[4, 28]. In contrast, no relationship was found between UE function and occupational therapy, hydrotherapy or practicing at home. We hypothesize that the absence of this relation might lie in the relatively short duration of these interventions, as they are only applied for a few hours per week or even less. Therefore, exposure to therapy might not be high enough for the therapy to be effective. Going to school or work, in contrast, stimulates the use of the arm and hand over a much longer time span, which could explain its positive relation with UE function.

A limitation of this study is that our results are based on a questionnaire that was primarily designed to gain insight in UE function in patients with DMD, not for the identification of variables associated with UE function. Thus, the possible variables associated with UE function in DMD were limited to those addressed in this questionnaire, leaving the possibility that there might be other variables associated with UE function that were not investigated. Another limitation is that the cross-sectional design of our study does not allow any inferences with regard to the nature of the observed relationships (cause vs. consequence). Thirdly, our results are entirely subjective in nature, as no objective tests of UE function, pain or stiffness were performed. Therefore, the results of this study should be interpreted with caution. Nevertheless, our study addressed 26 possible variables associated with UE function in more than 200 patients with DMD, which provides a good basis for

further (longitudinal) prognostic studies, using both subjective and more objective outcome measures, to improve our understanding of the most essential variables associated with function in DMD.

It is important to realize that several of the variables associated with UE function in DMD that were identified in this study can be influenced by proper clinical management. For example, use of corticosteroids and living an active life by participating in school and work related activities can be stimulated by clinicians. In addition, prevention of scoliosis, maintaining a stable sitting balance, and reduction of pain and stiffness complaints may be attainable by regular attention from physical and occupational therapists, including the prescription of optimal assistive devices. Future longitudinal research should investigate whether proper clinical management of patients with DMD can indeed slow down the progression of UE impairments, UE activity limitations, and related participation restrictions.

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PART 2

UPPER EXTREMITY FUNCTION EXPLORED BY MEANS OF FUNCTIONAL SCALES AND PHYSIOLOGIC OUTCOME MEASURES

CHAPTER 5

SURFACE EMG TO ASSESS ARM FUNCTION IN BOYS WITH DMD: A PILOT STUDY

Published as: Janssen MM, Harlaar J, de Groot IJ. Surface EMG to assess arm function in boys with DMD: a pilot study. J Electromyogr Kinesiol. 2015;25(2):323-8.

Abbreviations:

ADL	Activities of daily living
CBH	Combing hair
CLS	Touch contralateral shoulder
DMD	Duchenne muscular dystrophy
EFL	Elbow Flexion Extension
HTM	Hand to mouth
MVC	Maximal voluntary contraction
NStM	Non-standardized movements
PS	Pronation Supination
RFW	Reach forward at shoulder level
S90	Shoulder abduction with the elbow flexed 90 degrees
SFL	Shoulder Flexion/Extension
SAB	Shoulder Abduction
SAD	Shoulder Adduction
sEMG	Surface electromyography
SIE	Shoulder Internal rotation External rotation
StM	Standardized movements
QEMG	Quantitative electromyography

ABSTRACT

INTRODUCTION Preserving functional abilities of the upper extremities is a major concern in boys with Duchenne muscular dystrophy (DMD). To assess disease progression and treatments, good knowledge on arm function in boys with DMD is essential. Therefore, feasibility and validity of the use of surface electromyography (sEMG) to assess arm function in boys with DMD was examined.
METHODS Five boys with DMD and 6 age-matched controls participated in this study. Single joint movements and ADL activities were examined while recording sEMG of main shoulder and elbow muscles.
RESULTS All boys with DMD and controls were able to perform the non standardized movements of the measurement protocol, however one boy with DMD was not able to perform all the standardized movements. Boys with DMD used significantly more of their maximal muscle capacity for all muscles to conduct movements compared to controls.
DISCUSSION/CONCLUSION The measurement protocol was feasible to assess arm function in boys with DMD. This tool was able to discriminate between DMD patients and controls.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a progressive X-linked disorder characterized by progressive muscle wasting and weakness, resulting in a loss of functional abilities. There is no curative treatment for DMD. However, due to disease-retarding treatments and nocturnal ventilation, median survival in boys with DMD has increased from 14 years of age in the 1960s[1] to a current median survival of over 30 years[2, 3]. Since boys with DMD become wheelchair bound around the age of 10[3], they will be in a wheelchair for the remaining and largest part of their lives. With increasing life expectancy, maintaining upper extremity function becomes increasingly important as this is highly related to quality of life[4, 5].

Unfortunately, upper extremity function and weakness in boys with DMD have received little attention in research and literature[6, 7]. However, knowledge about upper extremity function can be very important to examine the effects of medical intervention on disease progression and is important to develop new techniques to support arm function.

The studies that have investigated the upper extremity in boys with DMD report a decline of upper extremity strength before the age of 10 years[8, 9]. In addition it was found that proximal muscles are weaker than distal muscles[7, 10]. As a result of the declining strength, functional abilities start to decline around the age of 10 years and a decline of hand function starting around the age of 15 years[11, 12].

Several instruments are used to define upper extremity function: Brooke's upper extremity functional grading scale[13]; Jebsen Test of Hand Function[14]; Manual Muscle Testing[15]; Functional Independence Measure[16]; Barthel Index[17] and the Motor Function Measure[18]. Unfortunately, the sensitivity for most instruments is low and not all instruments measure functional abilities or are only fairly limited. Therefore, a sensitive and valid measurement tool to measure upper extremity function in boys with DMD is needed.

Since the decline of muscle function is the primary consequence of DMD, electromyography (EMG) of the upper extremity muscles in boys with DMD has great potential to be the sensitive measurement instrument that is needed. Surface electromyography (sEMG) is already commonly used for functional assessment of the lower extremity[19]. In addition, quantitative electromyography (QEMG) was proven to be capable of providing information on disease severity in different muscular dystrophies[20-22]. QEMG, however, is an invasive method, because QEMG has to be measured intramuscularly. Furthermore, QEMG can give insight in myopathic changes in affected muscles, but not on the functional status of a patient, although they are related.

Therefore, this study explores the features of using sEMG in the upper extremity, for

the functional analysis of single joint movements and some activities of daily living (ADL) in boys with DMD. The aims of this study are to determine: (1) the clinical feasibility sEMG in boys with DMD, (2) to evaluate construct validity of sEMG: whether it enables to discriminate between healthy boys and boys with DMD.

MATERIALS AND METHODS

Study population

The study population consisted of 5 boys with Duchenne Muscular Dystrophy (DMD) and 6 age-matched controls. Inclusion criteria for boys with DMD were: a DNA established diagnosis of DMD; expected to be at the end of the ambulation phase or recently wheelchair confined; able to sit for 20 minutes without arm support but with low back support; and having a Brooke scale of 1 to 4 (i.e. at least able to raise one hand to the mouth)[6, 13]. Boys in this study were excluded if they were younger than 8 years old, if they had other disabling diseases influencing upper extremity mobility or if they had undergone a surgical scoliosis correction.

The recruitment of patients was done via the outpatient clinic in collaboration with a patient organization for DMD (i.e. the Duchenne Parent Project). Healthy subjects were recruited from primary and secondary schools in the neighborhood of Nijmegen. This study was approved by the medical ethical committee Arnhem-Nijmegen, the Netherlands, and subjects and their parents gave informed consent before participating in the study.

Surface electromyography

Wireless surface electromyography (sEMG) (Zerowire EMG, Aurion, Italy) was used on the biceps brachii, anterior deltoid and the lateral deltoid muscles to measure muscle activity. Disk shaped Ag-AgCL ARBO ECG electrodes (Tyco Healthcare, Neustadt, Germany) with a diameter of 24 mm were placed at an inter electrode distance of 24 mm after the skin was shaven, and scrubbed clean. Electrodes were placed according to the SENIAM guidelines[23] and Maximal Voluntary Isometric Contractions (MVICs) were used for sEMG normalization. The sample frequency for sEMG was 1000 Hz.

Experimental procedure

The experimental protocol consisted of 3 sets of tasks: Maximal Voluntary Isometric Contraction (MVIC); Standardized Single Joint Movements; and Non-Standardized Movements, which included some ADL activities.

MVIC measurements

MVICs of the left and right biceps brachii, anterior deltoid and lateral deltoid muscles were measured. Starting position and subject instructions for each muscle are shown in table1. For each muscle, 3 MVICs were kept for at least 3 seconds.

Table 1. Starting positions and subject instructions for MVC measurements

Muscle	Start position
Biceps Brachii	The upper arm is placed relaxed next to the torso. The elbow is flexed 90° and placed in the mid position (thumb upwards). The elbow is supported and the wrist is fixated. Instructions: Pull the lower arm to the shoulder as hard as possible, while the examiner holds the arm in the same place.
Anterior Deltoid	The straight arm is placed in 60° shoulder forward flexion, with the thumb pointing upward. The arm is fixated just above the elbow joint and at the wrist. Instructions: Push the whole arm upward as hard as possible, while the examiner holds the arm in place.
Lateral Deltoid	The straight arm is placed in 30° shoulder abduction, with the thumb pointing forward. The arm is fixated just above the elbow joint and at the wrist. Instructions: Push the whole arm sideward up as hard as possible, while the examiner holds the arm in place.

Standardized single joint movements

The single joint movements used in this study are elbow and shoulder movements that are mostly used in clinical practice and literature[24, 25]. Standardization for performing single joint movements was obtained by demonstrating the movements and correcting movements when compensatory movements were noticed. Standardizing the movement velocity was achieved by moving on the count of the examiner who corrected the movement velocity if necessary by asking the participant to perform the movement again at a slower or faster speed. Every movement started in the anatomical neutral position[26]. Each of the following standardized single joint movements were recorded 3 times: pronation/supination (PS); elbow flexion/ extension (EFE); shoulder abduction (SAB); shoulder abduction (with the elbow flexed 90°) (S90); shoulder adduction (in the horizontal plane) (SAD); shoulder flexion/ extension (SFE); shoulder internal/external rotation (SIER) (see figure 1).

Non-standardized movements

The single joint movements performed during the non-standardized condition were identical to the standardized movements. However, precise task execution was not standardized: the subject was instructed to execute the movement the way he preferred. Consequently, movement velocity could vary and compensatory movements might be used. In addition, 4 movements related to activities of daily living were performed: reach forward (RFW); touch contralateral shoulder (CLS); combing hair (CBH); bring the hand to the mouth(HTM)).

Outcome measures

The experimental protocol was found to be feasible if boys with DMD were able to understand the items and perform most of the items, either in a stereotyped way or, depending on the stage of their disease, by using compensatory movements (only during the non standardized movements). Similarly, healthy boys should be able to understand and perform the items without experiencing problems.

The outcome measures in this study were normalized sEMG amplitude, which was defined as the maximum sEMG amplitude during dynamic movements as a percentage of sEMG of MVIC amplitude (%).

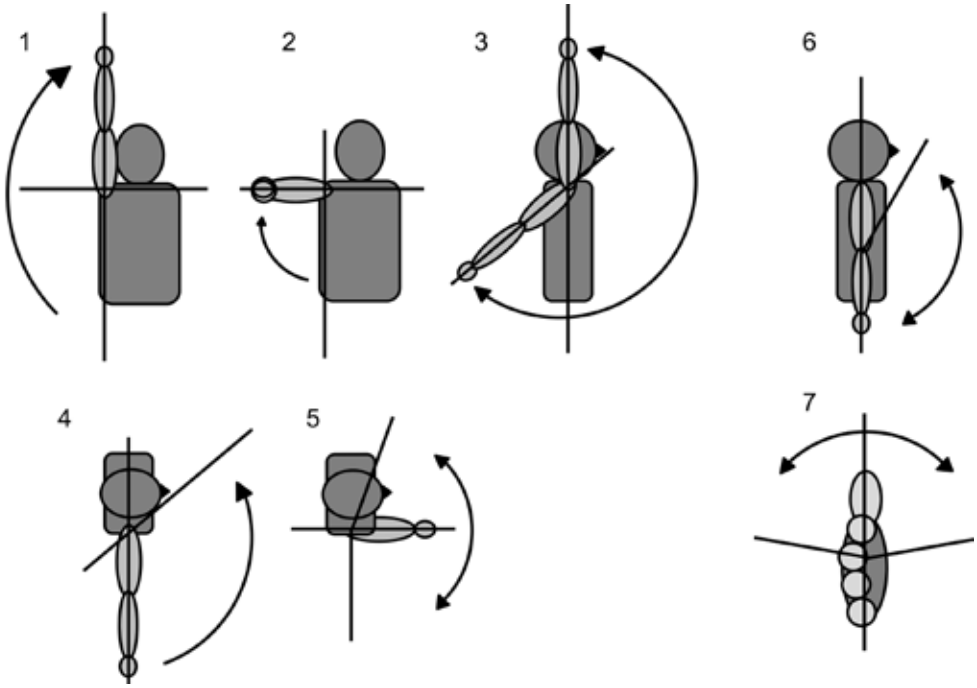

Figure 1: Single joint movements
Single joint movements that were included in this study. 1: shoulder abduction (SAB), 2: shoulder abduction (with the elbow flexed 90°) (S90), 3: shoulder flexion/extension (SFL), 4: shoulder adduction (in the horizontal plane) (SAD), 5: shoulder internal/external rotation (SIE), 6: elbow flexion/extension (EFL), 7: pronation/supination (EPS)

The construct validity of this experimental protocol was evaluated by testing the differences between healthy boys and boys with DMD. Sensitivity was explored by comparing the five boys with DMD at different stages of the disease.

Data analysis
Matlab® (Mathworks, Natick, USA) was used for data analysis of the sEMG signals. sEMG data was filtered using a band pass filter between 20 and 450 Hz to remove movement artifacts and baseline noise contamination[27]. Then, the signal was rectified and, after rectification, a low pass filter of 3 Hz was used to obtain the linear envelope[28].

For each MVIC trial, the maximal amplitude of the sEMG linear envelope was determined, the maximum sEMG amplitude out of 3 trials was chosen as the MVIC amplitude of the specific muscle. For the standardized and non-standardized movements the maximal sEMG amplitude per trial was calculated and the average of 3 trials was used for comparison with the MVIC amplitude.

Statistical analysis
Wilcoxon rank sum test for independent groups was used to compare differences

between the left and right arm and to compare differences between patients and healthy controls. SPSS® Statistics Version 20 (IBM®, Somers, USA) was used for calculations.

RESULTS

Standardized movements (StM) were performed completely by all healthy subjects and 4 boys with Duchenne Muscular Dystrophy (DMD); one boy with DMD was not able to conduct the standardized movements. This boy was older than the other boys and had a Brooke scale of 4. However, he was able to conduct the non-standardized movements (NStM). Table 2 shows the characteristics of the participants.

Table 2. Participant characteristics

	N	Age (years), Mean (±SD)	Age range (year)	Brook scale
DMD Patients	5	12.03 (±2.52)	8 to 15	1-4
Controls	6	11.11 (±1.80)	8 to 13	1

Number of patients/controls, mean age ± SD (year), age range (year) and Brook scale

All movements were performed with the right and left arm in both healthy subjects and subjects with DMD. No significant differences were found between the left and right arm; therefore, we combined the results of the left and right arm trials by averaging the sEMG amplitudes for the left and the right arm.

Standardized movements

Figure 2 shows the average of the surface electromyography (sEMG) amplitude as a percentage of maximal voluntary isometric contraction (MVIC) amplitude for boys with DMD and controls. Overall, boys with DMD used a larger percentage of their maximal possible muscle activation during the performance of standardized movements compared to controls. In addition, boys with DMD showed relatively larger biceps brachii activation during all shoulder and elbow movements, while controls only show increased biceps brachii activation during elbow movements. Boys with DMD had larger standard deviations compared to controls, pointing at a higher inter-subject variation of normalized sEMG amplitudes.

To explore whether elbow flexion, as seen in shoulder abduction of the arm, is a compensatory mechanism we studied the differences between normalized sEMG amplitude in SAB and S90. The strategy of using elbow flexion during shoulder abduction is often seen in clinical practice. The length of the lever arm is reduced when flexing the elbow, therefore less muscle strength is required to perform the movement. The lateral deltoid muscle was expected to be the main muscle for performing shoulder abduction. In boys with DMD, the normalized sEMG amplitude was 35.0% ($p = 0.208$) lower when using elbow flexion during shoulder abduction, compared to shoulder abduction with an extended elbow. In control subjects this was 30.8% ($p = 0.001$).

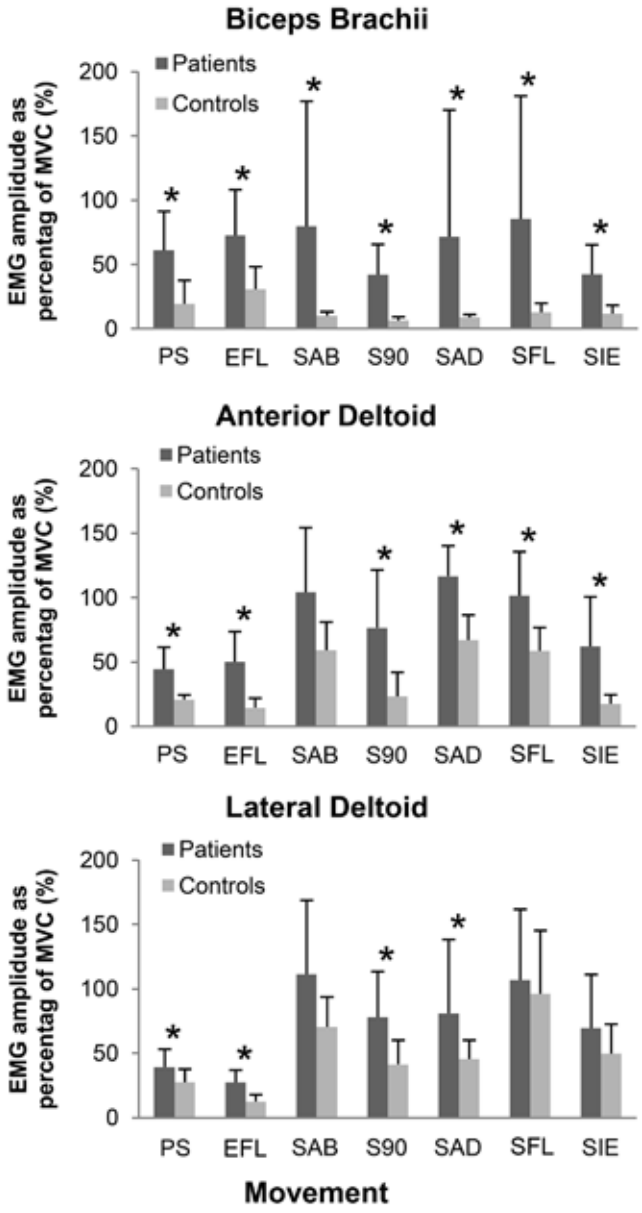

Figure 2. Normalized EMG amplitudes of standardized movements
Mean and standard deviation of normalized sEMG amplitudes of the biceps brachii, anterior deltoid and lateral deltoid, during 7 standardized movements for patients and controls. PS: Pronation/Supination, EFL: Elbow Flexion/Extension, SAB: Shoulder Abduction, S90: Shoulder abduction with the elbow flexed 90 degrees, SAD: Shoulder Adduction, SFL: Shoulder Flexion/Extension, SIE: Shoulder Internal/External Rotation. *Statistical significant difference ($p \leq 0.05$)

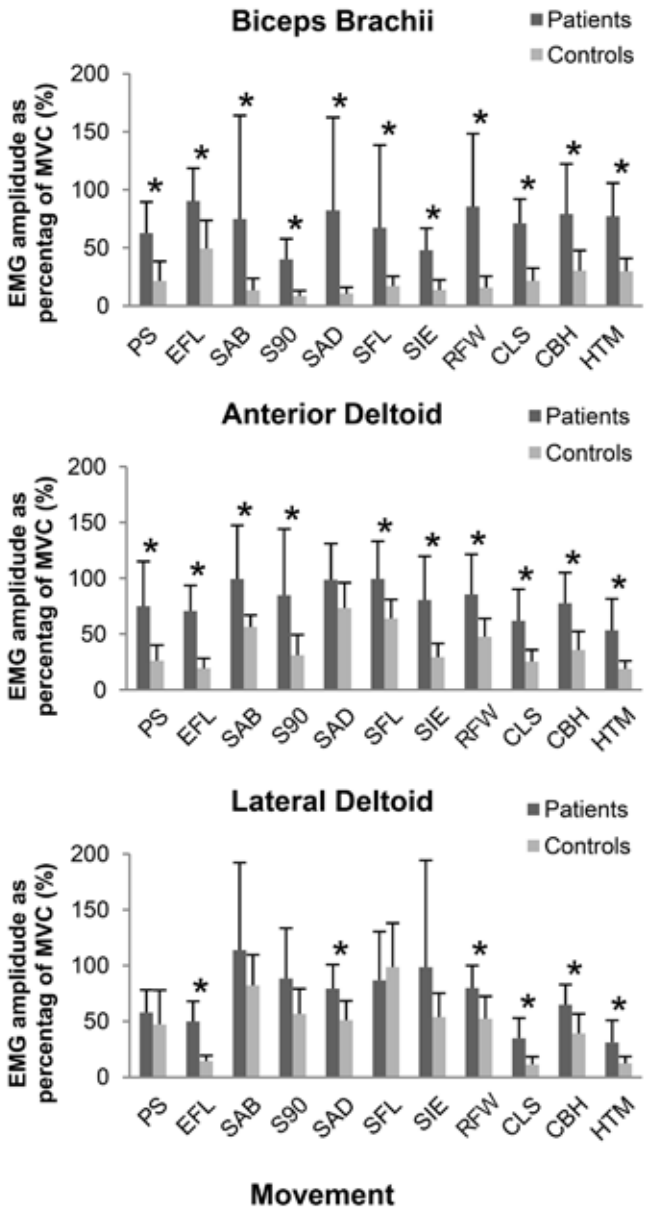

Figure 3. Normalized sEMG amplitudes of non-standardized movements

Mean and standard deviation of normalized sEMG amplitudes of the biceps brachii, anterior deltoid and lateral deltoid, during 11 non-standardized movements for patients and controls. PS: Pronation/Supination, EFL: Elbow Flexion/Extension, SAB: Shoulder Abduction, S90: Shoulder abduction with the elbow flexed 90 degrees, SAD: Shoulder Adduction, SFL: Shoulder Flexion/Extension, SIE: Shoulder Internal/External Rotation, RFW: Reach Forward, CLS: Touch Contralateral Shoulder, CBH: Combing Hair, HTM: Hand to Mouth. *Statistical significant difference ($p \leq 0.05$)

Non-standardized movements
Also, in non-standardized movements, an increase of sEMG amplitudes and variation was seen in boys with DMD compared to controls (Figure 3). This also held for ADL.

DISCUSSION

The first aim of this study was to determine if surface electromyography (sEMG) is feasible in boys with Duchenne Muscular Dystrophy (DMD). All boys in Brooke scale 1 to 3 were able to perform the standardized and non-standardized movements, confirming the feasibility of the measurement protocol in this group. The boy with Brooke scale 4 was not able to perform the standardized shoulder movements; however, sEMG signals could still be measured in shoulder and elbow muscles and some elbow movements could still be performed. A future recommendation to enable the use of this measurement tool in more severely affected patients is to include wrist movements and possibly hand movements in the measurement protocol, in order to extend its feasibility towards later stages of the disease.

The second aim was to evaluate if the presented sEMG based method will discriminate between healthy boys and boys with DMD. Considerable differences were found between patients and controls in all muscles, which, even in our small sample size were statistically significant. To determine if there is a relation between normalized sEMG amplitude and age or stage of the disease a larger sample size is needed. In a next study this relation will be further examined.
Some limitations of the study can be mentioned. The results show that some boys with DMD have normalized sEMG amplitudes close to or over 100% MVIC, especially in shoulder movements. Conceptually, it seems impossible to have normalized sEMG amplitudes over 100%. However a person's voluntary effort during MVC could be influenced by pain, protection from pain, restrictions in the range of motion and/ or motivation[29]. Therefore, subjects might not have been giving their maximal effort, despite the encouragement that was given to perform at maximal capacity. This could be the case in both healthy subject and boys with DMD. However, in boys with DMD the possibility that they experience pain while moving or experience stiffness due to contractures is higher. Therefore it is possible that the MVIC does not represent the maximum capacity of boys with DMD. For this reason several attempts are done to achieve the MVIC, but this is no absolute guarantee that the MVIC is the actual maximal capacity.

Re-examining the data of individual participants we saw that one patient showed much larger normalized sEMG amplitudes compared to the other patients. While most patients show normalized sEMG amplitudes of below or around 100% MVIC, one patients showed values of above 200% MVIC. Therefore we think that this patient did not perform at his maximal capacity when doing the MVIC attempts, despite the fact that he received the same instructions and encouragement as the

other participants. The results of this patient after re-analysis showed only slight influence on the statistical differences that were found between healthy subjects and DMD patients. The only changes that we found were that the difference of lateral deltoid muscle during SAD in the StM condition was no longer significant (P=0.092) and that the difference of lateral deltoid during S90 in the NStM condition became statistically significant between healthy subjects and boys with DMD (P=0.037).

Another explanation is that this study compares the sEMG amplitude of maximal isometric contractions in MVIC, to the amplitudes of dynamic contractions in StM and NStM. Several studies indicated that muscle activity during a maximal isometric contraction is smaller than during a maximal concentric contraction and, consequently, sEMG amplitude increases when movement velocity increases[30-32]. So, MVIC is probably an underestimation of the real maximal possible muscle activation, which explains normalized sEMG amplitudes of more than 100% MVIC when a subject is performing dynamic contractions close to their maximal capacity. This fact was not seen in our healthy control subjects, probably because healthy subjects are not performing close to their maximal capacity while performing unloaded single joint movements.

The measurement protocol used was quite extensive, including both standardized and non-standardized movements, and some items were difficult to perform, especially for the boys more severely affected by DMD. Consequently, fatigue and reduced concentration and motivation could have affected the results. Therefore, we suggest reducing the load on patients in future measurements. First, we recommend using only the standardized movements and randomize the order of movements to correct for fatigue. Secondly, we recommend performing the measurements unilaterally instead of bilaterally, since no differences were found between the left and right arm. In addition, we recommend adapting the item difficulty with regard to the Brooke scale of the DMD patients so that the number of movements participants have to perform is minimized.

Clinical implications

Although it was not the primary aim of this study and the sample size of this pilot study was small, we would like to reflect on the clinical implications of our findings. Normalized sEMG amplitudes shows a striking difference between boys with DMD and controls. Compared to healthy controls, boys with DMD use a larger percentage of their maximal possible muscle activation in the primary muscles for conducting a movement, but also in compensatory muscles.

To compensate for the reduction in muscle capacity, boys with DMD often use compensatory movements like the Gower's sign[33]. One of the compensatory movements that is often seen in the upper extremity is the use of elbow flexion during shoulder abduction. Our results indicate that elbow flexion during shoulder abduction is indeed an effective compensation mechanism to reduce the normalized

sEMG amplitude of the lateral deltoid muscle, compared to shoulder abduction with the elbow extended. Therefore using normalized sEMG amplitude is feasible method to distinguish between normal and compensatory movements.

This was a pilot study with a limited number of subjects. Therefore, the next step is to measure a larger population of both healthy subjects to establish normal values and boys with DMD in different stages of the disease. Such a follow-up study, with a limited number of tasks, should reveal more aspects of validity and reliability of the outcome measures used, and how the outcome measure relates to disease severity, as expressed by the Brooke scale.

CONCLUSION

Surface electromyography during standardized tasks was found to be feasible and valid for measuring arm function in boys with Duchenne Muscular Dystrophy (DMD). This justifies a follow-up study with a larger sample size.

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CHAPTER 6

DYNAMIC ARM STUDY: QUANTITATIVE DESCRIPTION OF UPPER EXTREMITY FUNCTION AND ACTIVITY OF BOYS AND MEN WITH DUCHENNE MUSCULAR DYSTROPHY

Published as: Janssen MMHP, Harlaar J, Koopman B, de Groot IJM. Dynamic arm study: quantitative description of upper extremity function and activity of boys and men with duchenne muscular dystrophy. J Neuroeng Rehabil. 2017;14(1):45

Abbreviations:

DMD	Duchenne Muscular Dystrophy
UE	Upper Extremity
ICF	International Classification of Functioning, Disability and Health
PUL	Performance of Upper Limb
sEMG	Surface Electromyography
MVIC	Maximal Voluntary Isometric Contraction

ABSTRACT

BACKGROUND Therapeutic management of upper extremity (UE) function of boys and men with Duchenne Muscular Dystrophy (DMD) requires sensitive and objective assessment. Therefore, we aimed to measure physiologic UE function of healthy subjects and DMD patients in different disease stages, and to evaluate the relation between these physiologic measures and functional UE scales.

METHODS Twenty-three DMD patients and twenty healthy controls (7-23 years) participated in this explorative case-control study. Maximal muscle torque, maximal and normalized surface electromyography (sEMG) amplitudes, muscle thickness, echogenicity and maximal passive and active joint angles were measured. At activity level, Brooke upper extremity rating scale and the Performance of Upper Limb (PUL) scale were used.

RESULTS Outcome measures related to proximal UE function could discriminate between disease stages. Increased normalized sEMG amplitudes were found in patients, even in early disease stages. Maximal active joint angles showed the strongest relation to Brooke scale ($R2 = 0.88$) and PUL scale ($R2 = 0.85$).

CONCLUSIONS The decline of muscle functions precedes the decline in performance of UE activities, and therefore may play a role in early detection of UE limitations. Increased sEMG levels demonstrate that DMD patients use more of their muscle capacity compared to healthy subjects, to perform daily activities. This might result in increased fatigability. Active maximal joint angles are highly related to functional scales, so preserving the ability to use the full range of motion is important for the performance of daily activities. Close monitoring of active joint angles could therefore help in starting interventions that minimize functional UE decline in DMD patients timely.

BACKGROUND

Duchenne Muscular Dystrophy (DMD) is a x-linked neuromuscular disorder with an incidence of 1:5,000 male newborns[1]. The disorder is characterized by a progressive loss of muscle strength, starting in the pelvic girdle, however, in later stages all muscles become affected. Boys with DMD become non-ambulant around the age of 10 years when untreated, and around the age of 13 years when treated with corticosteroids[2]. Arm function is already affected at this age [3, 4]. Although there is no curative treatment for DMD, life expectancy is rapidly increasing due to medical interventions[5, 6]. This means that boys and men with DMD have to live longer with their functional limitations and thus maintaining upper extremity (UE) function and measuring changes in UE function are increasingly important.

Loss of UE function can be delayed by several years by using corticosteroid treatment[7-10]. Physical exercise programs have also been found to be beneficial for retaining UE function[11-13]. However, in the long term, interventions that compensate for loss of UE function are still needed, for example arm supports, which reduce the effort that is needed to perform activities. To develop and evaluate such interventions, more insight in the upper extremity is needed. Insights on both International Classification of Functioning, Disability and Health (ICF)[14] function and structure level, and ICF activity level are necessary in order to unravel the mechanisms of UE decline.

The primary aim of this study is to give a quantitative description of UE functioning during a variety of meaningful UE task in boys and men with DMD in different stages of the disease, in comparison to their healthy peers. The secondary aim is to evaluate the relation between physiologic and structural UE functions and functional UE scales.

METHODS

Population

The study population consisted of 23 boys and men with DMD and 20 healthy boys and men. DMD patients were included if they were older than 6 years, had a DNA established DMD diagnosis, and had a Brooke scale[15] of 1-5, meaning that they were able to use their hands functionally. Patients were recruited through the Radboud University Medical Center (Radboudumc) outpatient clinic and by an advertisement on the website of the Dutch DMD patient organization ("Duchenne Parent Project"). Healthy subjects over 6 years, without UE mobility limitations, were included from schools in the neighborhood of the Radboudumc in the city of Nijmegen. This study was approved by the medical ethical committee Arnhem–Nijmegen, the Netherlands (Registration number 2012/135, NL nr.: 39126.091.12). Informed consent was obtained from all participants and from their parents when the subjects were under 18 years of age.

Outcome measures

Participant characteristics

The following participant characteristics were collected based on self-reports: age, arm preference, weight, height, year of diagnosis, wheelchair confinement and, if applicable the age of wheelchair confinement, and the occurrence of scoliosis.

Functional UE scales

Functional UE scales used in this study were: "Brooke upper extremity rating scale[15]" and the "Performance of Upper Limb (PUL) scale[16]". These functional scales measured participants' activity level. PUL items were performed once. Based on the score of the entry item, some subjects only performed a specific subset of the PUL. Sum scores of the 3 dimensions (high level shoulder, mid level elbow, distal wrist and hand) and the total sum score were calculated.

Muscle torques and surface electromyography

Muscle torques and surface electromyography (sEMG) signals were recorded of 7 different upper extremity muscles (Trapezius (descending part), Biceps Brachii (long head), Triceps Brachii (long head), Deltoid (lateral part), Pectoralis Major (clavicular head), wrist flexors and wrist extensors). Muscle torques were measured using a static frame myometer, consisting of a KAP-E Force Transducer, measurement range 0.2 – 2000 N (Angewandte System Technik, Dresden, Germany), and a height and position adjustable frame (designed and custom made by mechanical engineers from the VU medical centre, Amsterdam, the Netherlands). Wireless sEMG signals (Zerowire EMG, Aurion, Italy) were recorded with a sample frequency of 1000 Hz. Disk-shaped Ag–AgCL ARBO ECG electrodes (Tyco Healthcare, Neustadt, Germany) were placed at an inter electrode distance of 24 mm. Testing and electrode positions were based on literature[17, 18]. To make the measurement protocol more suitable for DMD patients, as they were often in a wheelchair or had joint contractures, we slightly adapted some of the testing positions. sEMG data were filtered using a 4th order band pass filter between 20 and 450 Hz, where after the signal was rectified and low pass filtered (3 Hz) to obtain the linear envelope[19, 20]. Torque data were filtered using a 3 Hz low pass filter of the 4th order.

All subjects performed two maximal voluntary isometric contractions (MVICs) to determine the maximal muscle torque and corresponding sEMG amplitude. If the examiner was not confident that a maximal effort was made, the measurement was repeated. The maximal value out of the two correct attempts was used for further data analysis. Normalized sEMG amplitudes were calculated for the performance of single joint movements and PUL items. Normalized sEMG amplitude was defined as the maximum sEMG amplitude that was reached during a movement as a percentage of the maximal amplitude of the same muscle during MVIC.

Data was processed with custom-written Matlab (Matlab® version R2014b, Mathworks, Natick, USA) routines.

Quantitative muscle ultrasound

Ultrasounds images of 6 upper extremity muscles (Trapezius, Biceps Brachii, Triceps, Deltoid, wrist flexors and wrist extensors) were recorded using a Z.One PRO Ultrasound System (Zonare Medical Systems, Mountain View, California, USA), with a L10-5 transducer. Three ultrasound recordings were made, at a depth of 4 cm, to calculate echogenicity (greyscale) and one recording, with no predefined depth, was made to determine the muscle thickness. Echogenicity is the extent to which a structure reflects ultrasound of a surface with high echogenicity indicating that more ultrasound is reflected, for example when high levels of fatty and connective tissue are present in a muscle. Ultrasound images were analyzed with computer-assisted greyscale histogram analysis, using custom software developed at Radboudumc (QUMIA). Echogenicity was determined by calculating the grayscale in the upper 1/3rd of the region of interest (the region that included as much muscle mass as possible without bone and fascia) in each muscle[21]. The average echogenicity out of 3 measurements was used for further analysis. Muscle thickness was determined by calculating the distance between two electronic calipers at standardized positions. Thickness of the Trapezius was measured between the deep and superficial fascia of the upper part of the Trapezius muscle. Thickness of the Deltoid, Biceps (combined with Brachialis) and Triceps muscles were measured between the humerus and the superficial fascia. Forearm flexor (Flexor Carpi Radialis) thickness was measured between a horizontal reference line at the height of the radius and the superficial fascia. Forearm extensors thickness was measured between the middle end of the radius and the superficial fascia.

Ultrasound results were compared to muscle specific reference values and expressed as Z-scores (representing the number of standard deviations from the mean)[22]. Reference values for calculation of the Z-scores were obtained from 60 healthy subjects using the same measurement protocol and ultrasound device (manuscript in preparation). Echogenicity and muscle thickness were corrected for age, weight and height if necessary using the method described by Scholten et al.[23].

Three dimensional motion analysis

Three dimensional motion analysis, using the kinematic model of Jaspers et al.[24] (figure 1), was performed with an 8 camera VICON motion analysis system (Oxford Metrics, Oxford, UK). After marker placement and anatomical landmark identification, maximal passive joint angles were determined for: 'shoulder abduction', 'elbow flexion and extension', 'pro- and supination of the lower arm', 'wrist flexion

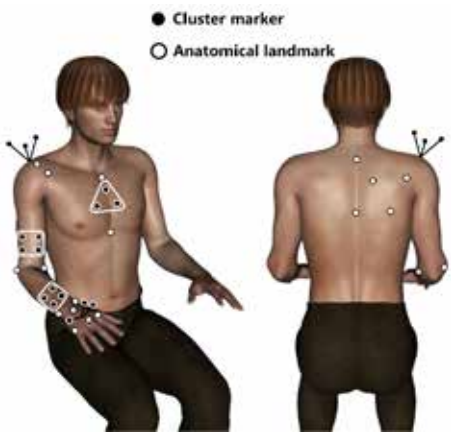

Figure 1. Marker positions
Positions of cluster markers (black center) and anatomical landmarks (white center)

and extension' and 'wrist ulnar and radial deviation'. Maximal active joint angles were determined for the same movements and also for 'shoulder flexion' and 'shoulder adduction (in the horizontal plane)' (figure 2). Some subjects did not perform all single joint movements as they were unable to perform the movements. All passive and active movements were performed 3 times at a controlled movement velocity.
Joint-kinematics were calculated using BodyMech (http://www.bodymech.nl) and additional custom-written Matlab routines. Kinematic data were filtered using a 4th order low pass filter of 20 Hz. Per movement, the minimal and maximal joint angles were determined. The average maximal joint angle over three measurements was used for further data analysis.

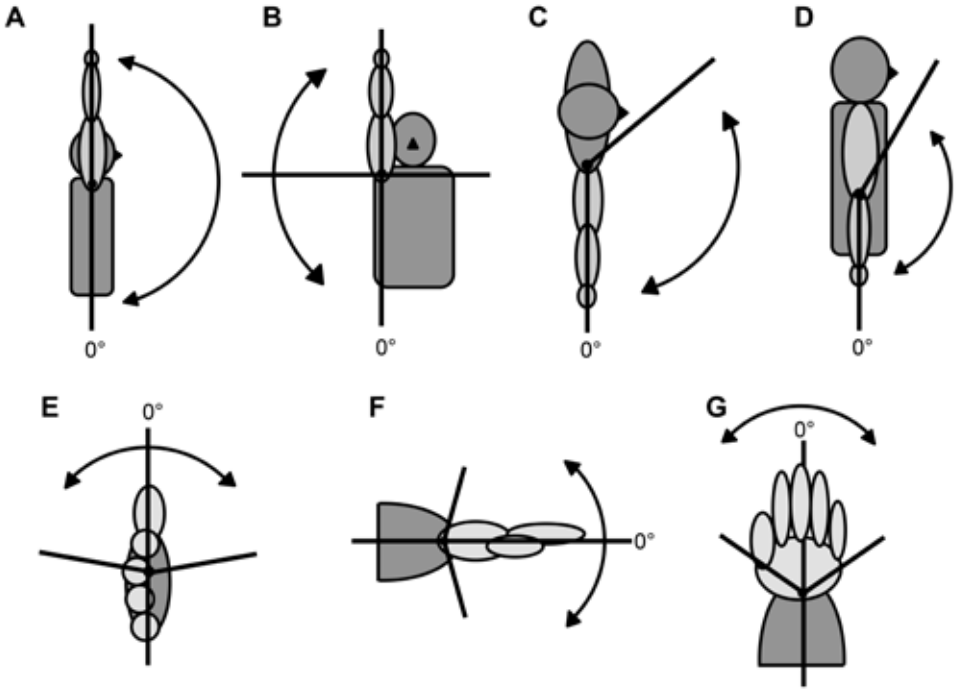

Figure 2. Single joint movements
A: shoulder flexion, B: shoulder abduction, C: shoulder adduction (in the horizontal plane), D: elbow flexion and extension, E: forearm pronation and supination, F: wrist flexion and extension and G: wrist ulnar and radial deviation.

Statistical analysis

Median values and ranges were used to describe the continuous participant characteristics and percentages were used to describe categorical participant characteristics. Wilcoxon rank sum tests were used to compare outcome measure sum scores between healthy subjects and DMD patients. Kruskal-Wallis tests were used to test for differences between DMD patients in different Brooke scales. To gain insight in the relation between functional UE scales (Brooke and PUL scale) and physiologic UE function (muscle torque, sEMG, echogenicity, muscle thickness,

passive and active joint angles) we calculated the coefficient of determination (R2) between the sum scores, or average scores for echogenicity and muscle thickness, of these outcome measures. The sum scores were calculated by adding the results of all values within one outcome measure. If one or more values were missing, the sum score was also reported as missing. If values were missing because patients were physically unable to perform the activity a score of 0 was used for the calculation of the sum scores. SPSS Statistics Version 20 (IBM, Somers, USA) was used for statistical analysis.

RESULTS

The median age of healthy subjects was 14.0 (range 7.4-23.4) years and the median age of DMD patients was 14.9 (range 8.1-21.7) years (Table 1). About 90% of the participants was right handed. The median age at diagnosis was 3.75 years (range 0-7 years) and 74% of the patients was non-ambulant. Thirteen percent of the patients had a mild scoliosis, and 22% had a severe scoliosis, of which 40% was surgically corrected. Corticosteroids were used by 74% of the patients, while 13% stopped using and 13% never used corticosteroids. Of the corticosteroid users, 12% used Deflazacort on a daily basis and 88% uses Prednisone/Prednisolone on a 10-days-on/10-days-off basis. Dosages vary between 4 and 45 mg.

Table 1. Participant characteristics

Variable	Healthy	DMD Brooke 1	DMD Brooke 2	DMD Brooke 3	DMD Brooke 4	DMD Brooke 5
N	20	5	8	4	3	3
Age (median, range)	14.0 (7.4-23.4)	11.1 (8.0-16.0)	12.4 (8.7-15.8)	15.8 (12.6-16.9)	17.1 (17.0-18.4)	18.2 (17.8-21.7)
BMI	19.1 (15.7-24.4)	21.9 (17.7-26.4)	20.7 (18.7-30.8)	23.0 (16.5-26.0)	17.6 (10.0-21.4)	22.5 (19.4-24.6)
Hand preference						
Right handed (%)	90	100	87.5	75	100	100
Left handed (%)	10	0	12.5	25	0	0
Age of diagnosis (median, range)	-	2.0 (0.0-5.0)	4.0 (2.5-7.0)	4.0 (2.5-6.0)	1.5 (0.0-6.0)	1.0 (0.0-6.0)
Percentage wheelchair confined (%)	-	0	87.5	100	100	100
Age wheelchair confined (median, range)	-	-	10 (7-13)	10 (8-10)	11 (10-11)	9 (8-10)
Scoliosis						
No (%)	-	75	87.5	75	33	0
Mild (%)	-	25	12.5	0	0	33
Severe (%)	-			25	67	67
Scoliosis correction (%)	-	0	0	0	33	67
Corticosteroid use						
No (%)	-	0	12.5	25	33	0
Not anymore (%)	-	0	0	25	0	67
Yes (%)	-	100	87.5	50	67	33

Statistically significant differences between healthy subjects and DMD patients were seen in all outcome measures except muscle thickness, as all the Z-values for muscle thickness were between -2 and 2 (table 2). In addition, differences between patients in different Brooke scales were present in most proximal muscles and movements requiring proximal muscles. PUL scores in all domains differed between DMD patients in different Brooke scales.

Normalized sEMG amplitudes of DMD patients and healthy controls differed significantly for all movements and muscles, except for Trapezius activation during

Table 2 Average UE outcome measures scores for healthy subjects and DMD patients in different Brooke scales

	Healthy			DMD Brooke 1			DMD Brooke 2			DMD Brooke 3			DMD Brooke 4			DMD Brooke 5				
	N	Mean	(95% CI)	N	Mean	(95% CI)	N	Mean	(95% CI)	N	Mean	(95% CI)	N	Mean	(95% CI)	N	Mean	(95% CI)	P-value healthy/ patient	P-value Brooke scale
Functional UE scales																				
Performance of Upper Limb Scale																				
PUL shoulder	20	16	(,;,)	5	13	(10;15)	8	6	(3;10)	4	0	(,;,)	3	0	(,;,)	2	0	(,;,)	**0,000**	**0,002**
PUL elbow	20	32	(,;,)	5	32	(31;32)	8	27	(22;32)	4	15	(6;24)	3	10	(4;15)	2	5	(-15;24)	**0,000**	**0,002**
PUL wrist	20	24	(,;,)	5	24	(23;24)	8	22	(21;23)	4	22	(21;23)	3	20	(15;26)	2	20	(,;,)	**0,000**	**0,014**
Sum score*	20	78	(,;,)	5	74	(71;76)	8	60	(52;68)	4	41	(31;50)	3	32	(21;43)	2	26	(6;45)	**0,000**	**0,001**
Physiologic UE outcome measures																				
Maximal muscle force (N)																				
Trapezius	20	476	(344;609)	5	147	(62;233)	8	109	(85;134)	3	138	(-4;280)	3	59	(29;90)	3	40	(-6;85)	**0,000**	**0,012**
Biceps	20	178	(139;217)	5	37	(27;47)	8	27	(19;34)	3	21	(17;24)	3	7	(-3;17)	3	5	(-2;12)	**0,000**	**0,003**
Triceps	20	152	(121;182)	5	27	(21;33)	8	17	(11;23)	3	13	(4;21)	3	8	(2;14)	2	7	(-40;53)	**0,000**	**0,011**
Deltoid	20	83	(64;102)	5	32	(24;40)	8	21	(14;27)	3	21	(17;26)	2	15	(3;26)	2	7	(-21;35)	**0,000**	**0,020**
Pectoralis major	20	199	(156;242)	5	69	(49;89)	8	45	(30;60)	3	40	(21;58)	3	14	(-6;34)	3	15	(7;23)	**0,000**	**0,003**
Wrist flexors	20	127	(102;152)	5	29	(14;44)	7	27	(11;42)	3	26	(-38;90)	3	19	(-9;47)	2	14	(-32;61)	**0,000**	0,386
Wrist extensors	20	120	(94;146)	5	32	(13;51)	7	30	(14;45)	3	30	(-20;80)	3	8	(-8;24)	2	14	(-19;47)	**0,000**	0,061
Sum score	20	1334	(1038;1631)	5	373	(271;474)	7	278	(212;344)	3	288	(16;561)	2	147	(-81;374)	2	110	(-192;412)	**0,000**	**0,024**
Maximal muscle torque (Nm)																				
Trapezius	20	86,4	(57,3;115,5)	5	24,6	(11,5;37,7)	8	16,2	(11,9;20,5)	3	24,8	(-6,0;55,5)	3	8,5	(2,4;14,6)	3	7,2	(-2,6;16,9)	**0,000**	**0.016**
Biceps	20	45,8	(33,8;57,7)	5	7,2	(4,8;9,6)	8	5,9	(4,1;7,6)	3	5,0	(2,8;7,2)	3	1,7	(-1,2;4,5)	3	1,3	(-0,7;3,3)	**0,000**	**0.010**
Triceps	20	38,2	(28,9;47,5)	5	5,4	(4,0;6,8)	8	3,8	(2,3;5,4)	3	3,2	(1,2;5,2)	3	1,8	(-0,4;4,0)	2	1,6	(-11,1;14,3)	**0,000**	**0.024**
Deltoid	20	41,4	(29,8;52,9)	5	11,1	(8,4;13,7)	8	8,6	(5,5;11,6)	3	9,5	(7,9;11,2)	2	5,6	(4,9;6,2)	2	2,7	(-10,0;15,4)	**0,000**	0.071
Pectoralis major	20	55,2	(41,2;69,3)	5	13,6	(9,4;17,7)	8	10,2	(6,9;13,6)	3	10,3	(7,0;13,5)	3	3,4	(-3,0;9,8)	3	3,8	(1,4;6,2)	**0,000**	**0.010**
Wrist flexors	20	8,4	(6,4;10,4)	5	2,9	(-0,5;6,2)	7	2,0	(0,5;3,4)	3	1,5	(-1,9;4,9)	3	1,1	(-0,9;3,1)	2	0,8	(-1,2;2,7)	**0,000**	0.311
Wrist extensors	20	7,9	(5,8;10,0)	5	3,2	(-0,8;7,2)	7	2,1	(0,7;3,6)	3	1,8	(-0,7;4,3)	3	0,4	(-0,3;1,1)	2	0,8	(-1,2;2,7)	**0,000**	**0.027**
Sum score	20	283,2	(207,5;358,9)	5	68,0	(48,1;87,8)	7	48,1	(34,0;62,2)	3	56,1	(19,0;93,2)	2	25,5	(-35,5;86,5)	2	19,5	(-65,0;103,9)	**0,000**	**0.026**
Maximal sEMG amplitude (mV)																				
Trapezius	20	0,38	(0,27;0,50)	5	0,19	(0,03;0,35)	8	0,16	(0,09;0,24)	4	0,09	(0,05;0,13)	3	0,07	(-0,04;0,19)	3	0,02	(0,00;0,03)	**0,000**	**0,032**
Biceps	20	0,89	(0,73;1,05)	5	0,19	(0,01;0,37)	8	0,15	(0,09;0,21)	4	0,11	(-0,06;0,28)	3	0,07	(-0,01;0,15)	2	0,02	(-0,18;0,21)	**0,000**	0,096
Triceps	20	0,61	(0,48;0,74)	5	0,10	(0,03;0,16)	8	0,07	(0,05;0,09)	4	0,03	(0,02;0,03)	3	0,04	(-0,02;0,09)	3	0,02	(-0,02;0,05)	**0,000**	**0,004**
Deltoid	20	0,61	(0,50;0,72)	5	0,17	(0,12;0,22)	8	0,20	(0,10;0,30)	3	0,07	(,;,)	2	0,06	(-0,14;0,25)	3	0,06	(-0,06;0,19)	**0,000**	**0,023**
Pectoralis major	20	0,57	(0,42;0,73)	5	0,12	(0,04;0,20)	8	0,08	(0,04;0,11)	4	0,03	(0,00;0,05)	3	0,05	(-0,04;0,14)	3	0,01	(0,00;0,03)	**0,000**	**0,007**
Wrist flexors	20	0,26	(0,19;0,32)	5	0,06	(0,04;0,09)	8	0,07	(0,04;0,11)	4	0,05	(0,02;0,07)	3	0,03	(0,01;0,05)	3	0,04	(0,02;0,06)	**0,000**	0,056
Wrist extensors	20	0,47	(0,38;0,56)	5	0,13	(0,06;0,20)	8	0,18	(0,08;0,28)	4	0,10	(0,05;0,15)	3	0,12	(-0,10;0,34)	3	0,05	(-0,03;0,12)	**0,000**	0,090
Sum score	20	3,79	(3,28;4,30)	5	0,96	(0,57;1,34)	8	0,92	(0,71;1,13)	3	0,39	(0,32;0,46)	2	0,51	(-1,08;2,09)	2	0,21	(-0,62;1,03)	**0,000**	**0,011**
Z-scores Echogenicity (1/3 ROI)																				
Trapezius	16	0,37	(-0,27;1,02)	5	3,24	(0,89;5,59)	8	3,23	(1,35;5,11)	4	2,90	(-0,60;6,40)	3	6,47	(5,02;7,91)	2	3,19	(2,61;3,76)		0,093
Deltoid	16	0,36	(-0,21;0,94)	5	5,07	(4,17;5,96)	8	5,48	(4,03;6,92)	4	4,53	(0,39;8,67)	3	9,30	(8,39;10,21)	3	7,64	(5,18;10,10)		**0,016**
Biceps	16	0,14	(-0,30;0,59)	5	5,73	(3,39;8,06)	8	5,74	(4,44;7,04)	4	6,35	(3,91;8,78)	3	7,38	(5,88;8,88)	3	6,96	(3,08;10,84)		0,418
Triceps	16	0,23	(-0,43;0,88)	5	4,92	(3,47;6,37)	8	7,20	(5,58;8,82)	4	7,51	(5,19;9,83)	3	6,73	(4,44;9,03)	3	7,39	(4,61;10,17)		0,114
Wrist flexors	20	0,47	(-0,04;0,97)	5	3,21	(2,57;3,84)	8	3,63	(2,48;4,78)	4	4,32	(3,20;5,44)	3	5,19	(2,77;7,60)	2	5,02	(0,12;9,91)		0,065
Wrist extensors	14	0,24	(-0,07;0,55)	5	2,91	(1,31;4,52)	8	3,03	(1,56;4,50)	4	2,97	(1,59;4,36)	3	4,57	(4,12;5,03)	2	4,68	(3,79;5,57)		0,372
Mean score	14	0,34	(0,01;0,68)	5	4,18	(3,08;5,28)	8	4,72	(3,66;5,77)	4	4,77	(2,83;6,70)	3	6,61	(5,79;7,43)	2	5,79	(2,61;8,97)		0,053

	Healthy			DMD Brooke 1			DMD Brooke 2			DMD Brooke 3			DMD Brooke 4			DMD Brooke 5				
	N	Mean	(95% CI)	N	Mean	(95% CI)	N	Mean	(95% CI)	N	Mean	(95% CI)	N	Mean	(95% CI)	N	Mean	(95% CI)	P-value healthy/ patient	P-value Brooke scale
Z-scores Muscle Thickness																				
Trapezius	15	-0,04	(-0,83;0,74)	4	0,54	(-1,15;2,23)	7	1,08	(-0,50;2,65)	2	1,53	(-17,15;20,21)	2	-1,40	(-14,49;11,69)	2	0,29	(-8,67;9,24)		0,401
Deltoid	16	0,02	(-0,77;0,80)	4	0,82	(-1,05;2,70)	4	0,88	(-0,96;2,71)	1	0,02	(.;.)	3	-1,86	(-5,64;1,91)	3	1,47	(-5,05;7,99)		0,289
Biceps	16	0,73	(-0,67;2,14)	5	-0,80	(-2,75;1,14)	7	-1,64	(-3,06;-0,22)	2	-1,61	(-35,98;32,77)	1	-0,26	(.;.)	2	1,14	(-26,69;28,97)		0,684
Triceps	16	-0,22	(-0,85;0,41)	5	0,28	(-1,40;1,96)	5	-1,01	(-2,27;0,25)	0	.	(.;.)	2	-1,72	(-5,08;1,65)	0	.	(.;.)		0,087
Wrist flexors	16	-0,31	(-0,96;0,33)	5	-1,08	(-1,94;-0,23)	7	-1,10	(-1,87;-0,33)	2	-1,86	(-11,70;7,99)	2	-1,46	(-9,97;7,05)	1	0,83	(.;.)		0,466
Wrist extensors	14	0,39	(-0,31;1,08)	5	-0,04	(-0,70;0,61)	8	0,88	(-0,34;2,10)	4	0,76	(-0,49;2,00)	3	-0,64	(-5,03;3,75)	1	0,97	(.;.)		0,494
Mean score	13	0,13	(-0,69;0,96)	3	-0,17	(-1,13;0,79)	4	-0,48	(-1,41;0,45)	0	.	(.;.)	1	-0,41	(.;.)	0	.	(.;.)		0,757
Passive maximal joint angles (°)																				
Shoulder abduction	20	149	(142;155)	5	155	(145;164)	8	151	(136;166)	4	151	(134;168)	3	128	(97;160)	2	114	(63;165)	0,420	**0,046**
Elbow flexion	20	145	(143;148)	5	133	(126;139)	8	138	(131;145)	4	134	(116;151)	3	135	(114;155)	3	129	(123;134)	**0,000**	0,595
Elbow extension	20	4	(-1;9)	5	4	(-7;15)	8	23	(15;32)	4	35	(-11;80)	3	50	(-45;146)	3	58	(18;98)	**0,001**	**0,031**
Pronation	20	94	(85;103)	5	70	(37;103)	8	56	(33;78)	4	73	(16;129)	3	76	(32;119)	3	57	(19;94)	**0,001**	0,665
Supination	20	-59	(-68;-50)	5	-56	(-79;-34)	8	-50	(-73;-27)	4	-7	(-64;50)	3	-35	(-152;83)	3	-9	(-75;56)	0,072	0,097
Wrist flexion	20	-76	(-82;-71)	5	-65	(-88;-42)	8	-63	(-83;-44)	4	-60	(-78;-42)	3	-32	(-127;63)	3	-43	(-73;-12)	**0,001**	0,187
Wrist extension	20	81	(72;91)	5	65	(54;76)	8	84	(74;95)	4	55	(-6;116)	3	65	(25;106)	3	29	(-41;99)	**0,019**	**0,047**
Radial deviation	20	-34	(-38;-30)	5	-37	(-54;-21)	8	-41	(-53;-30)	4	-29	(-52;-5)	3	-19	(-97;59)	3	-16	(-34;3)	0,893	0,188
Ulnar deviation	20	31	(28;34)	5	25	(9;42)	8	21	(0;43)	4	19	(13;25)	3	30	(-29;89)	3	20	(-13;52)	**0,047**	0,854
Sum score	20	666	(643;690)	5	603	(525;680)	8	581	(519;644)	4	492	(265;720)	3	470	(248;691)	2	398	(-381;1177)	**0,000**	0,109
Active maximal joint angles (°)																				
Shoulder flexion	20	140	(134;145)	5	142	(129;154)	8	126	(104;148)	4	36	(-3;75)	0	.	(.;.)	0	.	(.;.)	**0,003**	**0,001**
Shoulder abduction	20	141	(134;148)	5	142	(121;163)	8	125	(101;149)	4	36	(-2;73)	0	.	(.;.)	0	.	(.;.)	**0,002**	**0,001**
Shoulder adduction†	20	129	(124;135)	5	128	(120;137)	8	93	(70;116)	4	19	(-41;78)	0	.	(.;.)	0	.	(.;.)	**0,000**	**0,001**
Elbow flexion	20	138	(135;141)	5	122	(110;133)	8	130	(123;137)	4	117	(95;139)	3	110	(16;204)	0	.	(.;.)	**0,000**	**0,035**
Elbow extension	20	7	(2;12)	5	9	(1;17)	8	29	(17;41)	4	49	(12;86)	3	40	(-24;104)	0	.	(.;.)	**0,007**	**0,006**
Pronation	20	80	(73;87)	5	59	(34;84)	8	62	(51;73)	4	67	(0;134)	3	50	(2;99)	3	13	(-44;71)	**0,000**	0,148
Supination	20	-46	(-52;-41)	5	-39	(-54;-24)	8	-33	(-52;-14)	4	9	(-47;65)	3	-10	(-90;71)	3	-5	(-28;18)	**0,001**	0,066
Wrist flexion	20	-67	(-72;-61)	4	-57	(-76;-37)	8	-57	(-76;-38)	4	-57	(-63;-52)	3	-16	(-124;92)	3	-36	(-59;-12)	**0,003**	0,114
Wrist extension	20	80	(73;86)	4	78	(48;108)	8	77	(67;86)	4	46	(-28;119)	3	66	(35;96)	3	20	(-49;90)	**0,027**	0,063
Radial deviation	20	-30	(-35;-24)	4	-39	(-53;-25)	8	-36	(-48;-24)	4	-29	(-43;-14)	3	-25	(-97;47)	3	-14	(-23;-6)	0,365	0,177
Ulnar deviation	20	31	(29;33)	4	29	(8;50)	8	26	(19;34)	4	19	(9;30)	3	23	(-15;61)	3	14	(-6;33)	**0,007**	0,334
Sum score	20	875	(846;903)	4	838	(782;894)	8	736	(658;814)	4	367	(176;557)	3	260	(151;369)	3	102	(-60;265)	**0,000**	**0,001**

* PUL sum scores is calculated including the score of the entry item (maximal score = 78)

† Shoulder adduction in the horizontal plane (figure 2.C.)

P-values healthy/patient show the differences between healthy subjects and patients. P-values Brooke scale show the differences between DMD patients in different Brooke scales. P-values > 0.05 indicate a statistical significant difference and are displayed bold. P-values healthy/patient are not shown for echogenicity and muscle thickness z-scores, as the z-scores already indicate the difference with a healthy reference population.

shoulder abduction (Figure 3). Maximal active joint angle sum score shows the strongest correlations with Brooke scale (Figure 4) and PUL score (Figure 5) (R2 of 0.88 and 0.85 respectively), followed by maximal muscle torque and maximal sEMG amplitude sum scores (R2 > 0.5). Echogenicity and passive maximal joint angle sum scores explain about 30% of the variance of Brooke scale and PUL score.

In healthy subjects, a strong relation with age was present for maximal muscle torque sum score and mean muscle thickness z-score (Figure 6, R2 of 0.79 and 0.86 respectively). For DMD patients the strongest correlations with age were found for maximal active joint angle sum score and Brooke scale (R2 of 0.64 and 0.63 respectively).

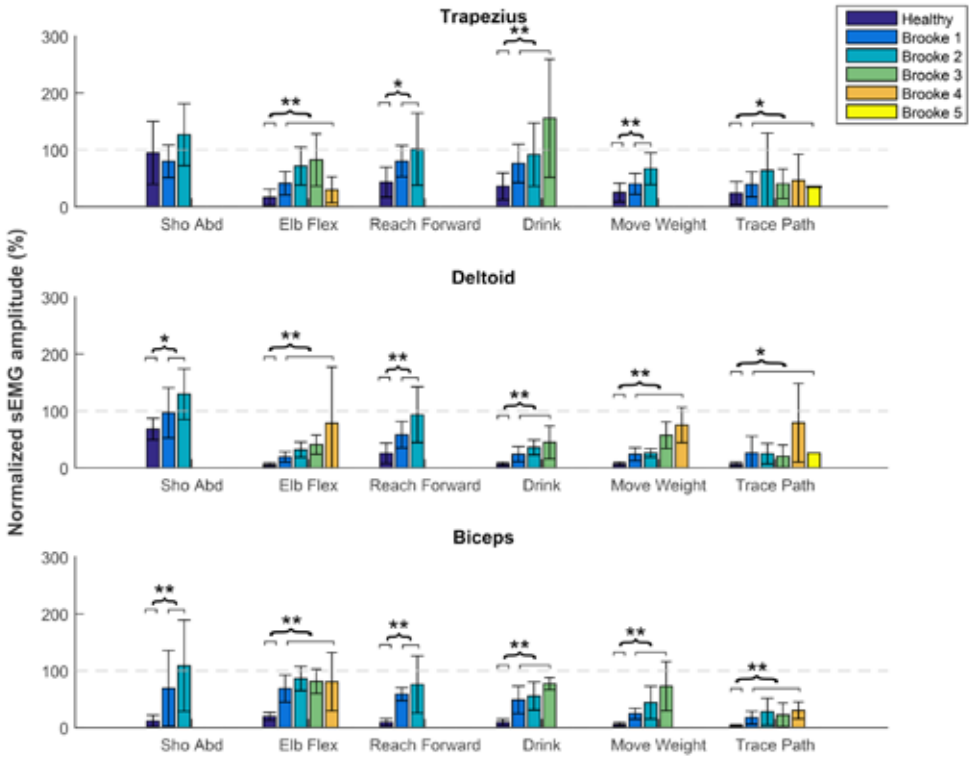

Figure 3. Normalized sEMG amplitudes
Normalized sEMG amplitudes of the Trapezius, Deltoid and Biceps Brachii muscles for 6 different upper extremity movements shown for healthy subject and DMD patients in different Brooke scales. Sho Abd = shoulder abduction; Elb Flex = elbow flexion; Reach Forward = reaching forward at shoulder level without weight (PUL item D); Drink = drinking from a full cup (200g) (PUL item F); Move Weight = moving a 100 g weight (PUL item H); Trace Path = tracing a path (PUL item O))

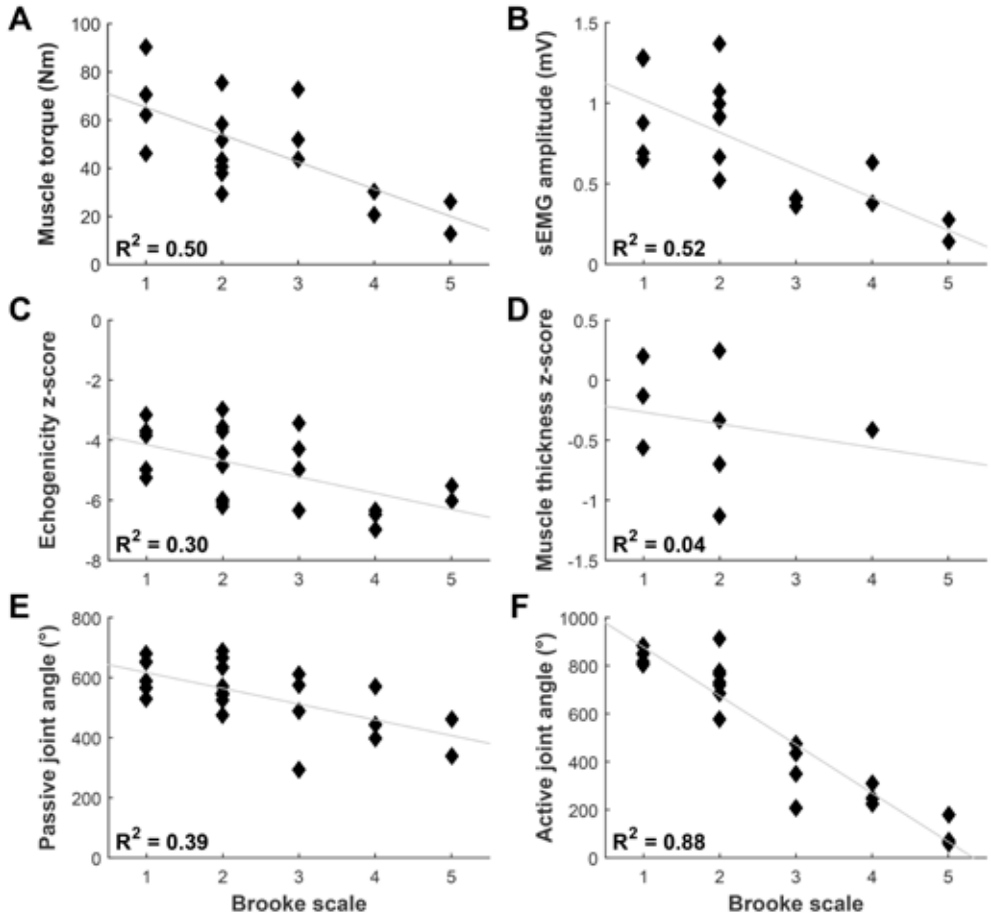

Figure 4. Correlations with Brooke scale

Correlations of DMD patients between Brooke score and A: maximal muscle torque sum score; B: maximal sEMG amplitude (MVIC) sum score; C: mean inverse z-score of echogenicity (inverse z-scores were used so that lower scores indicate worse UE function); D: mean z-score of muscle thickness; E: maximal passive joint angle sum score; F: maximal active joint angle sum score

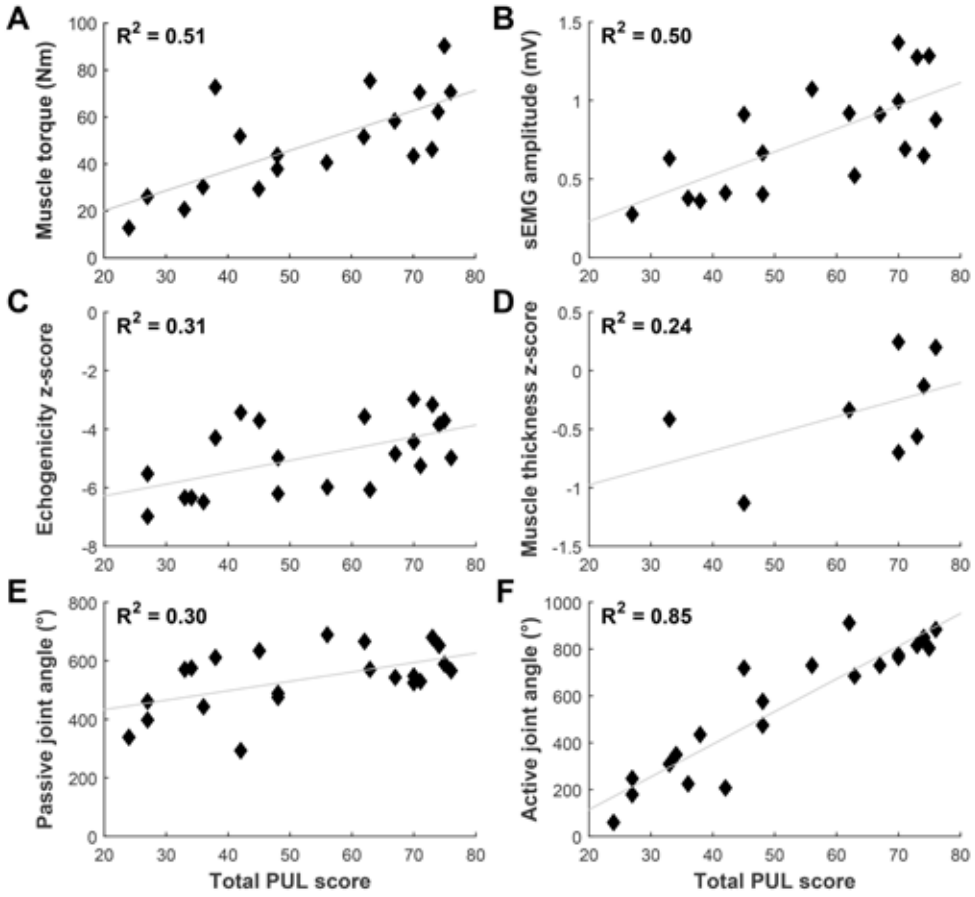

Figure 5. Correlations with PUL score
Correlations of DMD patients between total PUL score and A: maximal muscle torque sum score; B: maximal sEMG amplitude (MVIC) sum score; C: mean inverse z-score of echogenicity (inverse z-scores were used so that lower scores indicate worse UE function); D: mean z-score of muscle thickness; E: maximal passive joint angle sum score; F: maximal active joint angle sum score

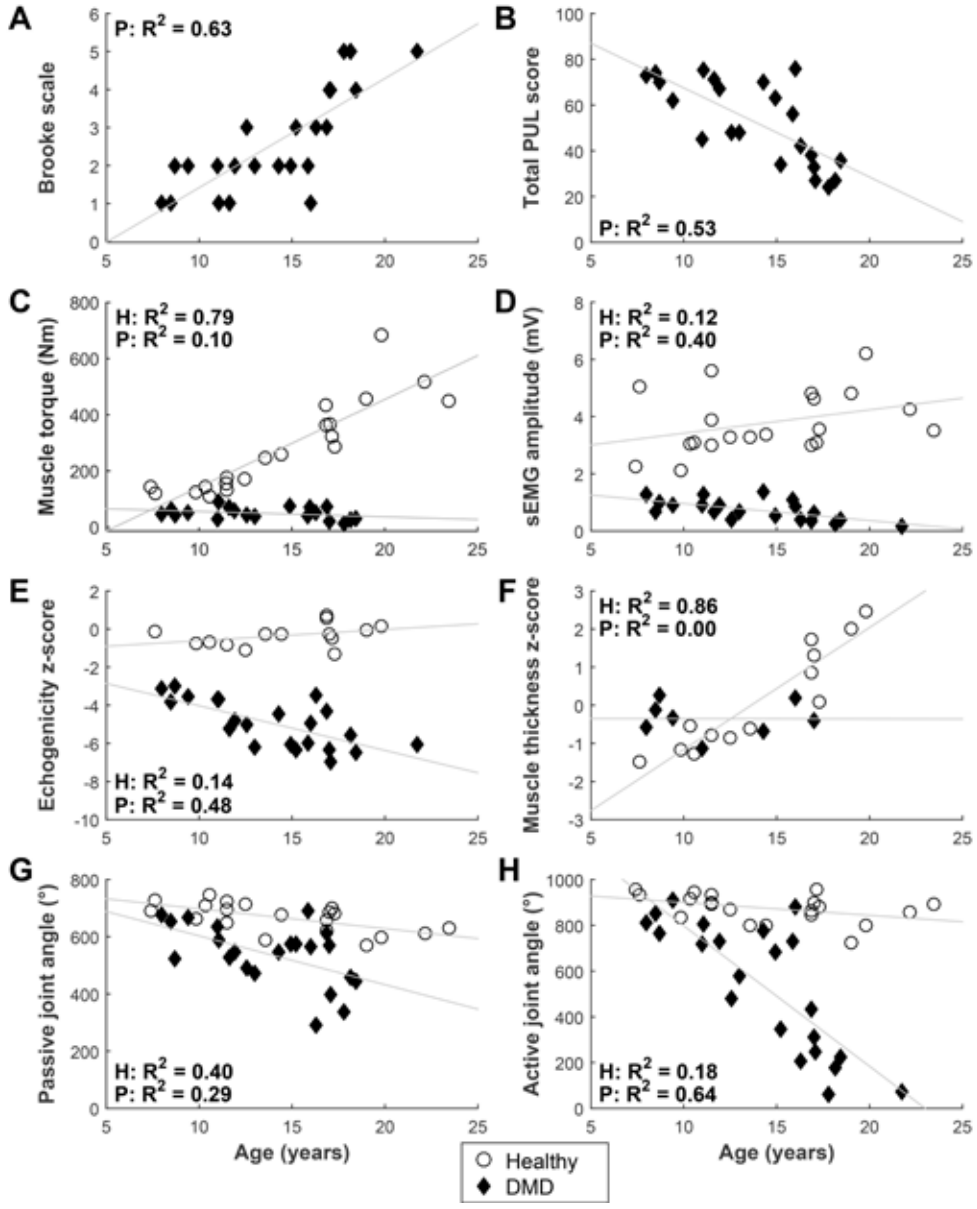

Figure 6. Correlations with age
Correlations of DMD patients and healthy subject between age and A: Brooke scale; B: total PUL score; C: maximal muscle torque sum score; D: maximal sEMG amplitude (MVIC) sum score; E: mean inverse z-score of echogenicity (inverse z-scores were used so that lower scores indicate worse UE function); F: mean z-score of muscle thickness; G: maximal passive joint angle sum score; H: maximal active joint angle sum score

DISCUSSION

Our study provides new insights in the muscles and movements that are affected most in DMD patients, and how this relates to functional UE scales. This is vital information for clinical decision making, but can also be used in the development of new outcome measures in clinical trials.

Currently, functional scales such as the Performance of Upper Limb (PUL) scale and the Motor Function Measure (MFM) are used as the gold standard for quantifying UE limitations in DMD. These measures, however, are not able to cover the entire spectrum of DMD patients, as they have floor and ceiling effects[16]. Furthermore, they do not give insight in the underlying working mechanisms of the UE. Daily activities require sufficient strength of multiple muscle groups and motion in multiple joints. Therefore, functional scales give insight in problems that result from a combination of many different physiologic aspects of UE function.

Our study shows that muscle functions (i.e. maximal muscle torque, maximal sEMG amplitude and echogenicity z-scores) of DMD patients already deviate from healthy subjects in an early disease stage (i.e. Brooke 1). A similar reduction of muscle force/torque in young DMD patients has been reported in previously[3, 25-27]. Echogenicity z-scores of all muscles are above two thus differ significantly from the healthy reference population. This finding indicates that muscles are infiltrated with fatty and connective tissue, which is in line with the results of other studies[21, 28, 29]. Consequently, these outcome measures are of great importance for early detection of UE impairments, as activity scales cannot be used in the earliest disease stage due to ceiling effects. Early detection is important to start interventions early, for example physical exercise training, which is proven to be effective in delaying functional deterioration [11-13]. The current study shows that mainly proximal muscles and movements requiring proximal muscle activation are sensitive to detect differences of UE function and activity. Maximal muscle torques and maximal sEMG amplitudes of proximal muscles can also detect differences in the later disease stages (Brooke 4 and 5), even though the muscles cannot initiate movements anymore. This could be important for evaluating the effects of arm supports, or other interventions aimed at late stage DMD patients.

To identify which limitations are primalily responsible for the inability to perform activities, and how this relates to weakness in specific muscles, insight in single joint movements is important. Single joint movements consist of movements over one joint, which often can be related to the activation of one primary muscle. In clinical practice, the measurement of maximal active single joint angles can give more insight in the mechanism responsible for activity limitations. This statement is supported by the very strong relation we found between maximal active joint angles and PUL score ($R2 = 0.85$).

Our results show that when the maximal Deltoid torque drops below approximately 10Nm, DMD patients start to have difficulties lifting their arms. A maximal Biceps torque below approximately 5Nm is related to restrictions in elbow motion. It is likely these are the minimum torques required to move the upper/lower arm against gravity, and could help to identify the suitable time to start using an arm support. Hence, regular assessment of deltoid and biceps torques may help clinicians plan interventions, anticipating functional decline.

We found that active and passive joint angles decline almost simultaneously. Therefore, we hypothesize that when a patient loses the ability to move a joint actively, the joint will be statically positioned for longer periods, which leads to contractures soon thereafter. This hypothesis is in line with the findings of McDonald et al, who showed the occurence of elbow flexion contractures appears to be related to static positions of the limb after wheelchair confinement[30]. Hence, we recommend to start interventions, such as stretching exercises, as soon as active joint angles start to decrease. In addition, we recommend stimulation of (supported) movement to limit static positioning and thereby prevent contracture formation[31].

A recent study has indicated that fatigue was strongly associated with health-related quality of life and that there should be a greater clinical focus on the reduction of fatigue[32]. In this study, we measured maximal sEMG amplitudes, which is a measure for the maximal muscle capacity. Normalized sEMG amplitudes show the percentage of this maximal muscle capacity needed to perform activities. When normalized sEMG amplitudes are high, a larger percentage of the muscle capacity is used, which leads to faster occurrence of fatigue[33]. Our results show that DMD patients use a larger percentage of their muscle capacity to perform movements and activities compared to healthy subjects, even in an early stage of the disease, and therefore might experience earlier and more fatigue. This increase in the percentage of muscle capacity is not only seen in prime movers, but also in secondary movers indicating the use of compensatory muscles to overcome loss of muscle strength. Future studies should try to determine normalized sEMG amplitudes and normalized sEMG median frequency during a fatigue protocol, in order to gain more insight in muscle fatigue of DMD patients compared to healthy controls.

Although most of our results are in line with existing literature, we also found some differences. The passive forearm supination angle of DMD patients in this study did not differ significantly ($p = 0.072$) from healthy subjects, as opposed to findings from Bartels et al.[27]. However, we found that the average forearm supination angles were reduced in patients from Brooke 3 onward, which is in line with the results of Bartels et al. who reported that 83% of the adult men with DMD had loss of supination[27]. As far as we are aware, the differences we found between healthy subjects and DMD patients for passive elbow flexion, forearm pronation, wrist flexion and ulnar deviation have not been reported before. Although the differences between healthy subjects and DMD patients are small, they could be of clinical relevance for the performance

of daily UE activities[34-36].

Muscle ultrasounds are able to make distinction between different stages of DMD[21, 28] We, however, found that echogenicity is less strongly related to disease stage compared to maximal muscle torque and maximal sEMG amplitude. We expect that echogenicity, which is a measure for muscle degeneration, is less discriminative in the explored muscles because the ultrasound images are heavily affected by attenuation. This is especially true for the later disease stages, as an increased amount of fat and connective tissue in the muscles prevents the ultrasound from penetrating deeper layers of the muscle, which results in a darker picture and therefore lowers Z-scores. For the same reason muscle thickness could not be measured accurately in older patients.

Study limitations

A limitation of this study is the relatively small number of patients in each group, especially in the latest disease stages. For this reason, post hoc comparisons between different disease stages were not performed. Furthermore, stratification of possible confounders, such as corticosteroid use and scoliosis, was not possible due to the small sample size. In addition, as this study is cross-sectional, we were unable to determine longitudinal changes of UE function. Therefore we recommend future UE studies to monitor changes of physiologic UE function over time in a cohort of patients. Nevertheless, our population is representative of the general DMD population, as the participant characteristics are comparable to literature.

A second limitation relates to our measurements of individual muscle strength. External muscle torque measurements, as we performed with the static frame myometer are unable to measure the maximal torque of isolated muscles. We attempted to mimic the activation of individual muscles as close as possible by choosing measurement positions that primarily required the activation of one muscle, the prime mover. We reported muscles torques as our primary outcome rather than muscle forces, which are more commonly used in literature. Muscle forces, however, do not account for the effect of lever arm, which we believe is more relevant in our study as we measured subjects in a wide age/height range[37]. For comparability we also reported maximal muscle forces in table 2.

Finally, the use of normalized sEMG amplitudes has some limitations as well. The maximal sEMG amplitude (in MVIC) can be influenced by pain, fear of pain, restrictions in the range of motion and/or motivation[18]. As a result normalized sEMG amplitudes over 100% MVIC were sometimes seen. This underperformance during MVIC measurements could affect both healthy subject and patients. However, in patients, pain might be of greater influence due to joint contractures. The obtained results, however, show large differences between healthy boys and DMD patients, which cannot be attributed solely to underperformance.
Despite these limitations, we think this study gives valuable and objective insights in

UE function and activity level of boys and men with DMD, which are of great clinical importance for the selection and evaluation of suitable interventions.

CONCLUSIONS

The decline of muscle functions precedes the decline in performance of UE activities, and therefore may play a role in early detection of UE limitations. Early detection can have important clinical implications as it allows for starting interventions, such as contracture prevention and physical exercise training, timely and minimize functional decline. Increased sEMG levels demonstrate that DMD patients use more of their muscle capacity compared to healthy subjects to perform daily activities. This might result in increased fatigability, which should receive attention in clinical practice as this is an important determinant of quality of life. Active maximal joint angles are highly related to functional scales, therefore preserving the full range of motion is important in daily life. Monitoring active joint angles can help to select appropriate interventions timely, to minimize UE decline. Finally, the results of this study can be used for the development of new composite outcome measures for clinical trials, that not only aim at the ICF activity level, but also on the ICF level of body functions and structures.

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CHAPTER 7

UNRAVELING UPPER EXTREMITY PERFORMANCE IN DUCHENNE MUSCULAR DYSTROPHY: A BIOPHYSICAL MODEL

Submitted: Janssen MMHP, Harlaar J, Koopman B, de Groot IJM. Unraveling upper extremity performance in Duchenne Muscular Dystrophy: a biophysical model

Abbreviations:

ADL	Activities of Daily Living
CSA	Cross Sectional Area
DMD	Duchenne Muscular Dystrophy
ICF	International Classification of Functioning, Disability and Health
MVIC	Maximal Voluntary Isometric Contraction
PUL	Performance of Upper Limb
sEMG	Surface Electromyography
UE	Upper Extremity

ABSTRACT

INTRODUCTION Duchenne Muscular Dystrophy (DMD) is a neuromuscular disorder which limits upper extremity (UE) function. Activity scales are currently used as the golden standard to assess UE limitations. These scales, however, are not able to expose the biophysical working mechanism these UE limitations. Therefore, this study aimed to identify critical physiological outcome variables underlying reduced UE task performance in DMD. These critical variables were used to propose an explanatory biophysical model of the UE working mechanism in DMD.

METHODS Twenty-three DMD patients (8-21 years) participated in this study. As functional scales, Brooke and Performance of Upper Limb (PUL) scales were used. As potential candidates for critical physiological outcome measures we identified: maximal muscle torque, maximal surface electromyography (sEMG) amplitude, echogenicity, maximal passive and active joint angles. Correlations with the functional scales and multivariable regression analysis were used to establish the strength of these critical physiological outcome variables.

RESULTS Correlations with Brooke scale and PUL score were very high (rs > 0.80) for maximal active joint angle sum score, high (rs = 0.60-0.79) for maximal muscle torque and maximal sEMG amplitude sum scores, and moderate (rs = 0.40-0.59) for mean echogenicity Z-score and maximal passive joint angle sum score. Multivariable regression analysis showed that maximal active joint angle and maximal muscle torque sum scores were significantly associated with Brooke score (R2=0.91). Maximal active joint angle, maximal passive joint angle and maximal muscle torque sum scores were significantly associated with PUL score (R2=0.94).

DISCUSSION Based on the most critical physiological outcome variables, we constructed an exploratory biophysical model of the working mechanisms leading to limitations in UE task performance. Better insights in these working mechanisms could support clinical management of UE limitations and facilitate the development of interventions. In addition, the model could form the basis for new composite outcome measures for clinical trials.

INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is an x-linked neuromuscular disorder that affects 1 in 5000 live born boys[1]. DMD is characterized by progressive muscle weakening. First the pelvic girdle is affected and later on all muscles become affected. Boys with DMD loose ambulation around the age of 13 when using corticosteroids[2] and their arm function also weakens around that age[3]. Consequently, DMD patients are in a wheelchair for the largest parts of their lives, and the ability to perform upper extremity (UE) activities becomes more and more difficult. As a result, focus of clinical practice and research in DMD has shifted towards preserving UE function, and a growing amount of UE interventions have become available. These interventions focus on treating different physiological aspects of the disease. For example, UE splinting or surgery can be used for contracture management, while corticosteroid treatment aims to improve muscle strength, arm supports attempt to increase the UE range of motion, and physical exercise training aims to improve both range of motion and strength. Ultimately, all these interventions try to improve or retain UE task performance in daily life. In order to optimize clinical management and select appropriate interventions, the working mechanisms that critically constitute a person' s UE function is very important.

The assessment of UE function in boys and men with DMD is commonly done using functional scales, such as the Brooke upper extremity functional rating scale[4], the Performance of Upper Limb (PUL) scale[5], and the Motor Function Measure (MFM) [6]. These scales give good insight in someone's ability to perform UE tasks, but they do not give insight into the underlying biophysical mechanisms leading to those impairments. Better understanding of these mechanisms, however, is important to support individual clinical decision making and optimize clinical management. For the lower extremity, the working mechanisms underlying reduced walking performance are assessed using gait analysis, in clinical settings as well as in research[7]. Until now, there is no standardized assessment for evaluating the working mechanisms of the UE in DMD patients.

In a previous study we described UE function in boys and men with DMD using a wide variety of physiological outcome measures and functional scales[8]. Although this study gave new insights in UE decline across the different stages of the disease, this study was descriptive and did not aim to identify the critical biophysical mechanisms resulting in UE limitations. Therefore, the aim of this study was to identify critical physiological outcome variables underlying reduced UE task performance in DMD. These critical variables were used to propose an explanatory biophysical model of the UE working mechanism in DMD.

METHODS

Population

The study population consisted of 23 boys and men with DMD (mean age 14.1 years, range 8-21 years). DMD patients were included if they had a DNA established DMD diagnosis, a Brooke scale of 1-5[4], and if they were older than 6 years. Patients were recruited through the Radboud University Medical Center outpatient clinic and by an advertisement on the website of the Dutch Duchenne Parent Project (organization run by parents of DMD patients). This study was approved by the medical ethical committee Arnhem–Nijmegen in the Netherlands (Registration number 2012/135, NL nr.: 39126.091.12). Informed consent was obtained from all subjects and from their parents when subjects were under 18 years of age.

Outcome measures

The outcome measures and procedures used in this study are concisely described below. For full details on the outcome measures and procedures we refer to Janssen et al.[8].

The Brooke upper extremity functional grading scale[4] and the Performance of Upper Limb (PUL) scale[5] were used to assess UE task performance. The physiological outcome measures we used were: maximal muscle torque, maximal sEMG amplitude, muscle thickness, echogenicity and maximal active and passive joint angles. Maximal muscle torque (measured with a static frame myometer), and maximal sEMG amplitudes (Zerowire EMG, Aurion, Italy) were recorded during maximal voluntary isometric contractions (MVICs) of 7 muscles of the right arm (Trapezius (descending part), Biceps Brachii (long head), Triceps Brachii (long head), Deltoid (lateral part), Pectoralis Major (clavicular head), wrist flexors and wrist extensors). Echogenicity and muscle thickness were calculated for the same muscles except for the Pectoralis Major, because the location of this muscle did not allow for reliable ultrasound measurements. Passive and active joint angles were obtained using three dimensional motion analysis (Vicon, Oxford Metrics, Oxford, UK.), in combination with the kinematic model of Jaspers et al.[9]. Passive joint angles were determined for: 'shoulder abduction', 'elbow flexion', 'elbow extension', 'pronation', 'supination', 'wrist flexion', 'wrist extension', 'ulnar deviation' and 'radial deviation'. Similar active joint angles were determined, including two more shoulder angles: 'shoulder flexion' and 'horizontal shoulder adduction'.

Statistical analysis

Statistical analysis was performed on individual outcome measures (scores per muscle/joint) as well as on sum scores. The sum scores were calculated by adding the results of all values of individual muscles/joints for one outcome measure. If one or more values were missing, the sum score was also reported as missing. If values were missing because patients were physically unable to perform the activity, a score of 0 was used for the calculation of the sum scores. Spearman correlation coefficients

were calculated between all sum scores, and between functional scales and individual physiological outcome measures. Correlations of the Brooke scale and PUL sum score with physiological outcome measures (muscle torque, sEMG amplitude, echogenicity, muscle thickness, and active and passive joint angels) were used to identify the critical outcome variables responsible for reduced UE task performance. Stepwise multivariable linear regression analysis using functional scales (Brooke and PUL scale) as dependent variables and sum scores of physiological outcome measures as independent variables was used to determine which physiological measures were significantly associated with task performance. SPSS Statistics Version 20 (IBM, Somers, USA) was used for statistical analysis.

RESULTS

Table 1 describes the Spearman correlation coefficients between all sum scores. Correlations with Brooke scale and PUL score were very high (rs >0.800) for maximal active joint angle sum score, high (rs = 0.600-0.799) for maximal muscle torque and maximal sEMG amplitude sum scores, and moderate (rs = 0.400-0.599) for mean echogenicity Z-score and maximal passive joint angle sum score. No significant relation was found between mean muscle thickness Z-score and Brooke and PUL scale, respectively.

Table 1. Spearman correlation coefficients sum scores

	1	2	3	4	5	6	7	8
1. Brooke scale (N=23)	1							
2. PUL score (N=22)	-0.95**	1						
3. Muscle torque (N=19)	-0.64**	0.71**	1					
4. sEMG amplitude (N=20)	-0.72**	0.67**	0.15	1				
5. Echogenicity (N=22)	-0.54*	0.56**	0.31	0.50*	1			
6. Muscle thickness (N=8)	-0.26	0.48	0.50	-0.26	0.14	1		
7. Active joint angle (N=22)	-0.93**	0.91**	0.55*	0.78**	0.57**	0.38	1	
8. Passive joint angle (N=22)	-0.58**	0.47*	0.33	0.51*	0.34	-0.31	0.69**	1

* Statistical significant correlation (p-value < 0.05) ** Statistical significant correlation (p-value < 0.01)

Table 2. Stepwise multivariable regression analysis

	Brooke scale β (95% CI)	**R^2 change**	**PUL score β (95% CI)**	**R^2 change**
Max. muscle torque sum score (Nm)	-0.015 (-0.028; -0.003)	0.04	0.181 (0.025; 0.338)	0.03
Max. sEMG amplitude sum score (mV)				
Mean echogenicity Z-score				
Mean muscle thickness Z-score				
Maximal active joint angle sum score	-0.004 (-0.005; -0.003)	0.88	0.066 (0.049; 0.083)	0.85
Maximal passive joint angle sum score			-0.054 (-0.093; -0.016)	0.06
	R^2=0.907		**R^2=0.938**	

Multivariable regression analysis (table 2) showed that both maximal active joint angle sum score and maximal muscle torque sum score were significantly associated

Table 3. Spearman correlation coefficients between functional scales and physiologic outcome measures (individual scores)

	Brooke scale (r_s)	N	PUL score (r_s)	N
Maximal muscle torque (Nm)				
Trapezius	-0,595**	22	0,591**	21
Biceps	-0,755**	22	0,816**	21
Triceps	-0,730**	21	0,673**	21
Deltoid	-0,583**	20	0,684**	20
Pectoralis major	-0,723**	22	0,768**	21
Wrist flexors	-0,485*	20	0,508*	20
Wrist extensors	-0,640**	20	0,648**	20
Maximal sEMG amplitude (mV)				
Trapezius	-0,642**	23	0,542**	22
Biceps	-0,557**	22	0,443*	21
Triceps	-0,767**	23	0,722**	22
Deltoid	-0,661**	21	0,674**	20
Pectoralis major	-0,738**	23	0,752**	22
Wrist flexors	-0,564**	23	0,522*	22
Wrist extensors	-0,482*	23	0,398	22
Z-scores Echogenicity (1/3 ROI)				
Trapezius	-0,270	22	0,364	21
Deltoid	-0,586**	23	0,573**	22
Biceps	-0,367	23	0,365	22
Triceps	-0,431*	23	0,346	22
Wrist flexors	-0,637**	22	0,593**	21
Wrist extensors	-0,320	22	0,408	21
Z-scores Muscle Thickness				
Trapezius	-0,180	17	0,260	17
Deltoid	-0,214	15	0,236	14
Biceps	0,077	17	-0,043	16
Triceps	-0,642*	12	0,529	12
Wrist flexors	-0,003	17	0,028	17
Wrist extensors	0,124	21	0,005	21
Maximal active joint angles				
Shoulder flexion	-0,866**	23	0,842**	22
Shoulder abduction	-0,866**	23	0,846**	22
Shoulder adduction†	-0,884**	23	0,904**	22
Elbow flexion	-0,472*	23	0,321	22
Elbow extension	0,056	23	-0,241	22
Pronation	-0,407	23	0,288	22
Supination	0,565**	23	-0,481*	22
Wrist flexion	0,471*	22	-0,450*	21
Wrist extension	-0,574**	22	0,411	21
Radial deviation	0,494*	22	-0,467*	21
Ulnar deviation	-0,401	22	0,230	21
Maximal passive joint angles				
Shoulder abduction	-0,569**	22	0,528*	22
Elbow flexion	-0,131	23	-0,015	22
Elbow extension	0,672**	23	-0,609**	22
Pronation	0,004	23	-0,109	22
Supination	0,463*	23	-0,310	22
Wrist flexion	0,462*	23	-0,406	22
Wrist extension	-0,309	23	0,067	22
Radial deviation	0,413	23	-0,294	22
Ulnar deviation	-0,125	23	-0,008	22

* Statistical significant correlation (p-value < 0.05), ** Statistical significant correlation (p-value < 0.01), † Shoulder adduction in the horizontal plane.

with Brooke scale and together explained 91% of the variance in Brooke scale. In addition, maximal active joint angle sum score, maximal passive joint angle sum score and maximal muscle torque sum score were significantly associated with PUL score, and together these variables explained 94% of the variance in PUL score.

Significant correlations between sum scores of physiological outcome measures were found for maximal active joint angle sum score with maximal muscle torque, maximal sEMG amplitude, maximal passive joint angle sum scores and echogenicity Z-score (rs = 0.55, 0.78, 0.69 and 0.57); and for sEMG amplitude with echogenicity Z-score and passive joint angle sum score (rs = 0.50 and 0.51).

The Spearman correlation coefficients between functional scales and individual (muscle/movement specific) physiological outcome measures are shown in table 3. Muscle torques of the Biceps, Triceps, Pectoralis major and Wrist extensors showed high correlation coefficients (rs > 0.6) with both Brooke scale and PUL score, as did maximal Deltoid torque with PUL score (rs = 0,684). Maximal sEMG amplitudes of the Triceps, Deltoid and Pectoralis major muscles correlated strongly with both Brooke scale and PUL score, while maximal Trapezius sEMG amplitude correlated strongly only with Brooke scale. Regarding echogenicity, moderate but significant correlations were found of Deltoid and Wrist flexor echogenicity with Brooke scale and PUL score. For muscle thickness, only the Triceps muscle significantly correlated with Brooke scale (rs = -0,642). Maximal active joint angles of the shoulder movements (flexion, abduction, adduction) correlated very strongly (rs > 0.8) with both Brooke scale and PUL score. Passive maximal elbow extension angle showed a high correlation with both Brooke and PUL score, and passive maximal shoulder abduction angle showed a moderate correlation with these scales.

DISCUSSION

This study aimed to identify critical physiological outcome variables underlying reduced UE task performance in DMD. Based on these critical variables we propose an explanatory biophysical model of the UE working mechanism. Critical physiological outcome variables were chosen based on the strength of their associations with functional scales (Brooke and PUL scale) as shown in this study, and on their ability to discriminate between DMD patients in different stages of the disease, as shown in our previous study[8]. Based on these results, we conclude that 'maximal active joint angle', 'maximal muscle torque', 'maximal sEMG amplitude' and 'maximal passive joint angle' are the most critical variables underlying reduced UE task performance in DMD.

Maximal active joint angle sum scores showed the strongest correlation with both Brooke and PUL score and uniquely contributed to their explained variance in the multivariate model. In addition, maximal active joint angle sum score significantly

discriminated between DMD patients in different stages of the disease[8]. The etiological interpretation is that - from a geometrical point of view - the attainable joint positions will directly affect the position of the end effector (task performance). Maximal muscle torque sum score also showed high correlations with both Brooke and PUL scores and uniquely contributed to their explained variance in the multivariate model. This shows that sufficient muscle force is needed to raise the arm against gravity. Moreover, maximal muscle torque sum score discriminated between DMD patients in different disease stages[8]. Maximal sEMG amplitude sum score was also identified as a critical variable, because it showed similar correlations and discriminative ability as maximal muscle torque sum scores. The maximal sEMG amplitude that can be measured is related to the capacity of the muscle, reflected in the amount of muscle fibers that can be depolarized. Maximal sEMG amplitude sum score, however, was not independently associated with Brooke and PUL scale (table 2). Maximal passive joint angle sum score was critical for UE task performance due to its ability to discriminate between DMD patients in different stages of the disease and its moderate correlation with both Brooke and PUL score. In addition, maximal passive joint angle sum score was significantly associated with PUL score. Both echogenicity Z-scores and muscle thickness were not identified as critical outcome variables, as they only showed moderate correlations with Brooke and PUL score. Moreover, we previously found that both ultrasound variables were not able to discriminate between patients with different Brooke scales[8]. Although these measures are intuitively appealing, our results question whether the capacity of a muscle to generate force in DMD can be validly measured using either muscle thickness or echogenicity obtained by ultrasound.

When looking more specifically into the individual muscles and movements that are critical for UE task performance, we found that the maximal muscle torque and maximal sEMG amplitude of mainly proximal muscles showed strong correlations with UE task performance. Proximal muscles are of great importance for movements involving the shoulder and elbow, which is the case in most UE tasks[10, 11]. The more proximal, the more (arm-) weight is loading the muscles. The large influence of proximal muscles/movements on task performance becomes also apparent from the large correlations between maximal active joint angles of the shoulder and UE task performance. It must be realized that even a small decrease in shoulder angle will result in large effects on the hand position at the end of the kinematic chain. Nevertheless, we expect that the function of distal muscles and the ability to perform distal (hand) movements becomes critically important when the disease is progressing. Therefore, clinicians should mainly focus at retaining strength and range of motion of muscles and movements that are most relevant at specific stages of the disease. In other words, clinicians should not focus on abilities that are already lost, but on abilities that can still be retained or potentially improved. Regarding maximal passive joint angles, we see that the joints that are most prone to develop contractures are also most strongly related to task performance. From the literature and previous research we know that passive elbow extension and passive forearm supination are most often

restricted[12, 13], and indeed these movements show a moderate but significant relation with UE task performance. In addition, passive shoulder abduction angle is surprisingly related to UE task performance. Shoulder contractures are not often described in the literature and the passive range of motion is usually still larger than the functional range of UE task performance. However, although the passive range is not critically restricted, increased stiffness of the muscle near its maximal elongation will increase the amount of force needed to move the arms.

The critical physiological outcome measures we identified are grossly in line with the literature. Bartels et al. stated that UE muscle strength and passive range of motion are strongly associated with UE function[12], and Uchikawa et al. showed that activities of daily living in patients with DMD are related to age and muscle strength[14]. To our knowledge, there are no studies published on the relation of both active range of motion and maximal sEMG amplitude with UE task performance. Active range of motion, however, has proven to predict UE function in post stroke patients[15].

For a better understanding of the working mechanisms that could lead to limitations in UE task performance, we constructed an explanatory biophysical model (Figure 1). The construction of this model was based on common knowledge of UE anatomy and physiology and supported by the statistical results of this study. Due to the relatively large amount of variables and the limited number of participants in this study, we were not able to construct a reliable model solely based on statistics.

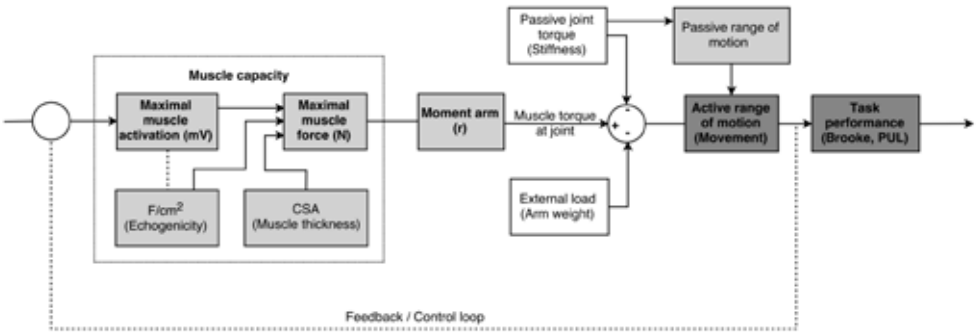

Figure 1. Explanatory biophysical model of the UE working mechanism in DMD
Note: mV = millivolt, N = Newton, F/cm2 = force per square centimeter of muscle, CSA = cross sectional area, r = radius

As indicated in the model, we consider task performance to be dependent on several biophysical characteristics, of which active range of motion is most closely related to task performance. Active range of motion is dependent on passive range of motion and the available muscle torque minus the external load and the passive joint torque. Passive joint torque is defined as the intrinsic torque that develops in the joint when moving due to elastic properties of the muscles around the joint[16, 17]. The available joint torque is based on the muscle capacity, where maximal muscle force is influenced by the maximal muscle activation and by the muscles cross sectional area

(CSA) and the unit of force that can be delivered per area of muscle[18, 19]. In DMD patients, CSA does not significantly differ from healthy subjects, although some muscles show signs of either atrophy or hypertrophy[20-23]. The ability to generate force per area of muscle, however, is much lower compared to healthy controls, due to muscle degeneration (infiltration of fatty and connective tissue) [8, 21-24]. As a result, we expect the influence of CSA on muscle strength in DMD patients to be much lower compared to healthy subjects.

The biophysical model was constructed based on a limited amount of data and variables. So, with the growing amount of knowledge that becomes available regarding UE function in DMD patients, it is possible that other critical variables for UE task performance will be added to the model in the future. Furthermore, the critical variables are determined based on statistical models that assume a linear relation, while in reality the relations might not be linear. Different critical variables may, for example, apply to different stages of the disease. Unfortunately, the limited number of participants in this study did not allow for examining the disease stage dependent relation between task performance and physiological outcome measures. Nevertheless, we believe that our model has several important clinical applications and, to the best of our knowledge, it is the first model attempting to explain the underlying mechanisms causing UE limitations in boys and men with DMD. The model can support the diagnosis of UE impairments at the International Classification of Functioning, Disability and Health (ICF)[25] level of body functions and structures instead of at the ICF activity level. In addition, this model can help to identify the mechanisms by which interventions, such as medication, may affect UE task performance. Based on the most critical physiological variables influencing UE task performance, new outcome measures for clinical trials can be developed and the selection of appropriate interventions can be based on biophysical characteristics.

We concluded that active joint range of motion (a measure of the amount of movement a person can produce) is the most critical biophysical aspect underlying UE task performance. The performance of activities of daily living (ADL) requires sufficient range of motion in multiple joints[10, 11]. As a result, we believe that interventions for improving UE function should be aimed at retaining the ability to use the full range of motion. For this purpose, contracture prevention is of utmost importance, as severe contractures can reduce the reachable workspace and make the performance of ADL more difficult[12, 26]. Despite the fact that research on the prevention of UE contractures is limited, it is recognized that stretching and splinting may be helpful, and that in severe and fixed contractures surgical intervention may be required[27, 28]. In addition, prolonged static positioning of the limb should be prevented[28]. Another intervention that can possibly retain UE range of motion is the use of a dynamic arm support. Dynamic arm supports reduce the effort that is needed to move the arms (mainly against gravity), which in turn reduces the muscle capacity that is needed to perform movements. As a result, the active range of motion of the arms increases and task performance improves.

Improving or retaining muscle strength is very important for UE task performance, and clinicians should consider interventions that can improve muscle strength. Corticosteroid treatment has proven to retain muscle strength[29-31], and also physical exercise training may improve muscle strength of DMD patients[32].

Regarding the ability to activate the muscle, normal nerve conduction velocities are seen in DMD patients[33]. Maximal sEMG amplitudes, however, are much lower in DMD patients compared to controls[8, 34]. These low maximal sEMG amplitudes are likely the result of muscle degeneration, resulting in smaller motor units (less muscle fibers per motor unit)[35]. So, muscle degeneration results in both smaller motor units and the infiltration of fatty and connective tissue in the muscles. This might explain the significant correlation we found between echogenicity (measure for infiltration of fatty and connective tissue) and maximal muscle activity in DMD patients ($r_s = 0.50$).

Next to the physiological factors described above, there are some other variables that may influence UE task performance. For example, chronic pain is known to have a negative impact on general physical functioning[36]. In addition, intrinsic and environmental factors such as muscle/joint stiffness, nutrition, motivation and other emotional aspects may influence task performance. Another important factor that may affect UE task performance is fatigue. Unfortunately, we did not measure fatigability directly and, therefore, (muscle) fatigue was not included in the model. Future research should, however, focus on the relation between fatigability and UE task performance.

There are some limitations of this study that should be mentioned. The sample size was relatively small, in particular regarding the DMD patients in the more advanced disease stages (Brooke 4 and 5). In addition, no longitudinal data were available. Therefore, we could not include in the model data related to changes of variables over time. Nevertheless, we found significant cross-sectional correlations and consider this model valid for a wide range of DMD patients, but further validation studies are necessary. The correlation coefficients we found were based on a linear relationship between variables, while some of these relations may not be linear. Future validation studies should attempt to gain insight in the order of these correlations. Longitudinal data of a large group of DMD patients in different stages of the disease should be collected to establish causal relations between the biophysical variables and to see whether there are other variables that might be added to the model. In this study, we only included participants with a Brooke scale of 1 to 5. In order to see if the model is also valid for the most severely affected patients, future studies should also include patients with a Brooke scale of 6. To this end measurement instruments might need to be adapted to the residual capacity of these patients, for example by focusing on strength and range of motion of the hands.

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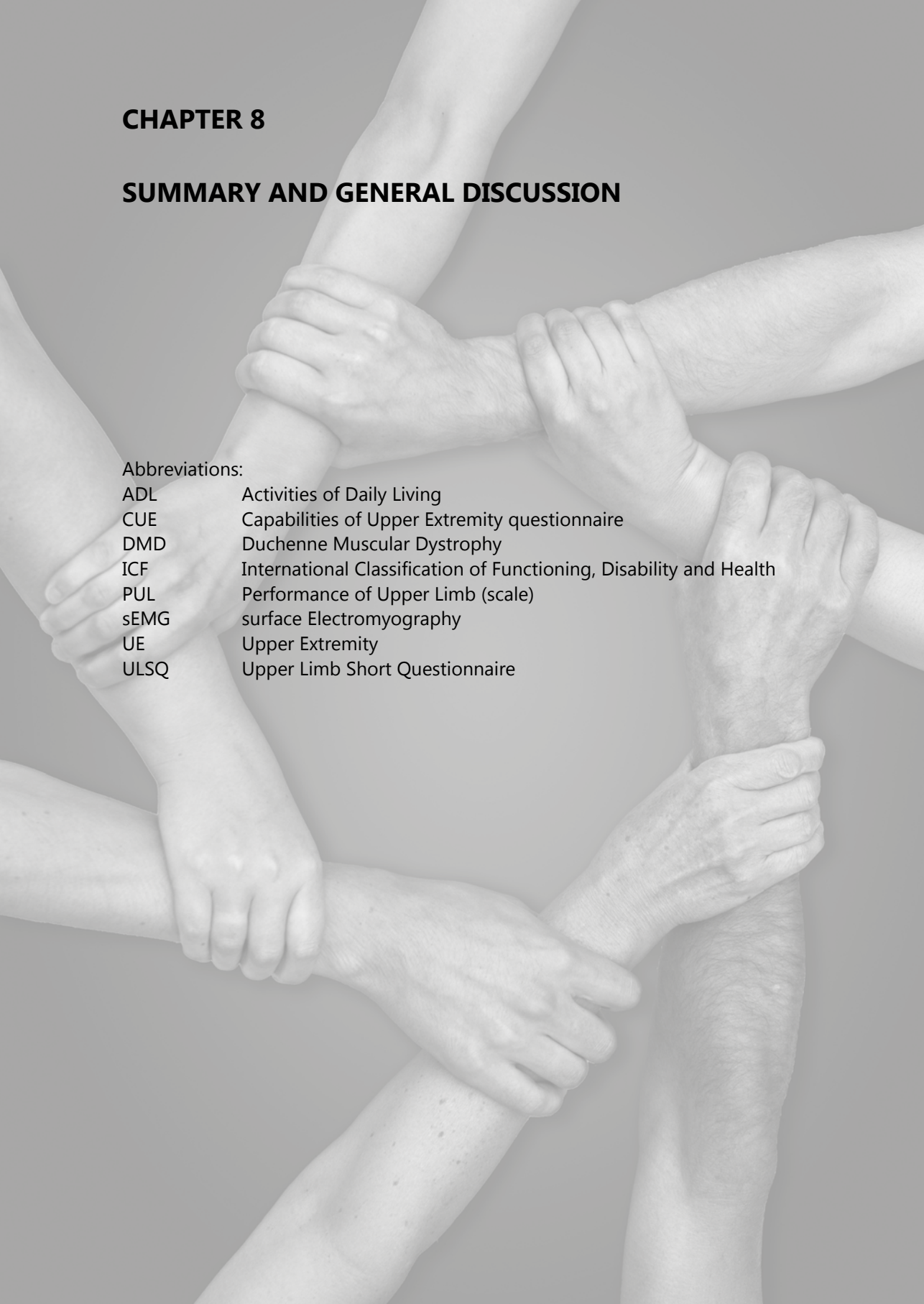
CHAPTER 8

SUMMARY AND GENERAL DISCUSSION



Abbreviations:

ADL	Activities of Daily Living
CUE	Capabilities of Upper Extremity questionnaire
DMD	Duchenne Muscular Dystrophy
ICF	International Classification of Functioning, Disability and Health
PUL	Performance of Upper Limb (scale)
sEMG	surface Electromyography
UE	Upper Extremity
ULSQ	Upper Limb Short Questionnaire

SUMMARY

Duchenne Muscular Dystrophy (DMD) is a genetic X-linked disorder affecting about 1:5000 boys[1]. DMD is caused by mutations in the dystrophin gene, which lead to an absence of, or defect in the dystrophin protein. Dystrophin plays an important role in the mechanical reinforcement of the sarcolemma, thereby protecting the cell membrane from stresses during muscle contraction. Absence of dystrophin makes muscle cells more vulnerable for cell damage, which results in the replacement of muscle cells with fat and connective tissue[2, 3]. As a result, boys and men with DMD will increasingly experience difficulties while performing daily activities. In the early stages of the disease, functions like running and climbing stairs become difficult. Later on, around 12 years of age, DMD patients become non-ambulant and their arms become affected as well. Although there is still no cure for DMD, life expectancy is rapidly increasing due to medical interventions, such as corticosteroid treatment and artificial ventilation[4, 5]. These interventions, however, only delay the loss of functional milestones for a few years. Meaning that boys and men with DMD are in a wheelchair the largest part of their live. Consequently, upper extremity (UE) function becomes increasingly important to maintain independence and quality of life over their life span. For the development of tailored treatments and interventions to retain or improve UE function, more knowledge is needed about the relation between disease progression and UE function and about the extent of UE involvement at the level of specific muscles, movements and activities. In this thesis we aimed to gain more insight in UE function in boys and men with DMD by means of a survey (questionnaires) (**part 1**) and based on biophysical outcome measures (**part 2)**.

PART 1: UPPER EXTREMITY FUNCTION BASED ON THE RESULTS OF AN INTERNATIONAL WEB-BASED SURVEY

Part 1 of this thesis is based on the results of an international web-based survey using questionnaires regarding UE function in boys and men with DMD, in which 213 participants from 14 countries participated. The questionnaire consisted of 4 parts: 'participant characteristics', 'pain and stiffness', 'UE activity', and 'social participation'. Participant characteristics gave insight in the age of onset of symptoms, the age of losing ambulation, use of medication and therapies, the occurrence of scoliosis, and the use of support devices. Pain and stiffness questions were modified from the University of Michigan Upper Extremity Questionnaire[6] and looked into frequency, severity and limitations due to pain and stiffness in the different UE segments. UE activity was examined using the Capabilities of Upper Extremity questionnaire (CUE) [7] and the ABILHAND questionnaire[8]. Concerning social participation, participants were asked whether they went to school, had a job, practiced sports, had hobbies, performed activities with friends, and/or were involved in a romantic relationship.

Using these questionnaires, **chapter 2** aimed to gain insight into the changing patterns of UE function during the course of DMD, focusing on all levels of the

International Classification of Functioning, Disability and Healt (ICF). Four disease stages were defined: 'early ambulatory stage', 'late ambulatory stage', 'early non-ambulatory stage' and 'late non-ambulatory stage'. We found that UE pain, stiffness, and activity limitations increased with disease stage. In contrast to our expectations, UE activity limitations already occurred in the early ambulatory stage, thus, far before ambulation was lost. These UE activity limitations affected social participation, as more than 50% of the participants in the early ambulatory stage indicated that they experienced limitations of their arms and/or their hands when participating in social activities, such as school, sports and hobbies. Despite the existence of UE impairments, only 9% of the respondents used supportive aids. Based on these results, we suggest that clinicians should pay attention to UE limitations already in an early stage of the disease, before patients with DMD lose the ability to walk. In addition, paying attention to adequate interventions, including the management of pain and stiffness, could help to reduce UE activity limitations and related restrictions in social participation.

The questionnaires used in chapter 2 provided useful insights in UE limitations over the course of the disease, however the extensive nature of the questionnaires renders them unfit for application in clinical practice. Therefore, **chapter 3** aimed to gain insight in the underlying dimensions of the questionnaires with the aim to develop a short questionnaire that clinicians can use for stepwise assessment of UE function, pain and stiffness in patients with DMD. This was done by means of factor analyses performed on the questions regarding UE function and activity, pain and stiffness. In addition, this chapter aimed to investigate the construct validity of the identified factors in boys and men with DMD. In total, 14 factors were identified. All had high internal consistency (Cronbach's alpha >0.89) and explained 80-88% of the variance of the original questionnaires. Construct validity was supported, because participants in the early ambulatory stage performed significantly better ($p < 0.001$) than participants in the late non-ambulatory stage. The factors identified from the set of questionnaires provided a valid representation of UE function, pain and stiffness in DMD. Based on the factor communalities, the Upper Limb Short Questionnaire (ULSQ) was constituted. The ULSQ might be a useful tool for investigating UE function of boys and men with DMD in clinical practice, and it could be used as an outcome measure in clinical trials. The validity, reliability and applicability of the ULSQ, however, will have to be examined in future studies.

The aim of **chapter 4** was to gain insight into the variables associated with UE function in boys and men with DMD. This was done by performing multivariable linear regression analyses, where the factors regarding UE function (based on chapter 3) were used as dependent variables. In addition, 26 variables regarding patient characteristics, medication, therapy, supportive aids, pain, stiffness and participation were included as independent variables. A total of twelve independent variables were associated with UE function. Variables with a negative association with UE function were: later disease stage, occurrence of scoliosis, higher age, use of UE splints, more

frequent stiffness complaints, more UE limitations due to stiffness, more frequent elbow pain, and having physical therapy. A positive association with UE function was seen for: going to school or work, use of corticosteroids, higher BMI, and higher age at diagnosis. These variables explained 56–81% of the variation of the different measures of UE function. Some of the variables associated with UE function can be influenced by clinical management, therefore, good clinical management of these variables might have a role in the reduction of UE limitations. The results of this study suggest that corticosteroid use and participation in school and work related activities are positively related to UE function in DMD patients. In addition, the reduction of pain and stiffness complaints and the prevention of scoliosis could also be beneficial for the preservation of UE function.

PART 2: UPPER EXTREMITY FUNCTION EXPLORED BY MEANS OF BIOPHYSICAL OUTCOME MEASURES

Part 2 of this thesis aimed to quantify UE function using objective, biophysical outcome measures and functional UE scales. **Chapter 5** describes the results of a pilot study aiming to determine the clinical feasibility of surface electromyography (sEMG) in boys with DMD, and to evaluate the construct validity of sEMG by determining if sEMG is able to discriminate between healthy subjects and boys with DMD. Five boys with DMD and 6 healthy controls participated in this study. sEMG signals were recorded from the anterior and lateral parts of the Deltoid muscles and from the Biceps Brachii muscles, while the participants performed single joint movements and activities of daily living (ADL) with their arms. The outcome measures used in this study were normalized sEMG amplitudes for each muscle, which was defined as the maximum sEMG amplitude during task performance as percentage of sEMG amplitude at maximal voluntary isometric contractions of that muscle. The results showed good feasibility, as sEMG signals could be recorded in all subjects. All boys with DMD and healthy controls were able to perform the non standardized movements of the measurement protocol, however, one boy with DMD was not able to perform all the standardized movements as he was not able to perform shoulder movements without using compensatory movements. Construct validity of the sEMG measurements was also confirmed, as we showed that boys with DMD used a significantly larger amount of their maximal muscle capacity for all muscles as compared to healthy controls. We concluded that sEMG measurements of single joint movements and ADL activities are feasible and valid to assess arm-muscle function in boys with DMD in comparison to healthy controls.

Chapters 6 and 7 are based on a study performed in a movement laboratory, in which UE function was assessed using a set of commonly used functional UE scales and biophysical UE outcome measures. Outcome measures used were: Brooke's UE functional grading scale[9], the Performance of Upper Limb (PUL) scale[10], active and passive range of motion, maximal and normalized sEMG amplitudes, muscle torques, echogenicity and muscle thickness. In total, 20 healthy subjects and 23 boys

and men with DMD in different disease stages participated in this study.

Chapter 6 aimed to quantify UE function of healthy subjects and DMD patients over the course of the disease, and to evaluate the relation between physiologic outcome measures and functional UE scales. We saw that the decline in muscle functions (torque, electrical activity, and echogenicity) preceded the decline in the ability to perform movements. As a result, the examination of muscle functions in clinical practice may lead to early detection of upcoming UE limitations, which is important to timely start interventions that will minimize UE decline. Outcome measures related to proximal UE function discriminated better between different disease stages, than outcome measures related to distal UE function. Proximal muscle torque and electrical activity could even distinguish between patients in later stages of the disease, when the ability to perform proximal movements was already lost. Normalized sEMG amplitudes were larger in DMD patients compared to healthy controls, indicating that DMD patients use much more of their muscle capacity to perform the same movements, which probably leads to increased fatigability. This increase in normalized sEMG amplitudes was already present in early disease stages. We also saw that maximal active joint angles are highly related to functional scales ($R2 = 0.88$ for Brooke scale and $R2 = 0.85$ for PUL scale), so preserving the ability to use the full joint range of motion is important to enable the performance of daily activities. Clinical examination of active joint angles could therefore help in selecting suitable interventions for retaining UE function.

The aim of **chapter 7** was to identify critical physiological outcome variables underlying reduced UE task performance in DMD. These critical variables were used to propose an etiologically biophysical model of the UE working mechanism in DMD. Critical physiologic outcome variables were chosen based on their associations with functional UE scales, and their discriminative ability as described in chapter 6. Based on these statistical characteristics, we identified maximal active joint angle, maximal muscle torque, maximal sEMG amplitude, and maximal passive joint angle as the most critical variables underlying UE task performance. In turn, these critical variables were used to construct an explanatory biophysical model of the UE working mechanism in boys and men with DMD (figure 1). This model showed that UE task performance is mainly dependent on the ability to move your arms actively, which is influenced by both passive range of motion and the available joint torque. The available joint torque is dependent on muscle capacity, and should be sufficient to lift the weight of the arm against gravity and to overcome passive joint torque (stiffness). Muscle capacity is influenced by both the ability to activate the muscle and the muscle force that is generated at the joint level. This model may have important clinical implications, however, the model was constructed based on a limited amount of data and needs further validation. Better insight in the mechanisms underlying UE task performance can support diagnosis of UE impairments at the ICF level of body functions and structures in addition to diagnosing UE limitations at the ICF level of activities. Furthermore, the model can help to identify the mechanisms by which

interventions may improve UE task performance. The model could also form the basis for new (composite) outcome measures for clinical trials.

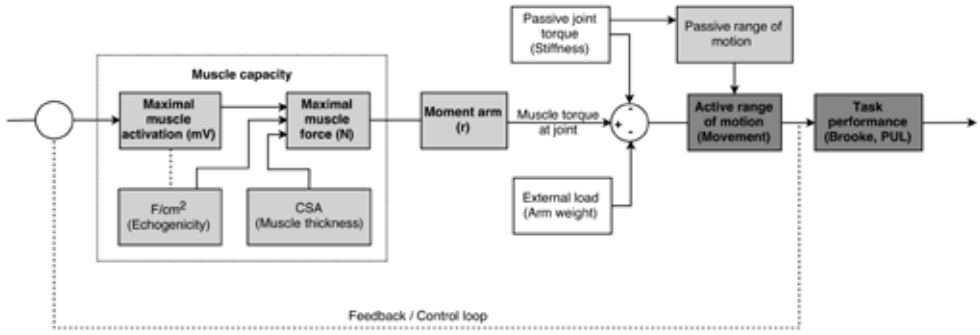


Figure 1. Explanatory biophysical model of the UE working mechanism in DMD
Note: mV = millivolt, N = Newton, F/cm2 = force per square centimeter of muscle, CSA = cross sectional area, r = radius

GENERAL DISCUSSION

In the last part of this thesis, I will emphasize the importance of the UE in DMD. I will show how UE function of healthy subjects compares to patients with DMD, and how UE function changes throughout the course of the disease. In addition, I will elaborate on the predictors of UE function, and I will explain how good clinical management may slow down function UE decline. Furthermore, I will suggest a new instrument for UE assessment in DMD and I will discuss how insight in biophysical measures of UE function can lead to more knowledge of underlying working mechanisms. Finally, the results will be placed in view of the development and evaluation of new arm supports for boys and men with DMD.

Upper extremity function in DMD: trending topic

Life expectancy of patients with DMD has rapidly increased over the last few decades due to medical interventions[4, 11]. In the 1960s, patients with DMD died in their teens, while nowadays they live up to their fourth decade[4, 12]. As a result, more patients reach adulthood. Unfortunately, medical interventions only delayed functional milestones by a few years, meaning that men with DMD are in a wheelchair for the largest part of their lives and experience long-term limitations while performing UE tasks. This increase in life expectancy has shifted the focus of research aimed at the design and evaluation of functional interventions more and more from the lower extremity to the upper extremity. Over the last decade, UE research has increasingly received attention in the literature and several new methods for the evaluation of UE function have been developed[8, 10, 13-15]. In addition, several interventions to improve UE function, such as corticosteroid treatment, physical exercise training and arm supports, have been developed and evaluated[16-19]. However, despite the newly acquired knowledge and interventions, UE limitations cannot be prevented completely and still have huge impact on the quality of life and social participation in boys and men with DMD. Therefore, this thesis aimed to build upon the already existing knowledge and give new and meaningful insights into UE function in DMD. We did this by examining the UE at the ICF levels of body function/structure, activity and participation in a large group of patients with DMD. We focused not only on UE function, but also on UE pain and stiffness, and we explored the mechanism of UE involvement by examining the contribution of individual muscles and movements in relation to functional limitations. These new insights gave us handles to improve clinical care and were used for the development of new interventions.

Attention for upper extremity function in Duchenne Muscular Dystrophy is highly relevant for maintaining functional independence and quality of life.

Progressive nature of DMD and implications for early detection of UE limitations

Due to the progressive nature of DMD, UE function will decline as boys and men get older. Knowledge about the rate of decline and the variability between patients

is, however, limited. In clinical practice, the UE often receives clinical attention only after boys with DMD become wheelchair-bound. Yet, in this thesis, we showed that UE muscle functions are already impaired before ambulation is lost. According to the web-based survey, 44% of the patients in the early ambulatory stage experience limitations when performing items from the Capabilities of Upper Extremity Questionnaire (CUE), and 25% of the patients in the early ambulatory stage experience difficulties when performing ABILHAND activities (chapter 2). Furthermore, we showed that muscle torque, muscle activation, and echogenicity are already abnormal in patients with Brooke scale 1 (i.e., before clear functional limitations are present) when compared to healthy controls (chapter 6). These results indicate that UE limitations are present well before patients with DMD become non-ambulant. Consequently, physicians should focus on early detection of UE limitations in these patients. Early detection might lead to better timing of interventions, for example to prevent joint contractures or to retain UE function and strength by physical exercise. Starting interventions early on during the course of the disease has proven to be beneficial in, for example, corticosteroid treatment[20] and psychosocial therapy[21]. Hence, early interventions are likely to be beneficial for preserving UE function as well.

Early detection of UE limitations and the underlying causes is important for optimizing the efficacy of interventions, and could contribute to the delay of functional limitations.

Upper extremity function in DMD: patterns of decline

The decline of UE functions is not necessarily linear throughout the disease. UE function in individual patients declines at different rates, and not all aspects of UE function decline at the same rate. Distinguishing the patterns of decline is important in clinical practice, as it can help with diagnosing UE limitations and selecting tailored interventions. In this thesis, we identified several patterns of UE functional decline.

Proximal versus distal UE function

The literature on UE impairments in DMD shows that proximal function is lost before distal function[22-24]. There is, however, some discussion on the rate of decline and the order in which UE functions are lost at a muscular level. In this thesis we were able to study UE decline in a large group of patients with DMD and showed that the inability to perform basic as well as complex movements starts with difficulties making shoulder movements, followed by difficulties while moving the elbow, wrists and hands (chapters 2 and 6). The decline of shoulder function starts already in the early ambulatory stage, for example, while lifting heavy objects (chapter 2). Later on, even lifting one's own arm becomes difficult, which limits the ability to move across the full range of motion (chapter 6). The inability to perform activities that require elbow movements starts around the time of wheelchair confinement. At that time, elbow flexion contractures develop, as they are directly related to prolonged static

positioning of the upper limb in flexion following wheelchair confinement [23]. Initially, elbow activities with additional weights are difficult, while later on even lifting one's own forearm becomes problematic. Limitations in wrist and hand movements occur mainly in the latest stages of the disease. Also in these joints, functional limitations coincide with joint contractures. Examples of such joint contractures are limitations in passive supination of the forearm and passive extension of the wrist[25], digital muscle shortness, boutonnière and swanneck deformities, and hyperextension of the digital interphalangeal joints[26]. Despite these contractures, the ability to manipulate small objects with the fingers remains, remarkebly, well preserved in many patients (chapters 2 and 6).

Compensatory mechanisms

When boys and men with DMD become weaker, compensatory mechanisms are often used to preserve the ability to perform UE tasks. The compensatory mechanisms that are used by these patients show a pattern throughout the stages of the disease and could help identifying the amount of muscular weakness in a clinical setting. The first compensatory mechanism is the activation of supporting muscles (chapters 5 and 6). Muscles that normally are not (or minimally) activated when performing a task become activated when the primary muscles needed for that task have reached their maximal capacity. sEMG analysis gives insight in the use of compensatory muscles and can help with diagnosing early UE limitations. When the activation of supporting muscles becomes insufficient, patients often try reducing the mechanical effort needed to perform a task, for example by using a different movement strategy. Joint torque can, for example, be reduced by bringing the weight of the arm closer to the body by flexing the elbow when performing shoulder movements (chapter 6). If this mechanism becomes insufficient as well, patients often use trunk movements and swinging movements to reduce the amount of muscle force needed to lift the arms, for example, by swinging the trunk laterally in order to accelerate the arm upward[27]. This use of compensatory trunk movements can also be seen in ambulatory boys during stair climbing[28]. When swinging movements become insufficient, the edge of the table or arm rest on the wheelchair may be used as a lever to flex the elbow with less force. Another compensatory mechanism that is often observed is the use of one arm or the mouth to support the other arm in order to maximize the force that can be used to perform a task. When compensatory mechanisms become insufficient, the ability to perform daily activities is gradually lost.

Muscle functions versus activity level

For successful performance of movements, many requirements need to be met. Firstly, sufficient joint range of motion is needed, followed by sufficient muscle capacity and finally one needs adequate movement control. In boys and men with DMD, impairments in muscle function are the primary causes of the inability to perform daily activities. We found that a decline in muscle functions is already seen before activity limitations occur. Muscle degeneration (i.e., the infiltration of fatty and connective tissue in the muscle), loss of muscle force/torque, and reduced electrical

muscle activity are observed already when boys with DMD are still ambulant (chapter 6). Despite this early decline in muscle functions, UE activity limitations only develop in a later stage. Apparently, only when muscle strength reduces below a certain level, people lose the ability to perform specific activities. In chapter 6, we have seen that when the maximal Deltoid torque drops below approximately 10Nm, patients start to get difficulties lifting their arms, so that level might be considered as a threshold. Similarly, a maximal Biceps torque below approximately 5Nm is related to limitations in the performance of elbow movements. When looking at the activity level, we see that tasks that require lifting weights become difficult in an early stage of the disease (chapters 2 and 6), which can be expected as such tasks increase the torques needed around the shoulder and elbow. Eventually, further decline in muscle strength will result in the inability to lift one's arm, which critically reduces the ability to perform daily activities and, therefore, increases one's dependence on others.

Pain versus stiffness

Different patterns can also be distinguished for UE pain and stiffness. On average, stiffness complaints are more frequent and severe, while also more limitations are experienced due to stiffness compared to pain. In addition, pain complaints seem to increase quite gradually as the disease progresses, while stiffness complaints remain rather constant during the first stages and increase only in the late non-ambulatory stage (chapter 2). Despite the increasing pain and stiffness scores in the more advanced stages of the disease, average pain and stiffness scores in patients with DMD remain low, even in the latest stages. On average, patients experience UE pain only a few times a year, while pain severity and UE limitations due to pain on average do not score above 1.5 out of 10. Although stiffness scores are about twice as high as pain scores, they are relatively low compared to other neuromuscular disorders[29]. Unfortunately, we did not collect normal (reference) data using the same measurement instrument, therefore, we cannot compare pain and stiffness experienced by patients with DMD to a healthy reference population.

Despite the average pain and stiffness scores being quite low, the percentages of patients with DMD that experience pain and stiffness are substantial. In chapter 2 we reported the percentage of patients that experienced pain based on a pain/stiffness combination score above 1. This value, however, is relatively hard to interpret, because it does not account for pain and stiffness severity. Therefore, we recalculated the percentage of respondents that experienced pain or stiffness in a different manner, which better compares to the literature (see Table 1). Here, we calculated the pain and stiffness sum scores (the sum of all segments and categories (frequency, severity, limitations)) as a percentage of the maximal possible score. This percentage also accounted for pain and stiffness severity and allowed us to define the percentage of patients that experienced no, mild, moderate, and severe pain and/or stiffness, based on the classification described in literature[30]. Over 50% of the respondents experienced at least mild pain and/or stiffness. In the last stage of the disease, this percentages increased, while pain and stiffness became more severe.

Therefore, we consider the examination of both pain and stiffness important for regular clinical practice. Especially stiffness seems to be an underestimated problem in patients with DMD and deserves more attention in clinical practice. In addition, it should be recognized that both pain and stiffness can influence the effects of UE interventions. For instance, the effect and safety of physical exercise training and the use of dynamic arm supports are influenced by the occurrence of pain and stiffness complaints[31, 32].

Table 1. Percentage of respondents that experienced pain or stiffness

	Total (N=213)	Early ambulatory stage (N=66)	Late ambulatory stage (N=29)	Early non-ambulatory stage (N=24)	Late non-ambulatory stage (N=94)
Pain					
No pain	46	73	52	38	28
Mild pain	50	27	48	54	65
Moderate pain	4	0	0	8	7
Severe pain	0	0	0	0	0
Stiffness					
No stiffness	45	65	52	46	28
Mild stiffness	40	32	41	50	43
Moderate stiffness	7	0	7	0	13
Severe stiffness	9	3	0	4	17

Social participation

At the ICF level of participation, we saw that UE limitations result in mild participation restrictions in more than 50% of the patients with DMD already during the early ambulatory stage (chapter 2). Severe restrictions in participation at school occur more often during the late non-ambulatory stage, while severe restrictions in sports related activities are present already in the early non-ambulatory stage. Participation restrictions during the performance of leisure activities (hobbies) dramatically increase during the late non-ambulatory stage. These results indicate the importance of retaining UE function for preserving social participation. As (minor) participation restrictions may already occur in a very early stage, interventions to optimize social participation should start as early as possible. One intervention that could both help retaining UE function and optimize social participation is being involved in sports, preferably in a team[33].

Model of decline

Figure 2 shows a model of functional decline in DMD, summarizing several key statements made in this thesis. This model includes decline of ambulation, UE muscle capacity, and UE task performance. Based on the results presented in this thesis, it can be concluded that loss of muscle capacity precedes functional decline (1), and UE functional decline starts already before ambulation is lost (2). In addition, functional decline can be categorized in three stages. The first stage (A) resembles

the natural reserve. In this stage, one is still able to function normally, while muscle capacity already has started to decline. The second stage (B) is the compensatory stage, where muscle functions have declined further and make normal functioning impossible. However, in this stage one is still able to perform daily activities when using compensatory mechanisms. The final stage (C), is the stage where one losses the ability to perform daily activities. The rate of functional decline can be influenced by interventions. Corticosteroids can for example slow decline of muscle capacity and functional decline of the upper and lower extremity, and arm supports can prolong the ability to perform UE tasks. Note that this model shows functional decline at a group level not taking into account the individual variation, therefore the model may not apply to all individual DMD patients. In addition, the figure presents decline as a linear curve, however, in reality a more stepwise curve applies better to functional decline in DMD patients, as they often quite suddenly lose the ability to perform a task.

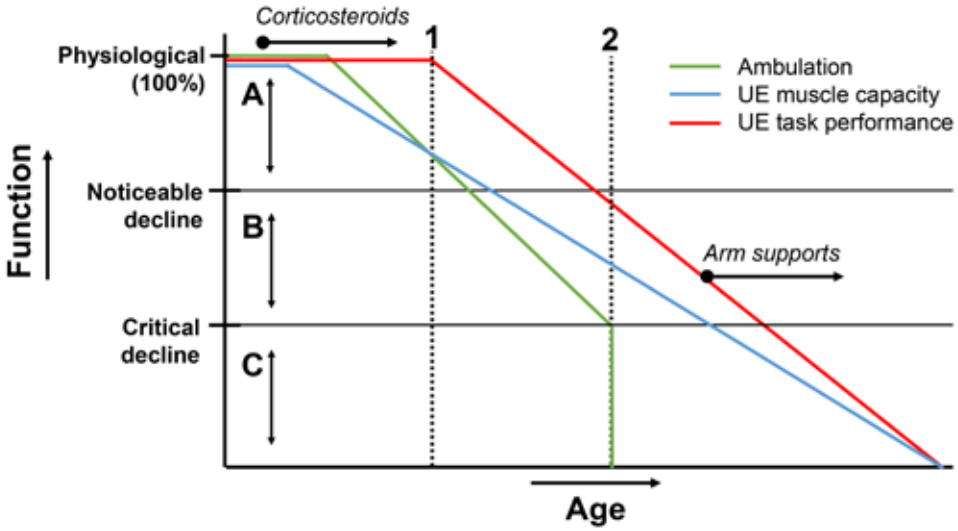


Figure 2. Model of functional decline in DMD.
A: natural reserve, B: compensatory phase, C: loss of function. 1: loss of muscle function precedes functional decline, 2: UE function decline starts already before losing ambulation

Insight in the patterns of decline of upper extremity function facilitates the diagnosis and clinical management of related functional limitations in patients with Duchenne Muscular Dystrophy.

Feasible and valid measures of upper extremity function in DMD

Many UE outcome measures have been developed over the last decades, covering multiple domains of the ICF. All of these outcome measures have their own clinimetric properties and focus on different aspects of UE function. In search for the most feasible and valid outcome measures of UE function in (non-ambulatory) boys and men with DMD, several studies have been published. In 2012, Mercuri et al.

reported the results of an international workshop on the assessment of UE function in DMD[34]. They examined the pros and cons of several functional UE assessment scales and concluded that none of these scales covered the whole spectrum of UE abilities in ambulant and non-ambulant boys with DMD. In the same year, Mazzone et al. published a review of functional assessment tools for the UE in DMD[35] that included both observational and self-reported outcome measures at the ICF activity level. They concluded that each scale provides useful information, but none reflects all the different levels of UE function in individuals with DMD. In 2015, Connolly et al. published a study on the reliability of outcome measures in non-ambulatory boys and men with DMD. They investigated physiological UE measures, such as muscle force and joint range of motion, as well as UE self-assessment tools and functional scales. They found that most outcome measures showed high or excellent reliability, but their feasibility, validity and responsiveness could be improved[36].

Based on these studies, we believe there is a lack of outcome measures that describe multiple dimensions of UE function, as most outcome measures focus either on the ICF level of body functions and structures or on the ICF activity level. In addition, there are relatively few scales that are easily applicable in clinical practice in terms of time consumption and equipment needed. The Upper Limb Short Questionnaire (ULSQ) (chapter 3) is a shortlist for the assessment of UE function, pain and stiffness. It consists of 14 questions regarding pain and stiffness, next to questions about the UE activity limitations. We have shown that on average more than 50% of the boys and men with DMD experience pain and stiffness in their upper limbs. In the later stages of the disease these percentages rise above 70% (table 1). This indicates that UE pain and stiffness are relevant problems and that clinicians should take pain and stiffness into account when examining UE function. The ULSQ might be a feasible and valid tool for this purpose, however, its validity should be further examined before the ULSQ can be used in general practice.

Currently, most clinical trials are focused on walking ability, and most outcome measures are therfore also related to ambulation[37, 38]. However, the majority of the patients with DMD is not ambulant anymore. This means that a lot of people with DMD are not eligible to partcipate in clinical trials, while new treatments might benefit those patients as well. In addition, participation of non-ambulant patients in clinical trials could benefit the feasibility of such trials as well, because more patients can be included. However, before non-ambulant patients can be included in clinical trials, valid, responsive and reliable outcome measures for the upper extremity are needed. Outcome measures that are currently most often used for UE assessment are the Motor Function Measure (MFM)[13] (dimension 3) and the Performance of Upper Limb (PUL)[10]. These, however, suffer from floor and ceiling effects in the early ambulatory and late non-ambulatory disease stages, and do not give insight in the underlying mechanisms of the activity limitations that those instruments examine. A solution to overcome these limitations is to add physiological outcome measures to clinical trials. We have shown that muscle capacity is already reduced

in the early ambulatory stage and keeps declining up to the late non-ambulatory stage. In addition, we have shown that muscle capacity is strongly related to UE task performance.

While there are some ideas to measure a persons capacity as mentioned above, there are still no outcome measures that can assess UE function at the ICF level of 'performance' (i.e., a qualifier of the ICF activity level that refers to the actual behaviour in daily life). Although the name of the Performance of Upper Limb (PUL) scale suggests otherwise, it is aimed at the ICF level of 'capacity' (a qualifier of the ICF activity level that refers to the motor behaviour under optimal test conditions). We expect that measuring performance in daily life can give useful additional insights in UE related problems in DMD. Performance is, for instance, not only dependent on the UE capacity, but also on the (mental and physical) effort that is required to (repeatedly) perform a task in daily life, which is strongly related to fatigability and quality of life. Therefore, we recommend the development of valid measures of UE performance.

New upper extremity outcome measures in Duchenne Muscular Dystrophy should focus on both physiological measures of underlying impairments (e.g. muscle force, muscle activity and range of motion) and measures of daily life performance.

Variables associated with upper extremity function in DMD - leads for treatment

Unravelling underlying impairments can be of great importance for the clinical management of UE activity limitations in patients with DMD. In chapter 7, we propose a biophysical model, which contains several critical variables that influence UE task performance. All the biophysical variables in this model can, directly or indirectly, be influenced by interventions. Figure 3 shows the biophysical model described in chapter 7, as well as possible interventions that can influence the different variables at each level of the model. Interventions are based on the model of interdisciplinary management of DMD [21, 39]. In addition to these interventions aimed at the biophysical level, there are interventions that may influence UE function by affecting relevant determinants as discussed in chapter 4.

Corticosteroid treatment

Several studies have shown that corticosteroids delay UE functional decline in DMD[40-43]. Corticosteroid treatment improves muscle strength and decreases muscle degeneration by reducing inflammation damage and fat deposition in the muscles[16, 44]. Starting with corticosteroid treatment is recommended in the plateau phase of the disease (when motor skills no longer improve, but functional decline has not yet set in), which is roughly between 4-8 years[21].

Physical activity

In chapter 4 we have shown that going to school and working are positively associated

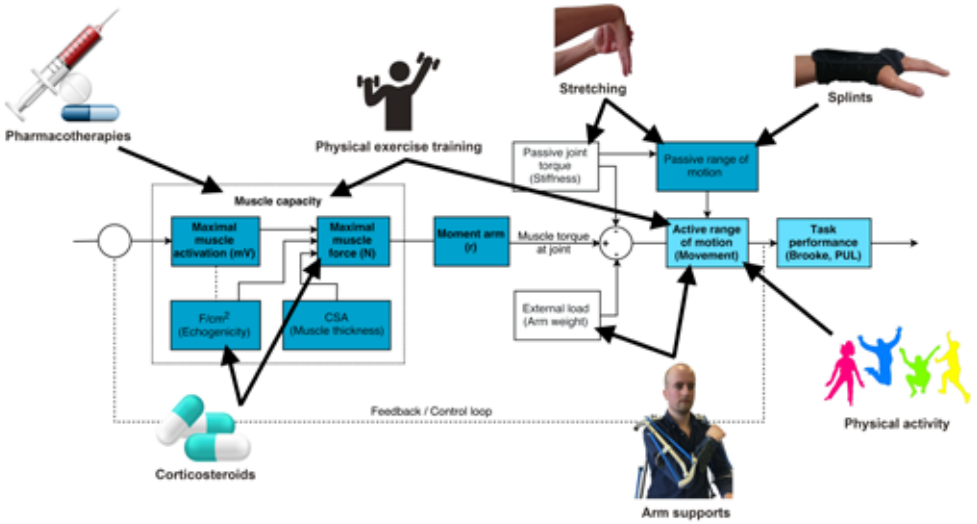


Figure 3. Biophysical model of the UE working mechanism in DMD, including treatment options at different levels

with UE function. We speculated that this might be due to the fact that patients who participated in school or work activities are probably more active than patients who do not participate in such activities. Higher levels of physical activity can indeed be related to less functional dependency[18, 45]. It is, however, well known that the physical activity level of boys and men with DMD is much lower than the activity level of healthy control subjects[46].

Physical exercise training might be an intervention that can enhance the physical activity of patients with DMD by improving or retaining UE function[18, 19]. Physical exercise training should start in an early stage of the disease to prevent 'disuse'[18]. Too much training can, however, also induce (muscle) fatigue, with possibly a negative impact on the level of physical activity in the long term. A solution to overcome this ambiguity might be the use of dynamic arm support during physical exercise training[17].

Contracture prevention and treatment

Chapters 6 and 7 have shown that a reduced passive range of motion (i.e. contractures) negatively influences UE function. Hence, preventing contractures is of utmost importance to retain UE function. Although research on the prevention of UE contractures in DMD is limited, it is assumed that stretching and splinting of the UEs may be beneficial in the phase when ambulation is lost[39]. Stretching might also reduce stiffness and pain complaints[12]. Prevention of a prolonged static body position in the wheelchair may also reduce contracture formation, as occurrence of elbow contractures is related to the age of wheelchair confinement[23, 47]. When contractures are severe and fixed, surgical intervention may help to improve UE posture and function.

Arm supports

Dynamic arm supports can compensate for gravitational forces and, thereby, reduce the forces needed to lift the arm. Such arm supports will promote daily activities and reduce physical fatigue[27]. Within the Flextension A-Gear project we have worked on the development of a new dynamic arm support for boys and men with DMD that can support the arms during activities of daily living. An overview of the Flextension A-Gear project can be found in box 1.

Regarding dynamic arm supports, we expect that a timely start will be beneficial for initiating a training effect and preserving UE function. Passive arm supports (without motorized actuators) might be beneficial as soon as a patient starts to experience lack of strength or increased fatigue during UE activities. Active (motorized) arm supports can be used when passive arm supports become insufficient. The amount of support given by any device should preferably be adaptable to prevent 'disuse'.

Prevention and treatment of scoliosis

In chapter 4, we have shown that scoliosis has a negative effect on UE function. In addition, scoliosis surgery is known to have a negative effect on arm function[48]. Therefore, prevention of scoliosis is of utmost importance. Scoliosis in patients with DMD develops mostly around puberty, after ambulation has been lost. Corticosteroids can reduce the risk of scoliosis, however, also increase the risk of spinal fractures [39, 40]. When scoliosis does occur, surgical spinal fusion can be performed to straighten the spine, prevent worsening of deformity, eliminate pain due to vertebral fracture, and slow the rate of respiratory decline[49]. When spinal surgery cannot be performed, a thoraco-lumbar-sacral orthosis can be considered[39].

Pain management

Adequate pain management may also improve UE function, as pain is known to have a negative effect on general functioning and UE function in particular[50]. Regular pain medication can be used to alleviate pain. It is, however, also important to have a good positioning of the body in the wheelchair and to prevent scoliosis formation to minimize pain complaints.

Pharmacotherapy

Next to corticosteroid treatment there are several other pharmacotherapies that might delay disease progression, or that improve quality of life in patients with DMD. Although many of these therapies are still being investigated in mouse studies and only a few are already being tested in clinical trials, some treatments have already shown a positive effect in small numbers of patients. Because most of these pharmacotherapies aim at a systemic effect, we expect that such therapies affect UE function as well. Currently, there are several types of pharmacotherapies under investigation. Stop codon readthrough agents aim to skip a premature stop codon, which creates an incomplete dystrophy protein, by allowing ribosomes to insert alternative amino acids at the location of the mutant stop codons, so that

translation can continue creating full-length dystrophin[51]. Exon-skipping agents aim to skip faulty exons in pro-mRNA, thereby restoring the reading frame to produce truncated dystrophin, which is similar to the dystrophin found in Becker muscular dystrophy[52]. Utrophin Modulators aim to replace dystrophin by increasing the expression of the Utrophin gene (an autosomal analog of dystrophin, present in fetal muscles[53], which leads to increased Utrophin levels in muscles and may decrease dystrophic symptoms[54]. In addition, there are several symptomatic agents that do not focus on treating the cause of DMD, but on alleviating DMD-related symptoms. These agents aim at preventing muscle damage, reducing inflammation, accelerating muscle repair, increasing blood flow to the muscles, or stopping muscle fibrosis[52].

Knowledge of the impairments underlying upper extremity activity limitations in Duchenne Muscular Dystrophy will help to select appropriate interventions to attenuate upper extremity functional decline.

Upper extremity treatment: individual or population based?

General patterns of UE functional decline can be recognized in patients with DMD (chapters 2 and 6). However, predicting functional decline in individual patients is challenging due to large between-subjects variability. In this perspective, it is important that UE treatment is based on the results of objective measurements of individual UE function across the life span on both the physiological and activity level. We have shown that physiological UE functions and UE activities are related and that specific interventions have optimal effectiveness at specific stages of the disease. Taking this into account, guidelines for UE treatment in DMD, that are based on individual UE function, should be developed. These guidelines should include the already existing knowledge of UE function in DMD, and they should be as generic as possible to make them applicable for a large group of DMD patients. The biophysical model described in chapter 7 may serve as a basis for the development of such guidelines.

Upper extremity treatment in patients with Duchenne Muscular Dystrophy should be individualized, but based on a strong foundation of generic, evidence-based knowledge about prevention of upper extremity functional decline.

The development of new dynamic arm supports

Although many people are working on the development of curative treatment therapies for people with DMD, no such treatment is available yet. Current treatment in DMD is therefore aimed at improving quality of life by preserving functional capacity and performance, and by reducing complications. Within the Flextension A-Gear project (Box 1) we worked on the development of a arm support that fits the needs of people with DMD (as described in the virtual case mention in the introduction of this thesis). But how did the knowledge of UE function in DMD,

gathered in this thesis, help us with the design of such an assistive device?

First of all, the results of the questionnaires helped us with setting the problem definition and goals of the Flextension A-Gear project. We saw that arm supports were only used by a small percentage of the patients with DMD (chapter 2), and that the majority of patients that used an arm support already had very limited arm function (late non-ambulatory stage, Brooke 5). This limited use of arm supports had several causes. Most importantly, the functional gain of using an existing arm support is apparently not sufficient to outbalance the drawbacks, such as expenses and appearance[55, 56]. Therefore, the aim of the Flextension A-Gear project was to develop an inconspicuous (appearance) and natural (functional) arm support that could support the growing needs of boys and men with DMD across their life span. In addition, the results of the questionnaires gave us insight in the activities that caused the biggest problems in daily life due to UE impairments, and in the effects of these UE limitations on social participation. This knowledge helped setting the general requirements for the development of the A-Gear arm supports.

More specific requirements could be based on the knowledge of physiological UE functions, gathered in chapters 5 and 6. The patterns in which UE movements became more difficult and muscles became gradually affected throughout the course of the disease helped defining the required parameters for the passive and active A-Gear. Complementing already existing literature, this thesis showed that proximal UE functions decline before distal UE functions, and therefore proximal functions should be supported first. In addition, we have also shown that in an early stage of the disease only gravitational forces should be supported, while later on movement in the horizontal plane should be supported as well. So, based on the remaining muscle strength, we could set the requirements for the amount of support that is required in the different stages of DMD. In addition, the knowledge of both physiological measures and activity scales was important for defining the outcome measures we used to examine the effectiveness of the prototype arm supports. We expect that both improvements on the activity level and reduction of fatigue are very important features for an arm support. We showed that the passive A-Gear was able to improve arm function and reduce the amount of muscle capacity needed to perform UE movements, which resulted in reduced fatigability[27].

Finally, we have seen that both muscle force and electrical activity could be measured in all stages of the disease, even in adult DMD patients with very limited arm function [31, 57, 58]. Using a computer simulation we showed that even the lowest measured sEMG activity level could theoretically be used to control an actuated arm support[57]. This was a first step towards establishing the feasibility of arm supports for adult DMD patients with minimal UE function. In addition, this knowledge was very important for the design of the control interface of the active A-Gear.

Box 1 - Flextension A-Gear - Conclusions

The goal of the Flextension A-Gear project was to develop an inconspicuous and natural arm support that can support the growing needs of boys and men with Duchenne Muscular Dystrophy (DMD) throughout their daily life span. During the development of this arm support we reached the following conclusions:

Adaptive support
DMD is a progressive disease and, therefore, the level of support should be increased during the course of the disease. The strategy of the Flextension A-Gear project was first to develop a passive system (the Passive A-Gear[27] and, then, to upgrade it to an active system with motorized joints and a control interface (the Active A-Gear[59]). We have developed and implemented EMG- and force-based control interfaces for the Active A-Gear[31, 59]. Comparative studies between EMG and force-based control interfaces indicated that, in general, EMG-based control interfaces are better suited for adults with DMD than force-based control interfaces, because the former systems are experienced as less fatiguing. Nevertheless, force-based control interfaces can be an alternative for those cases in which voluntary forces are higher than the intrinsic forces of the arms.

Inconspicuousness and natural support
The aesthetic appearance of arm supports plays an important role in users acceptance[60-62]. Therefore, our strategy was to make a slender arm support, with the long-term goal that it could be worn underneath the clothing. In addition, we chose to make an "exoskeleton-like" arm support that could mimic the biomechanics of the human arm and trunk allowing natural movements. We found that the design of "close-to-body" structures was challenging, as it compromised balancing quality of the weight compensation mechanism, proper alignment of the human joints with the device, and range of motion. Through the development of the A-Arm[63], a non-wearable and planar active arm support, we investigated an alternative strategy. We found that inconspicuousness could also be reached by simplifying the design and integrating the arm support in the wheelchair of the user. Finally, natural support was addressed by using EMG- and force-based control interfaces, which derive the movement intention from signals that are implicitly related to the intended movement.

Translating clinical knowledge to technical requirements
In order for an arm support to be used in practice, the wishes and abilities of patients should match the design requirements. Upper extremity function of boys and men with DMD, over the course of the disease, was studied using questionnaires and quantitative outcome measures, such as 3D motion analysis, muscle force, surface electromyography, muscle ultrasound and the Performance of Upper Limb scale These studies showed that arm function already starts decreasing in an early stage of the disease. Activity limitations already occur before boys with DMD become non-ambulant and muscle forces deviate from healthy subjects even before

activity limitations are seen (chapters 2 and 6). In addition, different upper extremity muscles deteriorate at a different pace, which warrants the development of adaptive arm supports giving just the right amount of support for individual patients.

Taking these findings into account, we expect that starting the use of an arm support early in the course of the disease might be beneficial. With an arm support, boys are stimulated to keep using their arms, which in turn can lead to a training effect, preventing a vicious circle of 'disuse'[18].

Evaluation of arm supports

Despite the fact that several arm supports are commercially available[64], no studies have systematically compared their efficacy, advantages and limitations. Some publications have described the design and efficacy of a specific arm support [27, 65-67], yet they did not compare these characteristics with other devices. As a consequence, there is a lack of knowledge about which device or working principle is most suitable for a specific type of impairment or task. Within the Flextension A-Gear project, we have evaluated prototypes using both subjective and objective outcome measures[27, 68] and conducted several comparative studies[31, 69] that evaluated the feasibility, efficacy and acceptance of EMG- and force-based control interfaces. These studies assessed the suitability of different arm supports and control interfaces for patients with DMD with different levels of upper extremity function. Similar studies should be carried out to compare the efficacy of current with new arm supports to provide evidence-based clinical recommendations. User requirements such as aesthetics and ease of use should always be taken into account.

Future persepectives

Although the assistive technology developed in the Flextension A-Gear project focused on the specific needs of the DMD population, people with other neuromuscular disorders may benefit from many of the findings of this project. Passive gravity compensation and active assistance based on force- and EMG-based control have been successfully used by people with different neuromuscular disorders[65, 70-74].

The goal of the Flextension A-Gear project was to develop arm supports that could be used in daily life. In the course of this project, however, we have not been able to test our prototypes in the home situation due to time constrains. Future studies should be conducted to test the effectiveness of prototypes over longer periods of time in a home situation. The first steps in this direction are being made in the "A-Gear @ Home" project (figure).

This section is based on the overall work carried out by the Flextension A-Gear Research Team (www.flextension.nl).

Future research

Although current outcome measures of UE functioning in boys and men with DMD primarily focus on the ICF activity level, UE functionioning should be viewed from a broader perspective, including all levels of the ICF (body functions/structures, activities, participation). In addition, outcome measures should not only focus on measuring capacity, but also on measuring daily life performance. We recommend to apply these outcome measures in a large group of DMD patients to find out whether specific patterns of UE functional decline can be recognized and used for the development of new (orthotic/robotic) interventions. In addition, future research should focus on developing and evaluating guidelines for individual UE management, taking into account the proposed biophysical model of UE impairments in DMD. Such guidelines can optimize clinical decision making and prevent unnecessary treatment.

Knowledge of upper extremity functional decline is needed to set the requirements for the development of new interventions, such as passive and active arm supports, making this process a team effort in which clinicians, technicians, researchers and patients should be involved.

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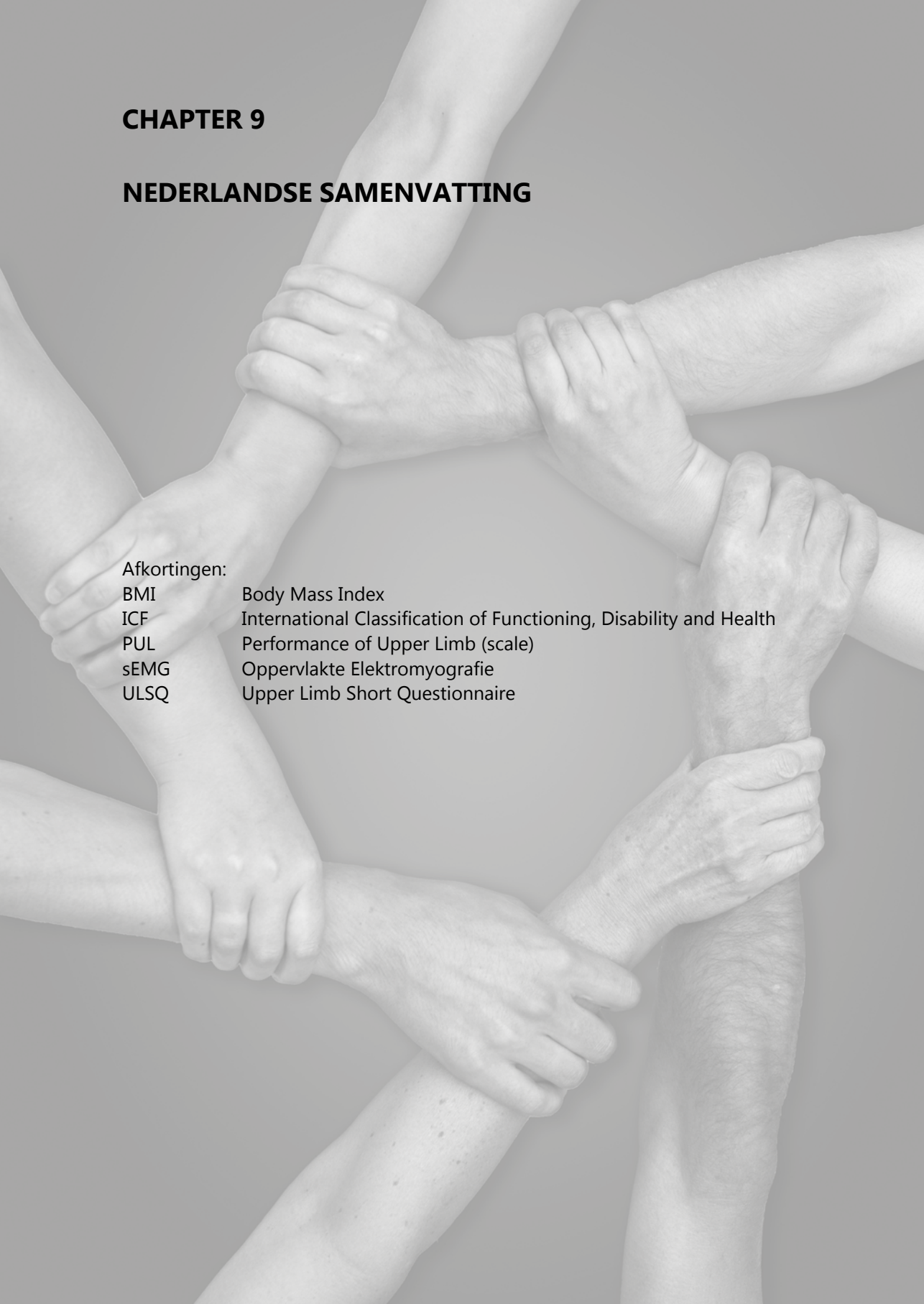
CHAPTER 9

NEDERLANDSE SAMENVATTING



Afkortingen:

BMI	Body Mass Index
ICF	International Classification of Functioning, Disability and Health
PUL	Performance of Upper Limb (scale)
sEMG	Oppervlakte Elektromyografie
ULSQ	Upper Limb Short Questionnaire

SAMENVATTING

Duchenne spierdystrofie is een genetische aandoening welke ongeveer 1:5000 jongens treft. Door een mutatie op het dystrofine gen ontstaat een tekort aan het eiwit dystrofine. Dit eiwit is belangrijk voor de stevigheid van het membraam van spiercellen. Een tekort aan dystrofine zorgt ervoor dat spiercellen kwetsbaar zijn en sneller beschadigen, waardoor spierweefsel wordt vervangen door vet en bindweefsel. Gedurende het leven beschadigen de spiercellen van jongens met Duchenne spierdystrofie steeds verder, waardoor ze steeds meer moeite krijgen met het uitvoeren van dagelijkse activiteiten. In een vroeg stadium van de ziekte zijn vooral functies als rennen, springen en traplopen moeilijk. Later wordt ook het lopen erg moeilijk waardoor jongens met Duchenne spierdystrofie rond hun 12e levensjaar in een rolstoel terecht komen. Vanaf dat moment wordt ook het kunnen uitvoeren van dagelijkse aciviteiten met de armen steeds moeilijker.

Helaas is genezing van Duchenne spierdystrofie nog niet mogelijk, maar de laatste decennia is de levensverwachting van jongens met Duchenne spierdystrofie wel sterk gestegen door inzet van nieuwe medische technieken en hulpmiddelen. Denk daarbij aan behandeling met corticosteroïden, behandeling van scoliose (kromming van de rug) en kunstmatige beademing. Deze behandelingen verlengen het kunnen lopen echter maar met enkele jaren, waardoor jongens met Duchenne spierdystrofie het grootste gedeelte van hun leven in een rolstoel zitten. Door het functieverlies van de benen wordt het zelfstandig kunnen blijven gebruiken van de armen extra belangrijk. Daarom wordt op dit moment onderzoek gedaan naar diverse nieuwe interventies die armfunctie kunnen behouden of verbeteren. Om de ontwikkeling van deze interventies te ondersteunen is kennis nodig over de achteruitgang van armfunctie en over de specifieke spieren, bewegingen en activiteiten die zijn aangedaan. Daarom richt dit proefschrift zich op het onderzoeken van de armfunctie van jongens en mannen met Duchenne spierdystrofie. Dit wordt gedaan door middel van vragenlijsten (**deel 1**) en fysiologische uitkomstmaten (**deel 2**).

DEEL 1: FUNCTIES VAN DE ARMEN GEBASEERD OP EEN INTERNATIONALE VRAGENLIJST

Deel 1 van dit proefschrift is gebaseerd op de resultaten van een internationale, digitale vragenlijst met betrekking tot armfunctie van jongens en mannen met Duchenne spierdystrofie. In totaal hebben 213 deelnemers uit 14 verschillende landen de vragenlijst ingevuld. De vragenlijst bestaat uit 4 onderdelen, namelijk: 'achtergrond informatie', 'pijn en stijfheid', 'arm activiteiten' en 'maatschappelijke participatie'. De verkregen achtergrond informatie geeft inzicht in de leeftijd van diagnose, het verlies van de loopfunctie, het gebruik van medicatie, het hebben van een scoliose en het gebruik van hulpmiddelen. Pijn en stijfheid zijn uitgevraagd met een aangepaste versie van de Michigan Upper Extremity vragenlijst, waarbij gekeken is naar de ernst, frequentie en beperkingen als gevolg van pijn en stijfheid. Arm

activiteiten zijn onderzocht met de Capabilites of Upper Extremity vragenlijst en de ABILHAND vragenlijst. Met betrekking tot maatschappelijk participatie is deelnemers gevraagd of ze naar school gaan, werk hebben, sport beoefenen, hobby's hebben, activiteiten met vrienden doen en of ze een relatie hebben.

Met behulp van deze vragenlijst zijn in **hoofdstuk 2** veranderingen van armfunctie in verschillende ziektestadia beschreven. Daarbij is armfunctie beschreven volgens alle 3 de niveaus van de International Classification of Functioning, Disability and Health (ICF), namelijk het niveau van lichaamsfuncties en structuur, activiteitenniveau en participatieniveau. De ziektestadia die zijn onderscheiden zijn de 'vroeg ambulante fase', de 'laat ambulante fase', de 'vroeg niet-ambulante fase', en de 'laat niet-ambulante fase'. Te zien is dat pijn, stijfheid en beperkingen bij het uitvoeren van activiteiten ernstiger zijn in de latere ziektestadia. In tegenstelling tot de verwachtingen en eerdere beschrijvingen in literatuur is te zien dat beperkingen bij het uitvoeren van arm activiteiten al optreden in de vroeg ambulante fase, dus voordat jongens met Duchenne spierdystrofie rolstoel gebonden raken. Deze beperkingen bij het uitvoeren van activiteiten zorgen ook voor een verminderde maatschappelijke participatie. Meer dan 50 procent van de deelnemers in de vroeg ambulante fase geeft aan dat beperkingen in de armen/handen worden ervaren tijdens participatie in o.a. sport, school, werk en hobby's. Ondanks deze beperkingen gebruikt maar 9 procent van de deelnemers ondersteunende hulpmiddelen voor de armen. Op basis van deze resultaten wordt voorgesteld dat artsen al in een vroeg ziektestadium aandacht moeten besteden aan armfunctie, zodat verlies van armfunctie zo veel mogelijk geremd kan worden. Dit moet gebeuren voordat jongens met Duchenne spierdystrofie in een rolstoel terecht komen. Daarnaast moeten artsen voldoende aandacht besteden aan interventies om armfunctie te behouden en pijn- en stijfheidklachten te verminderen. Dit kan helpen bij het behoud van armfunctie en daardoor ook maatschappelijke participatie bevorderen.

De vragenlijst gebruikt voor hoofdstuk 2 geeft vele bruikbare inzichten in de beperkingen van de armen en handen bij jongens en mannen met Duchenne spierdystrofie. Echter is deze uitgebreide vragenlijst niet geschikt voor gebruik in de dagelijkse, klinische praktijk. Daarom zijn in **hoofdstuk 3** de onderliggende dimensies van de vragenlijst vastgesteld op basis waarvan een korte, klinisch bruikbare vragenlijst is ontwikkeld voor het stapsgewijs onderzoeken van armfunctie, pijn en stijfheid bij jongens en mannen met Duchenne spierdystrofie. Hiervoor is een factor analyse uitgevoerd op de vragen die betrekking hebben tot armfunctie, pijn en stijfheid. Daarnaast is de construct validiteit van de geïdentificeerde factoren onderzocht. In totaal zijn 14 verschillende factoren geïdentificeerd. Deze factoren hebben een hoge interne consistentie (Cronbach's alpha >0.89) en verklaren 80-88% van de variatie van de originele vragenlijsten. Alle factoren zijn in staat onderscheid te maken tussen armfunctie, pijn en stijfheid bij jongens in de vroeg ambulante fase in vergelijking met jongens in de laat niet-ambulante fase. Dit bevestigt de construct validiteit van de factoren. Op basis van de overeenkomsten van de vragen in de verschillende factoren

is een nieuwe vragenlijst opgesteld, de Upper Limb Short Questionnaire (ULSQ). De ULSQ kan een bruikbaar middel zijn voor het onderzoeken van armfunctie, pijn en stijfheid in de dagelijkse praktijk, en kan mogelijk bruikbaar zijn als uitkomstmaat in klinische studies. De validiteit, betrouwbaarheid en toepasbaarheid van de ULSQ moeten echter nog aangetoond worden in toekomstige studies.

Het doel van **hoofdstuk 4** is om inzicht te krijgen in variabelen die geassocieerd kunnen worden met armfunctie van jongens met Duchenne spierdystrofie. Hiervoor is gebruik gemaakt van multivariabele lineaire regressie analyse, waarbij de factoren onderscheiden in hoofdstuk 3 zijn gebruikt als afhankelijke variabelen. Daarnaast zijn 26 onafhankelijke variabelen geïncludeerd, welke betrekking hadden op patiënt karakteristieken, medicatie, therapie, hulpmiddelen, pijn, stijfheid en maatschappelijke participatie. In totaal kunnen 12 onafhankelijke variabelen geassocieerd worden met armfunctie. De variabelen die een negatieve associatie hebben met armfunctie zijn: een later ziektestadium, het hebben van een scoliose (kromming van de rug), hogere leeftijd, het gebruik van hand/arm spalken, vaker last van stijfheid, beperkingen als gevolg van stijfheid, vaker pijn in de elleboog en fysiotherapie. De variabelen met een positieve associatie met armfunctie zijn: naar school gaan of werken, corticosteroïden gebruik, een hoger BMI, en een hogere leeftijd bij diagnose. Deze variabelen samen verklaren 56-81% van de variatie van de verschillende armfunctie uitkomstmaten. Sommige van deze variabelen kunnen beïnvloed worden door goed klinisch handelen en daardoor wellicht invloed hebben op het verminderen van beperkingen in de armen. Voorschijven van corticosteroïden en stimuleren om naar school/werk te gaan kunnen armfunctie positief beïnvloeden. Daarnaast kan het behandelen van pijn en stijfheid en het tegengaan van scoliose de armfunctie positief beïnvloeden.

DEEL 2: FUNCTIES VAN DE ARMEN DOOR MIDDEL VAN FYSIOLOGISCHE UITKOMSTMATEN

Deel 2 van dit proefschrift richt zich op het kwantificeren van armfunctie door middel van objectieve, fysiologische uitkomstmaten en functionele schalen. **Hoofdstuk 5** beschrijft de resultaten van een voorstudie naar de haalbaarheid van het gebruik van oppervlakte elektromyografie (sEMG) voor het in kaart brengen van spieractiviteit, om zo inzicht te krijgen in de beperkingen van de armfunctie bij jongens met Duchenne spierdystrofie. Daarnaast is ook de construct validiteit van sEMG bepaald door te kijken of sEMG onderscheid kan maken tussen gezonde jongens en jongens met Duchenne spierdystrofie. Vijf jongens met Duchenne spierdystrofie en 6 gezonde jongens hebben deelgenomen aan deze studie. sEMG signalen van het voorste en middelste deel van de deltoideus spier en van de biceps brachii spier zijn opgenomen tijdens het uitvoeren van bewegingen met de armen. Genormaliseerde sEMG amplitudes van deze spieren zijn in deze studie gebruikt als primaire uitkomstmaat. Dit is het percentage van de maximale sEMG amplitude gemeten door middel van de maximale vrijwillige isometrische aanspanning die

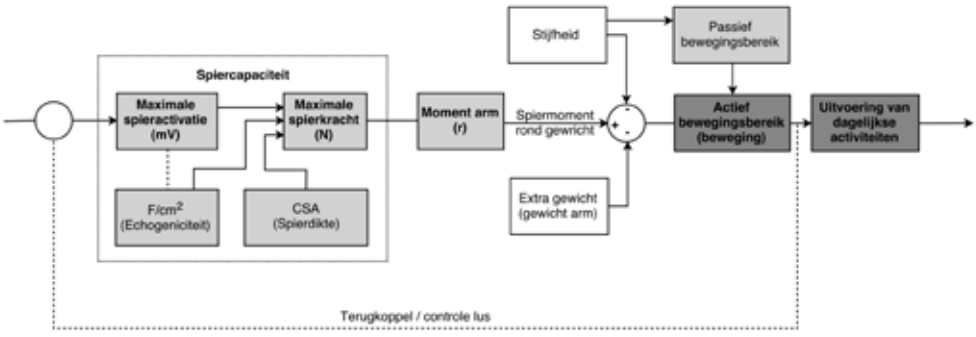
wordt gebruikt voor het uitvoeren van bewegingen. sEMG signalen zijn gemeten bij alle deelnemers, wat aantoont dat het gebruik van sEMG haalbaar is voor jongens met Duchenne spierdystrofie. Daarnaast is ook de construct validiteit van sEMG aangetoond, aangezien jongens met Duchenne spierdystrofie significant meer van hun maximale sEMG amplitude gebruiken tijdens het uitvoeren van bewegingen in vergelijking met gezonde jongens. Daaruit wordt geconcludeerd dat het meten van sEMG tijdens het uitvoeren van bewegingen gebruikt kan worden om functie van de armspieren van jongens met Duchenne spierdystrofie in kaart te brengen.

Hoofdstukken 6 en 7 zijn gebaseerd op een studie uitgevoerd in het bewegingslaboratorium van het Radboud universitair medisch centrum, waarin armfunctie is onderzocht met behulp van verschillende fysiologische uitkomstmaten, aangevuld met enkele veelgebruikte functionele schalen voor de armen. De gebruikte uitkomstmaten zijn: Brooke's upper extremity functional grading scale, de Performance of Upper Limb (PUL) scale, actief en passief bewegingsbereik, maximale en genormaliseerde sEMG amplitudes, spiermomenten, echogeniciteit en spierdikte. In totaal hebben 20 gezonde personen en 23 jongens en mannen met Duchenne spierdystrofie in verschillende stadia van de ziekte deelgenomen aan deze studie.

Hoofdstuk 6 richt zich op het kwantificeren van armfunctie bij gezonde mensen en jongens en mannen met Duchenne spierdystrofie in verschillende stadia van de ziekte. Daarnaast is de relatie tussen fysiologische uitkomstmaten en functionele schalen bekeken. Te zien is dat spier functies (spiermoment, spieractiviteit en echogeniciteit) eerder achteruit gaan dan de mogelijkheid om bewegingen uit te voeren. Het tijdig in kaart brengen van deze spierfuncties is dan ook erg belangrijk voor het vroeg detecteren van achteruitgang van armfunctie in de klinische praktijk, wat vervolgens weer kan bijdragen aan het tijdig starten van interventies voor behoud/ verbetering van armfunctie. Daarnaast is te zien dat uitkomstmaten met betrekking tot proximale functie (o.a. schouder functie) beter onderscheid kunenn maken tussen verschillende ziektestadia, dan uitkomstmaten met betrekking tot distale functie (o.a. pols/hand functie). Spiermomenten en spieractiviteit van proximale spieren kunnen zelfs onderscheid maken tussen de armfunctie van Duchenne spierdystrofie patiënten in latere ziektestadia, zelfs wanneer het niet meer mogelijk is om de armen zelfstandig te bewegen door verzwakking van deze spieren. Genormaliseerde sEMG amplitudes zijn hoger bij jongens en mannen met Duchenne spierdystrofie in vergelijking met gezonde controles. Dit geeft aan dat jongens en mannen met Duchenne spierdystrofie meer van hun spiercapaciteit gebruiken voor het uitvoeren van dagelijkse bewegingen, waardoor ze waarschijnlijk ook sneller vermoeid raken. Deze toename van genormaliseerde sEMG amplitudes is al zichtbaar in een vroeg ziektestadium. Tevens is te zien dat het maximale actieve bewegingsbereik sterk samenhangt met functionele schalen. Daarom wordt gedacht dat het behoud van het bewegingsbereik van de armen erg belangrijk is voor het kunnen blijven uitvoeren van dagelijkse activiteiten. Klinisch onderzoek van het actieve bewegingsbereik kan daarom helpen bij het selecteren van de juiste interventies voor het langer behouden

van armfunctie.

Het doel van **hoofdstuk 7** is om fysiologische uitkomstmaten te identificeren die belangrijk zijn voor het kunnen uitvoeren van dagelijkse taken door jongens en mannen met Duchenne spierdystrofie. Deze kritische variabelen zijn vervolgens gebruikt om een model voor het werkingsmechanisme van armfunctie op te stellen. De kritische fysiologische uitkomstmaten zijn geselecteerd op basis van hun relatie met functionele schalen en het vermogen van deze uitkomstmaten om onderscheid te maken tussen ziektestadia (zoals beschreven in hoofdstuk 6). De meest kritische uitkomstmaten die worden geïdentificeerd zijn: maximaal actief bewegingsbereik, maximale spiermoment, maximale spieractiviteit en maximale passieve bewegingsbereik. Deze uitkomstmaten zijn gebruikt om een model te maken van het werkingsmechanisme van armfunctie bij Duchenne spierdystrofie (figuur 1). Dit model laat zien dat de mogelijkheid om taken uit te voeren met de armen met name afhangt van het actieve bewegingsbereik, welke beïnvloed wordt door het passieve bewegingsbereik en het beschikbare moment rond een gewricht (kracht bij een bepaalde afstand tot het gewricht). Dit beschikbare moment wordt vervolgens weer beïnvloed door de spiercapaciteit, welke voldoende moet zijn om de zwaartekracht en de stijfheid in het gewricht te overwinnen. Spiercapaciteit wordt vervolgens weer beïnvloed door de mogelijkheid om spieren aan te spannen en de spierkracht die wordt gegenereerd rond het gewricht. Ondanks dat dit model is gebouwd op basis van een beperkte hoeveelheid gegevens en het model nog verder gevalideerd moet worden kan het belangrijke klinische implicaties hebben. Beter inzicht in het werkingsmechanisme kan helpen bij het diagnosticeren van beperkingen van armfunctie op het ICF niveau lichaamsfuncties en structuur en op ICF activiteitenniveau. Daarnaast kan het model helpen bij het identificeren van de mechanismen waarop hulpmiddelen armfunctie kunnen beïnvloeden en kan het model gebruikt worden als basis voor nieuwe uitkomstmaten voor medicatieonderzoek.



Figuur 1. Model van het werkingsmechanisme van armfunctie bij Duchenne spierdystrofie.
Opmerking: mV = millivolt, N= Newton, F/cm2 = kracht per vierkante centimeter spier, CSA = oppervlakte van dwarsdoorsnede spier, r = radius.

APPENDICES

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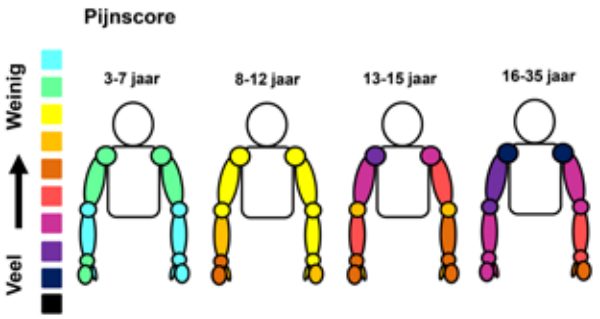
LEKEN SAMENVATTING

Duchenne spierdystrofie is een erfelijke aandoening die bij ongeveer 1 op 5000 jongens voorkomt. Jongens met Duchenne spierdystrofie hebben als gevolg van deze aandoening steeds meer moeite met bewegen. Hierdoor komen ze rond hun 12e levensjaar in een rolstoel en kunnen ze ook hun armen steeds minder goed bewegen. Het kunnen bewegen van de armen is echter erg belangrijk voor het zelfstandig uit kunnen voeren van dagelijkse activiteiten. Daarom is men op zoek naar hulpmiddelen die de armfunctie zo goed mogelijk kunnen behouden. Voor het ontwikkelen van deze hulpmiddelen is meer kennis nodig over hoe de armen van jongens en mannen met Duchenne spierdystrofie bewegen. Dit proefschrift richt zich daarom op het onderzoeken van armfunctie van jongens en mannen met Duchenne spierdystrofie. Dit doen we met behulp van vragenlijsten (**deel 1**) en door middel van metingen in het bewegingslaboratorium (**deel 2**).

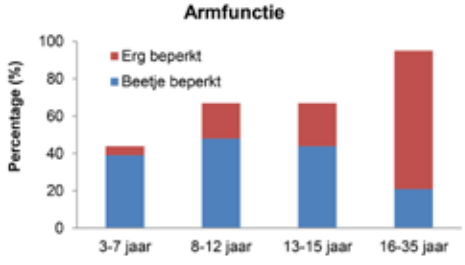
Deel 1: armfunctie gebaseerd op vragenlijsten

In deel 1 is de armfunctie onderzocht met behulp van vragenlijsten. Deze vragenlijsten zijn ingevuld door 213 jongens en mannen met Duchenne spierdystrofie en bevatten allerlei vragen over onder andere medicijngebruik, pijn, stijfheid, activiteiten die kunnen worden uitgevoerd, en deelname aan activiteiten zoals sport, hobby's en school.

De antwoorden op de vragenlijsten laten zien dat armfunctie al achteruit gaat als jongens met Duchenne spierdystrofie nog kunnen lopen. Daarnaast is te zien dat zowel armfunctie, als pijn en stijfheid steeds verder achteruitgaan als jongens met Duchenne spierdystrofie ouder worden (zie figuur 1 en 2).



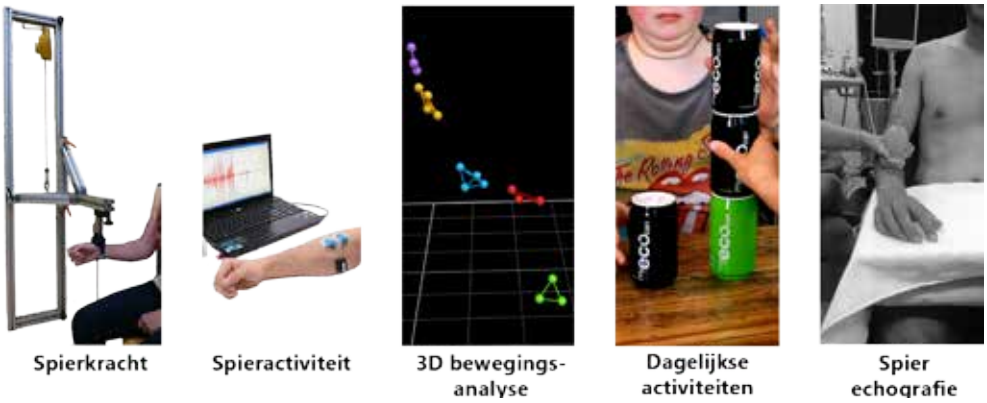
Figuur 1. Pijn bij verschillende leeftijden



Figuur 2. Beperkingen van armfunctie bij verschillende leeftijden

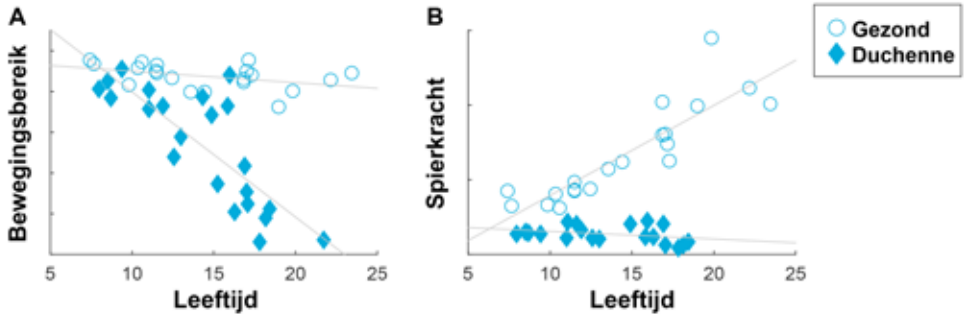
In deel 1 is ook onderzocht welke factoren invloed kunnen hebben op de functie van de armen bij jongens met Duchenne spierdystrofie. Te zien is dat onder andere het gebruik van corticosteroïden en het naar school gaan of werken samenhangen met een betere armfunctie en dat scoliose (kromming van de rug), pijn en stijfheid gepaard gaan met een slechtere armfunctie.

Deel 2: armfunctie gebaseerd op metingen in het bewegingslaboratorium
Voor deel 2 zijn 20 gezonde jongens en 23 jongens en mannen met Duchenne spierdystrofie gemeten in het bewegingslaboratorium van het Radboudumc. Er is o.a. gekeken naar spierkracht, spieractiviteit, bewegingsbereik, het kunnen uitvoeren van dagelijkse activiteiten. Daarnaast zijn er spierecho's gemaakt om te kijken hoe dik de spieren zijn en of er veel bindweefsel aanwezig is in de spieren (zie figuur 3).



Figuur 3: meetinstrumenten

De resultaten van dit onderzoek laten zien dat het bewegingsbereik (figuur 4.a) op jonge leeftijd nog niet beperkt is terwijl spierkracht (figuur 4.b) op jonge leeftijd wel al lager is in vergelijking met gezonde jongens. Daarnaast is te zien dat met name het bewegingsbereik bepalend is of dagelijkse activiteiten uitgevoerd kunnen worden. Dus wanneer het bewegingsbereik van de armen kleiner wordt, wordt het steeds moeilijke om activiteiten te doen. Verder is gemeten dat eerst de schouder spieren zwakker worden, terwijl de spieren van de onderarm/hand redelijk lang goed blijven functioneren.



Figuur 4: bewegingsbereik en spierkracht van gezonde mannen en mannen met Duchenne spierdystrofie

Uiteindelijk worden de resultaten van dit onderzoek gebruikt voor de ontwikkeling van nieuwe hulpmiddelen, zoals armondersteuners (figuur 5). Daarnaast kunnen artsen met deze informatie beter beperkingen van de armen vaststellen en daardoor betere behandelingen voorschrijven. Bovendien kunnen de resultaten gebruikt worden om nieuwe meetinstrumenten te ontwikkelen voor medicatie studies.

Figuur 5: prototype armondersteuner (Flextension A-Gear)

DANKWOORD

Het is zover! Mijn boekje is af. Na jaren met veel plezier aan dit promotietraject te hebben gewerkt is dit de afsluiting van een mooie periode, maar tegelijkertijd ook de start van nieuwe uitdagingen! Maar ik heb het niet alleen gedaan. Tijdens mijn promotietraject ben ik door velen ondersteund op zowel inhoudelijk als mentaal vlak. Ik wil graag iedereen bedanken die een bijdrage heeft geleverd aan mijn promotie!

Allereerst wil ik alle deelnemers bedanken! Zonder de vragenlijsten die jullie hebben ingevuld zou het eerste deel van dit proefschrift niet mogelijk zijn geweest. En natuurlijk wil ik alle deelnemers bedanken die speciaal voor het tweede deel van dit proefschrift naar het bewegingslab in Nijmegen zijn gekomen. Jullie lieten me keer op keer het belang van dit onderzoek voelen en motiveerden me om deze studie tot een goed einde te brengen. Ik hoop dat ik via dit proefschrift een bijdrage heb geleverd aan de ontwikkeling van nieuwe hulpmiddelen waar jullie zo geduldig op wachten.

Daarnaast wil ik mijn promotoren en co-promotor hartelijk bedanken. Sander, ondanks dat je mijn eerste promotor bent hebben we elkaar niet heel frequent gezien. Toch heb je een hele belangrijke bijdrage geleverd aan dit proefschrift. Je inhoudelijke kijk en kritische aanvullingen op mijn artikelen hebben van mij een betere wetenschapper gemaakt. Daarnaast ben je een voorbeeld voor me als het gaat om het hebben van een brede kijk op wetenschap. Het verbaast me nog steeds hoe ontzettend veel kennis je hebt over uiteenlopende onderwerpen. Jaap, ook jou wil ik graag hartelijk bedanken voor je begeleiding en bijdrage aan dit proefschrift. Ik ben nooit vergeten hoe je tijdens één van onze eerste overleggen vertelde dat op de wetenschap vaak het principe 'kill your darlings' van toepassing is. En dit heb ik geweten! Maar wel altijd met sterkere stukken als resultaat. Ik bewonder je om je technische blik en je vermogen om verbanden te leggen tussen uiteenlopende onderwerpen. We konden heerlijk sparren over de data en je bent een prettige persoon om mee samen te werken! Imelda, als dagelijks begeleider tijdens mijn promotie ken je me het best. We leerden elkaar in 2008 kennen toen ik mijn bachelor stage bij je deed en daarna heb ik voor de start met mijn promotie ook nog een master stage bij je gedaan. Blijkbaar was er een klik! Ik waardeer je om je hart voor de patiënten. Je stelt het belang van hen altijd bovenaan en wist me daardoor te motiveren en enthousiasmeren voor dit onderzoek! We konden heerlijk inhoudelijk sparren over de opzet en de resultaten van de verschillende onderzoeken. Daarnaast heb je een belangrijke bijdrage geleverd aan mijn persoonlijke ontwikkeling. Door je open en eerlijke feedback heb ik veel over mezelf geleerd en ik vond het fijn dat je de inspanningen om mezelf te verbeteren opmerkte en benoemde. Enorm bedankt voor je inspanningen en het vertrouwen dat je me nog steeds geeft!

Ook wil ik graag de leden van de manuscriptcommissie bedanken. Prof. Dr. M.A.A.P. Willemsen en Prof. Dr. B. Steenbergen, bedankt voor de kritische beoordeling van

mijn manuscript en fijn dat jullie aanwezig kunnen zijn tijdens mijn verdediging. Prof. Dr. J.J. Han (UC Irvine Medical Center, USA), thank you for being part of my thesis committee and for making the visit to the Netherlands for my defense. During my PhD I got the chance to visit you at UC Davis. You showed me your enthusiasm for clinical work as well as science. I hope we will be able to collaborate in future research.

Natuurlijk wil ik ook graag al mijn mede auteurs bedanken. Jullie hebben een belangrijke bijdrage geleverd aan de inhoud van dit proefschrift. Arjen, Jan, Bart, Sander, Jaap en Imelda, bedankt voor de prettige samenwerking en jullie kritische blik! Ook wil ik de mede auteurs van het Flextension team bedanken. Peter, Gerard, Joan, Bart, Micha, Arvid, Peter, Arno, Just, Arjen, Edith, Kostas, en Imelda, we hebben samen heel wat artikelen geschreven die niet konden worden opgenomen in dit proefschrift, maar die de ontwikkeling van nieuwe hulpmiddelen voor jongens en mannen met Duchenne stappen dichterbij hebben gebracht. Bedankt voor de fijne samenwerking!

Peter, Gerard en Joan, ik heb 4 jaar intensief met jullie samengewerkt aan het Flextension A-Gear project. Ondanks dat we het niet altijd met elkaar eens waren heb ik met heel veel plezier met jullie samengewerkt! We versterkten elkaar en hebben dit mooie project tot een goed einde gebracht. Peter, jij was degene die de groep bij elkaar hield en het belang van de patiënten altijd voorop stelde. Ook was jij de man van de planning en maakte je de mooiste ontwerpen. Je bent creatief en jouw doorzettingsvermogen was heel belangrijk voor het succes van het A-Gear project. Gerard, jij was degene van de berekeningen. Een echte wetenschapper die het liefst eerst alle scenario's onderzocht. Jouw berekeningen, ontwerpen en kritische blik hebben een belangrijke bijdrage geleverd aan het project. Joan, you were our control guy. We performed many measurements together and learned to understand each other. Your motivation and effort are remarkable! I still cannot believe how much work you were able to do in 4 years. I like the fact that after the project was finished we kept in touch and hopefully we will keep collaborating in the future.

Naast mijn mede projectleden van het Flextension A-Gear team wil ik ook graag alle begeleiders bedanken! Micha, Ruud, Jaap, Just, Bart, Peter, Arno, Edsko, Imelda en Arjen, jullie hebben het A-Gear project intensief begeleid en we hadden elk kwartaal een overleg waarop volop gebrainstormd werd. We werden vrijgelaten waar mogelijk en ondersteund waar nodig. Bedankt voor jullie begeleiding!

Ook wil ik de gebruikerscommissie van het Flextension project graag bedanken. TTW (voorheen STW), United Parent Projects Muscular Dystrophy, Prinses Beatrix Spierfonds, Spieren voor Spieren, Johanna Kinderfonds, Kinderrevalidatiefonds Adriaanstichting, Focal Meditech, OIM Orthopedie, Ambroise en stichting Flextension, dankzij jullie steun werd het Flextension A-Gear project financieel en inhoudelijk ondersteund. Onze halfjaarlijkse bijeenkomsten waren nuttig, gezellig,

en motiveerden ons allemaal om dit project tot een goed einde te brengen.

Tijdens mijn promotie heb ik ook een aantal stagiaires mogen begeleiden. Dit heb ik altijd met veel plezier gedaan. Kyra, Laura, Nina en Wieneke, bedankt voor jullie inzet en enthousiasme voor de projecten die jullie succesvol hebben uitgevoerd. Ik heb veel van jullie geleerd, en ik hoop dat dit andersom ook het geval is!

Verder wil ik graag mijn Radboud collega's bedanken! Kamergenoten: Nicole, Chantal, Annemieke, Anita, Merel, Arjen, Geert, Jilske, Laura, Mariëlle, Rosemarie, Ellen en Rosanne, met jullie kon ik zowel inhoudelijke als persoonlijke zaken bespreken. Bedankt voor de mogelijkheid om samen te sparren en natuurlijk voor de gezelligheid! Onderzoekscollega's, en oud collega's: Vivian, Roland, Roos, Jorik, Sjoerd, Hanneke, Noortje, Joyce, Digna, Lotte, Milou, Frank, Jolanda, Bas, Renee, Marian en Jos, bedankt voor jullie hulp en gezelligheid. Samen lunchen was altijd een heerlijke onderbreking van de dag!

Da Vrije Denkers, samen met jullie mocht ik de Radboud Da Vinci Challenge beleven. Maarten, Jorik, Jimmy, Chella, Sandra, José, Janna, Jeanette, Marcia en Jennifer, wat een ervaringen hebben we gedeeld en wat een avonturen hebben we beleefd. Jullie hebben me geholpen mezelf verder te ontwikkelen, mijn toekomst vorm te geven en mede dankzij jullie heb ik het zelfvertrouwen om mijn dromen na te jagen. Ellen en Kees, bedankt voor jullie fijne begeleiding tijdens dit traject. Ik zal de wijze lessen nooit vergeten!

Lieve vriendinnen, de meeste van jullie ken ik via onze studie. Linda, Rianne, Jacqueline, Nicolien, Carolien, Mireille en Mieke. Wat is het fijn om gezellig met jullie samen te zijn. De meesten van jullie weten wat het is om te promoveren en hebben me laten zien dat ondanks vele tegenslagen je toch een heel mooi resultaat kunt boeken. Samen spelletjes spelen, feestjes vieren en weekendjes weg, ik zie er altijd enorm naar uit en hoop dat we dit nog velen jaren blijven doen! Anke, we kennen elkaar sinds onze geboorte en ook al zien we elkaar niet heel vaak, het is altijd gezellig als ik je zie! Jij en Marloes zijn mijn 'zusjes van andere ouders', wat kunnen we lachen met z'n allen! Hopelijk blijven we dat nog heel lang doen.

Bram, Nabil en Manon, jullie zijn mijn Taekwon-Do maatjes. Ik kan altijd op jullie rekenen bij de Taekwon-Do en Tiger lessen, die jullie regelmatig van me overnamen als ik verplichtingen had voor mijn promotie. Jullie hebben de tenets in een hoog vaandel staan en ik ben blij dat ik de passie voor Taekwon-Do met jullie mag delen.

Beste paranimfen, Arjen en Chrissy. Bedankt voor jullie steun bij de laatste loodjes! Arjen, wat leuk dat je mijn paranimf wilt zijn. Je bent vanaf het begin betrokken bij het Flextension project en ik kon altijd bij je terecht als het even stroef liep. Je hebt een groot deel van mijn wetenschappelijke ontwikkeling meegemaakt en ik ben blij dat we deze fase samen kunnen afsluiten. We hebben genoeg mooie ideeën voor

de toekomst waarover we volop filosoferen. Bedankt voor je steun, ik hoop dat we samen nog veel mooie projecten mogen opstarten. Chrissy, lieve zus. Wat fijn dat je mijn paranimf wilt zijn. Kun je eindelijk een feestje organiseren (ook al is het geen bruiloft).

Lieve familieleden. Opa, oma, ooms, tantes, neven en nichten. Bedankt voor jullie interesse in mijn project. Hopelijk komen jullie allemaal een feestje vieren. Lieve Ruud, Chrissy, papa en mama, bedankt voor jullie onvoorwaardelijke steun. Jullie hebben altijd in me geloofd en dat waardeer ik enorm! Ik houd van jullie!

Lieve Stephanie, we kennen elkaar pas kort, maar ik wil je enorm bedanken voor je lieve woorden en geduld tijdens de laatste loodjes van mijn promotie. Ik hoop dat we samen een mooie toekomst tegemoet gaan!

Bedankt allemaal!

CURRICULUM VITAE

Mariska Janssen was born in Boxmeer on September 18th, 1986. She graduated from high school in 2005 and started her study biomedical sciences at the Radboud University Nijmegen that same year. As part of her bachelor studies, Mariska performed a research internship at the department of rehabilitation of the Radboud University Medical Center (Radboudumc), where she became interested in child rehabilitation and neuromuscular disorders. During her master human movement sciences, Mariska got interested in 3D motion analysis, through internships at the Radboudumc and the Sint Maartenskliniek. Her final internship at the department of rehabilitation of the Radboudumc was about 3D motion analysis of the upper extremity in Duchenne muscular dystrophy, which after her graduation in 2011, would result in her PhD assignment. Following graduation Mariska worked shortly as coordinator gait analysis at the Sint Maartenskliniek and as research assistant for the department of neurology at Radboudumc. In 2012, Mariska started her PhD regarding upper extremity function in Duchenne Muscular Dystrophy. Simultaneously Mariska started her own company, Tigers4life, which provides resilience training for young children. During her PhD, Mariska participated in the Radboud Da Vinci Challenge, a program that offers excellent PhD students and post-docs the opportunity to experience broad personal development. Currently, Mariska is working as a post-doc researcher at the department of rehabilitation at Radboudumc, where she performs several studies related to neuromuscular disorders, 3D motion analysis, fatigability and martial arts. Furthermore she continues developing Tigers4life and teaching resilience to children and adults. Mariska is currently living in Boxmeer, where she is planning to expand her own company and combine this work with her work as post-doc researcher.

CURRICULUM VITAE

Mariska Janssen werd geboren in Boxmeer op 18 september 1986. Ze behaalde haar VWO diploma in 2015, en startte datzelfde jaar met haar studie biomedische wetenschappen aan de Radboud Universiteit Nijmegen. Als onderdeel van haar bachelor studie deed Mariska een stage bij de afdeling revalidatie van het Radboud Universitair Medisch Centrum (Radboudumc). Hier werd haar interesse in kinderrevalidatie en spierziekten gewekt. Tijdens haar master bewegingswetenschappen raakte Mariska geïnteresseerd in 3D bewegingsanalysen door middel van stages bij de Sint Maartenskliniek en het Radboudumc. Haar afstudeerstage, wederom bij de afdeling revalidatie van het Radboudumc, was gericht op de 3D bewegingsanalyse van de bovenste extremiteit bij jongens en mannen met Duchenne Spierdystrofie. Deze opdracht zou later, nadat Mariska in 2011 afstudeerde, leiden tot haar uiteindelijke promotie opdracht. Voordat deze opdracht van start ging heeft Mariska nog kort gewerkt als coördinator gangbeeldanalysen in de Sint Maartenskliniek en als onderzoeksassistent bij de afdeling neurologie van het Radboudumc. In 2012 ging Mariska van start met haar promotie opdracht met betrekking tot de functie van de bovenste extremiteit bij jongens en mannen met Duchenne spierdystrofie. Tegelijkertijd startte Mariska met haar eigen bedrijf, Tigers4life, welke weerbaarheidstrainingen verzorgt voor jonge kinderen. Tijdens haar promotie nam Mariska deel aan de Radboud Da Vinci Challenge, een programma dat talentvolle promovendi en post-docs de mogelijkheid tot brede, persoonlijke ontwikkeling bied. Op dit moment werkt Mariska als post-doc onderzoeker bij de afdeling revalidatie van het Radboudumc, waar ze verschillende studies met betrekking tot neuromusculaire aandoeningen, 3D bewegingsanalyse, vermoeibaarheid en martial arts uitvoert. Daarnaast ontwikkelt Mariska ook Tigers4life verder en geeft ze weerbaarheidstrainingen aan zowel kinderen als volwassenen. Mariska woont op dit moment in Boxmeer, waar ze in de toekomst haar bedrijf verder wil uitbreiden en dit wil combineren met haar werk als post-doc onderzoeker.

LIST OF PUBLICATIONS

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