Patient-Reported Outcomes in Neuromuscular Disorders – Health-Related Quality of Life and Psychosocial Adjustment in Post-Polio Syndrome and Duchenne Muscular Dystrophy

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Abstract

Neuromuscular disorders (NMDs) have a large impact on many aspects of life. Disabilities caused by an impaired muscle function often can lead to a wide range of secondary problems in daily life and affect psychosocial aspects such as the quality of life and psychosocial adjustment. Due to improvements in symptomatic treatments and increased life expectancy in patients with NMDs, these problems become more and more evident. In order to develop appropriate intervention programs for patients with NMDs, it is very important to evaluate patients' quality of life and to understand its association to physical functioning thereby improving health outcomes. Furthermore, patients that are at high risk of psychosocial impairments should be detected to be able to start an early intervention.

The aim of the present work is to investigate patient-reported outcomes, such as the health-related quality of life (HRQOL) and psychosocial adjustment in patients with post-polio syndrome (PPS) and Duchenne muscular dystrophy (DMD) and their association to motor abilities.

First, a prospective observational study in patients with PPS is performed focusing on HRQOL, self-reported impairments and activities of daily living and their association with clinical muscle function outcomes.

Afterwards, in a cross-sectional study we extensively study the HRQOL in ambulant and non-ambulant patients with DMD and its association to motor function.

Finally, we focus on the psychosocial adjustment in children with DMD and its possible association to parental stress and other sociodemographic and disorder-related items.

Abbreviations

6MWD - 6 Minute Walking Distance

CBCL - Child Behavior Checklist

DMD – Duchenne Muscular Dystrophy

HRQOL – Health-Related Quality Of Life

IBM-FRS – Inclusion Body Myositis – Functional Rating Scale

MFM - Motor Function Measure

NMD – Neuromuscular disorder

PARS-III - Psychosocial Adjustment and Role Skills Scale III

PedsQL™ – Pediatric Quality of Life Inventory

PPS – Post-polio syndrome

PROM - Patient-reported outcome measure

PSI-SF - Parenting Stress Index–Short Form

SIPP-RS – Self-Reported Impairments in Persons with late effects of Polio Rating Scale

WHO - World Health Organization

WHOQOL-BREF – World Health Organization quality of life abbreviated scale

YSR – Youth Self Report

1. Introduction

1.1. Neuromuscular disorders and physical impairments

Neuromuscular disorders (NMDs) are rare, chronic diseases which include all diseases caused by dysfunction of the motor units (anterior horn cells, brainstem motor neurons, motor roots, neuromuscular junction, peripheral nerves, and muscles) (Morrison, 2016). In NMDs, muscle function is impaired and declines over time. Common functional impairments as a consequence of various NMDs include muscle weakness, impairment in muscle endurance, involuntary muscle activity, sensory loss, autonomic dysfunction and impairment in the control of voluntary movements (Morrison, 2016). This can result in loss of mobility up to loss of independent walking ability and total dependence in daily living activities (Katirji, Kaminski, & Ruff, 2013; Piccininni, Falsini, & Pizzi, 2004). In this perspective, NMDs are besides being chronic diseases also progressive disabilities that affect different aspects of peoples' lives. The relevant NMDs for this PhD thesis are briefly characterized below.

The post-polio syndrome (PPS) manifests with new neuromuscular symptoms that occur in polio survivors after at least 15 years of stability after an acute attack of paralytic poliomyelitis. Clinically, PPS includes symptoms such as new muscle weakness and fatigue in skeletal or bulbar muscles and atrophy of previously unaffected muscles (Baj et al., 2015). While the actual incidence of PPS is still unknown, the reported prevalence rate varies between 20-75% among polio survivors (Baj et al., 2015). Since the exact cause of PPS is still unclear, the most widely accepted hypothesis so far refers the symptoms to a distal degeneration of axons in the greatly enlarged motor units developed during recovery from acute paralytic poliomyelitis (Trojan & Cashman, 2005). PPS can affect bodily functions, mobility, and physical strength; therefore the disease impacts an individual's ability to maintain an

independent life. In the absence of effective clinical interventions, rehabilitation management is considered the mainstay of treatment (Koopman, Beelen, Gilhus, de Visser, & Nollet, 2015). Due to the disabilities caused by PPS patients suffer from a wide range of problems in daily life which may have a negative impact on their quality of life (Jacob & Shapira, 2010; Thoren-Jonsson & Grimby, 2001).

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disease with the second highest incidence considering all genetically inherited illnesses (Bushby et al., 2010). DMD affects 1 in 3500 to 6000 male births (Mendell et al., 2012). The disease occurs as a result of mutations, mainly deletions, in the dystrophin gene leading to an absence of or defect in the protein dystrophin. This deficiencies lead to progressive degeneration of the muscles and loss of independent walking ability by the age of 13-16 years (Bushby et al., 2010). The use of corticosteroids enables to prolong ambulation. Moreover, improved symptomatic treatments have resulted in increased life expectancy in patients with DMD. Nowadays 60% of the affected individuals will live into their 20s and beyond (Passamano et al., 2012), therefore the population of patients with DMD whose needs must be met by health services is growing.

1.2. Neuromuscular disorders and patient-reported outcomes

NMDs have a large impact on many aspects of life. To date, a great number of studies have focused on treatments or interventions of NMDs resulting in improvement in survival and disease management (Ke et al., 2019; Lo & Robinson, 2018; Vita, Vita, Musumeci, Rodolico, & Messina, 2019). In addition, the World Health Organization (WHO) highlights in their definition of health besides the physical dimension also mental and social factors, which should be considered (Conference, 2002). Therefore, using patient-oriented assessments of patients' state of health have become

increasingly important. Clinicians, researchers and regulatory agencies such as the US Food and Drug Administration have recognized the importance of patient-reported outcome measures (PROMs) as a central outcome both in clinical practice and in new treatment trials to determine clinical meaningful changes in patients with NMDs (Mendell et al., 2007). In addition, patients with NMDs themselves prioritize their interest in future research on quality of life, disease adaptation as well as research on mobility (Nierse, Abma, Horemans, & van Engelen, 2013). Hence, there is a need for including the patient's perspective for a more comprehensive insight into diseases' impact. Research on psychological outcomes in patients with NMDs can complement the biological and pathophysiological research on NMDs and points to the need for more interdisciplinary research. The inclusion of PROMs allows to understand broader and deeper person's own perception of the difficulties of everyday life and represents a reliable method to assess patients with NMDs at risk for psychological difficulties. In the next sections we investigate previous literature regarding several relevant psychological outcomes in NMDs.

1.3. Health-related quality of life

Quality of life as a measurable construct has become essential not only in psychology but is increasingly also an important subject of research in medicine (Ravens-Sieberer et al., 2006). Quality of life is a broad multidimensional concept defined by the WHO as the perceived quality of an individual's daily life, including physical, psychological, social and environmental aspects of the individual's life (WHO, 2019). Health-related quality of life (HRQOL) is more narrowly defined than quality of life. HRQOL is largely viewed from a medical perspective and is defined as the perceived quality of life when affected by a disease or disabilities and therefore focuses specifically on the impact of

illness and treatments on physical, psychological, and social aspects of life (Davis et al., 2006).

Literature investigating HRQOL in patients with NMDs is conflicting. Several studies reported reduced HRQOL (Kling, Persson, & Gardulf, 2000; Landfeldt et al., 2016; Uzark et al., 2012; Wei, Speechley, Zou, & Campbell, 2016) in patients with PPS and DMD, whilst others demonstrated no difference between HRQOL scores of patients with DMD and PPS and healthy people or people suffering from other chronic diseases (Henricson et al., 2013; Houwen-van Opstal, Jansen, van Alfen, & de Groot, 2014). Particularly in DMD, studies reported repeatedly poorer HRQOL in patients with DMD compared to healthy control groups, especially in the physical and psychosocial domains (Landfeldt et al., 2016; Uzark et al., 2012; Wei et al., 2016). In contrast, Vuillerot and colleagues found no difference in comparing adolescents with NMDs with a healthy control group for vitality, body image, relationships with their parents and friends, as well as physical and psychological well-being (Vuillerot et al., 2010).

Many factors may affect HRQOL in patients with NMDs. However, most of previous studies have several limitations such as neglecting the impact of medical treatment (e.g. corticosteroid treatment) and not controlling for confounding variables. Moreover, to date little has been reported on the association between HRQOL and objectively assessed physical function (Garip et al., 2017; McDonald et al., 2010; Messina et al., 2016) Also, in DMD most of the results are based only on parental estimates. Therefore, a greater understanding of the relative impact of NMD-related disabilities on HRQOL is needed.

1.4. Psychosocial adjustment

A major task of chronically ill or physically disabled individuals is to cope with the challenges of their chronic medical condition (de Ridder, Geenen, Kuijer, & van Middendorp, 2008). Research has displayed that in comparison to healthy peers patients with a chronic condition and physical disability are considered at a higher risk of problems with psychosocial adjustment, internalizing problems and somatic complaints (Barlow & Ellard, 2006). Patients suffering from neurological disorders and impairments in motor functioning face an even higher risk of adjustment problems (Hysing, Elgen, Gillberg, & Lundervold, 2009). Darke et al. reported in their study on psychosocial adaptation that 41.5% of the children affected by NMDs experience problems in behavior, communication and other social areas (Darke, Bushby, Le Couteur, & McConachie, 2006).

Despite the devastating nature of DMD and its early presentation, little is known about the psychosocial development of patients affected by DMD. In fact, there is only a small number of studies that investigates neurobehavioral and emotional functioning in this patients. Findings from previous studies concerning psychosocial adjustment are equivocal. Early research reports that between 30% and 50% of affected individuals experience psychosocial problems including general emotional or behavioral disturbance (Firth, Gardner - Medwin, Hosking, & Wilkinson, 1983; Leibowitz & Dubowitz, 1981; Polakoff, Morton, Koch, & Rios, 1998), symptoms of depression, anxiety, social isolation (Fitzpatrick, Barry, & Garvey, 1986; Livneh & Antonak, 1994), and social problems (Hinton, Nereo, Fee, & Cyrulnik, 2006). In contrast, most recent research reports no indication of decreased psychosocial adjustment or behaviour problems in children with DMD compared to healthy population and other chronic medical conditions (Hendriksen et al., 2009; Hendriksen & Vles, 2006). Based on the

results published so far, it is not possible to draw a consistent picture of the psychosocial adjustment in children with NMD.

Further, NMDs may have implications not only on the psychosocial well-being of the affected individuals but also the families caring for patients. Research to date indicates that most families having a child with DMD experience significant chronic psychological stress and their stress level is higher than in families with healthy children or children affected by other chronic illnesses (Nereo, Fee, & Hinton, 2003; Reid & Renwick, 2001). Literature on adjustment in childhood chronic medical conditions such as DMD suggests that complex behavioral and emotional transactions take place between family members, and that these transactions are central to the psychological adjustment process of the affected individuals (Hullmann et al., 2010). Therefore, previous literature suggests that parental factors such as parental stress may contribute to the psychosocial functioning in children with DMD (Nereo et al., 2003). In fact, more attention needs to be given to the role of paternal variables in this process in order to describe more precisely the transactional nature of child and parent adaptation.

1.5. Research objectives

The present PhD thesis aims to investigate several relevant psychological outcomes in two NMDs. The advances in medicine with new interventions and treatments of NMDs result in improvements in disease progression and survival rate of patients with NMDs. Using patient-oriented assessments of the state of health adds to the understanding of the patient experience of NMDs and has become increasingly important in these diseases (Black, 2013). Therefore, PROMs are required as central outcomes to determine clinical meaningful changes in patients with NMDs both in

clinical practice and in new treatment trials. Thus, the present work is intended to be exploratory aiming at having a global overview of relevant psychological outcomes, such as the HRQOL and the psychosocial adjustment, in patient with PPS and DMD.

First, a prospective observational study in patients with PPS was performed, where patient-reported outcomes including HRQOL, self-reported impairments and activities of daily living and their association with clinical muscle function outcomes during 6 months were investigated. This study was followed by a cross-sectional study exploring the HRQOL in ambulant and non-ambulant patients with DMD. Moreover, the association between HRQOL and motor function was investigated. Finally, we investigated the psychosocial adjustment in children with DMD and assessed its association to parental stress and other sociodemographic and disorder-related items.

2. Publications

2.1. Manuscript 1: Health-related quality of life, self-reported impairments and activities of daily living in relation to muscle function in post-polio syndrome

Journal: Journal of Patient-reported Outcomes – submitted

Authors: Gocheva V, Hafner P, Orsini AL, Schmid S, Schaedelin S , Rueedi N, Rubino-Nacht D, Weber P, Fischer D

Abstract: Background: The symptoms of the post-polio syndrome (PPS) and the resulting disabilities can affect quality of life and the ability to perform daily activities. No study has comprehensively analysed how various patient-reported outcome measures (PROMs) are associated to objectively assessed physical function and in patients with PPS.

Aim: To investigate health-related quality of life (HRQOL), self-reported impairments and activities of daily living during 6 months and evaluate their association with clinical muscle function outcomes in individuals with PPS.

Methods: Twenty-seven patients with PPS were included in the study. At baseline and 6 months, patients were administered PROMs measuring HRQOL (WHOQOL-BREF), self-reported impairments related to PPS (SIPP-RS) and activities of daily living (IBM-FRS). Clinical muscle function outcomes included 6 minute walking distance (6MWD) and motor function measure (MFM).

Results: Total HRQOL, self-reported impairments, activities of daily living and muscle function outcome measures remained stable during 6 months. Patients reported significantly lower HRQOL scores in the psychological health domain at 6 months compared to baseline. Moreover, participants experienced higher HRQOL scores in the social relationships and environmental health domains compared to the general population. Activities of daily living were positively associated to the clinical muscle function outcomes.

Conclusions: HRQOL may be used in clinical trials to obtain additional information on disease evolution compared to self-reported and objectively assessed physical disability. By limiting the impact of reported impairments and disabilities in activities of daily living, physical abilities may be improved. Interdisciplinary rehabilitation programs considering individual needs should primarily target participants' activity and participation in society.

Health-related quality of life, self-reported impairments and activities of daily living in relation to muscle function in post-polio syndrome

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physical abilities may be improved. Interdisciplinary rehabilitation programs considering individual needs should primarily target participants' activity and participation in society.

Trial registration: ClinicalTrials.gov Identifier (NCT02801071) registered June 15, 2016. https://clinicaltrials.gov/ct2/show/NCT02801071

Keywords: post-polio syndrome, health-related quality of life, impairments, daily living function, patient-reported outcomes, motor function

Background

The post-polio syndrome (PPS) is a condition that affects polio survivors years after an acute poliomyelitis infections leading to flaccid paralysis. Survivors often (partially) recover from these paralysis [1]. PPS is defined as "the development of new muscle weakness and fatigue in skeletal or bulbar muscles, unrelated to any known cause, beginning 25-30 years after an acute attack of paralytic poliomyelitis" [2]. Additional symptoms of PPS include muscle atrophy, generalized fatigue, muscle, and joint pain and sensitivity to cold [3]. Primary symptoms and impairments such as sleep disturbances, memory and concentration difficulties may be disabling in certain areas of life and may affect independence [4-6]. While studies report that 40% to 80% of polio survivors already have PPS, the actual incidence of PPS is still unknown [7]. To date, the exact cause of PPS is still unclear. The most widely accepted hypothesis refers the symptoms to a distal degeneration of axons in the greatly enlarged motor units developed during recovery from acute paralytic poliomyelitis [8]. As no curative treatment is available for PPS, rehabilitation management is considered the mainstay of treatment [9].

The symptoms of PPS and the resulting disabilities can affect quality of life, often influence the ability to perform daily activities and lead to a wide range of problems in daily life [10-12]. Previous studies reported poorer health-related quality of life (HRQOL) in persons with PPS compared to general population [4; 13]. Moreover, health-related problems were referred to housework, employment, and leisure [12]. The greatest impact of PPS symptoms was found on mobility-related activities [14].

In clinical practise, objective measurements of muscle function and walking distance are commonly used when the consequence of PPS are evaluated [15; 16]. However, functional outcomes only partially capture the different aspects of impairments and walking limitations that persons with PPS perceive. The patient’s perspective should be taken into consideration

for a more comprehensive understanding of the disease's impact. Patient-reported outcome measures (PROMs) are increasingly advocated and used to achieve this [17]. PROMs are used extensively in a clinical research setting, the Food and Drug Administration has recognized their importance in natural history and clinical trials [18]. PROMs allow patients to consider their real-world experiences integrated over time and provide a broader and deeper understanding of persons' own perception of everyday difficulties [19].

To date, little has been reported on if and how different PROMs relate to objectively assessed physical function and its changes over time [20; 21]. Therefore, a more comprehensive analysis is warranted of how patient-reported variables such as self-reported impairments related to PPS, HRQOL and activities of PPS are associated to motor function. To the best of our knowledge, no study has investigated these associations.

The aim of this study was therefore to assess self-reported evaluations with three PROMs regarding HRQOL, impairments related to PPS and activities of daily living during 6 months in patients with PPS. Additionally, we aimed to examine whether there was a relationship between the PROMs and objectively assessed muscle function and walking distance.

Methods

Study design

This study is a prospective observational study involving patients with PPS recruited at the Division of Neuropediatrics, University Children's Hospital Basel in Switzerland and followed for 6 months. This study is part of a lager randomised controlled trial designed to assess the efficacy of L-citrulline in patients with PPS, which involves a 24-week observational (untreated) natural history period followed by a 24-week treatment period. This analysis used baseline and 6 months data of the untreated participants with PPS during the

natural history period. Details of the clinical trial protocol and design are reported elsewhere [22].

Study population

For this study, participants were recruited among the PPS patient organization in Switzerland (www.polio.ch). Eligible participants were included in the study only after providing written informed consent. Ethics approval had been obtained from the local Ethics Committee (EKNZ 2015-221) and the National Swiss Drug Agency (Swissmedic, Reference number: 2016DR2067). The study was registered at ClinicalTrials.gov (NCT02801071) prior to starting recruitment. The PROMs and the clinical measures investigated in this study were all part of the larger randomised controlled study and therefore part of the original informed consent. Inclusion criteria for the larger study were defined as follows:

(i) prior paralytic poliomyelitis with evidence of lower motor neuron loss

(ii) a period of partial or complete functional recovery after acute paralytic poliomyelitis

(iii) slowly progressive and persistent new muscle weakness or decreased endurance, with or without generalized fatigue, muscle atrophy, or muscle and joint pain

(iv) ≥18 years of age at inclusion

(v) ability to walk at least 150 m in the 6 minute walking distance test with or without walking stick(s), and

(vi) no other significant medical condition or malignancy.

Out of thirty-three screened participants with PPS two patients were excluded from participation because they did not meet inclusion criteria. Between baseline and follow-up assessment at 6 months four patients withdrew informed consent, resulting in a final number of 27 participants.

Measurements

Self-Reported Impairments in Persons with Late Effects of Polio Rating Scale

The Self-Reported Impairments in Persons with Late Effects of Polio Rating Scale (SIPP-RS) is a 13-item self-report assessment of impairments related to PPS [23]. The participants rate how much they have been bothered directly (i.e., muscle weakness, fatigue) or indirectly (i.e., sensory disturbances, mood swings) by various impairments related to late effects of polio during the past two weeks. The items consider: muscle weakness, muscle fatigue, muscle and/or joint pain during physical activity and at rest, sensory disturbance, breathing difficulties during physical activity and at rest, cold intolerance, general fatigue, sleep disturbances, concentration difficulties, memory difficulties, and mood swings. Response categories include a 4-point-Likert-scale, ranging from 1 (not at all) to 4 (extremely). The total sum score ranges from 13-52 points, a higher score indicating more self-reported impairments. The SIPP-RS has good psychometric properties, it is Rasch-analysed and unidimensional, which allows sum score and parametric analyses [23].

Inclusion Body Myositis Functional Rating Scale

The Inclusion Body Myositis Functional Rating Scale (IBM-FRS) is a 10-item functional rating scale that assesses activities of daily living [24]. Respondents rate their functional ability in 10 areas including swallowing, handwriting, use of utensils, fine motor tasks, dressing, hygiene, turning in bed, standing, walking and climbing stairs. Response categories include a 5-point-Likert-scale, ranging from 4 being normal to 0 being unable to perform. The total score ranges from 40 (best functional status) to 0 (complete dependency). The IBM-FRS has been shown to be a reliable and valid measure of disease severity in inclusion body myositis [24; 25]. The IBM-FRS is known to be a sensitive measure of disorders affecting the peripheral motor nerves or muscles in inclusion body myositis [24]. Therefore, and due to the

clinical similarities of inclusion body myositis and PPS (late adult onset, slowly progressive weakness and atrophy, asymmetric affection of proximal and distal limb muscles, and lack of central nervous system involvement) [2; 3], the IBM-FRS was used to assess activities of daily living in this trial.

World Health Organisation Quality of Life Abbreviated Scale

The World Health Organisation Quality of Life Abbreviated Scale (WHOQOL-BREF) is a 26-item scale that assesses an individual's HRQOL [26]. Response categories include a 5-point-Likert-scale, ranging from 1 to 5, with higher scores indicating a better HRQOL. The WHOQOL-BREF was scored after its administration to the study participants; the raw scores were converted to transformed scores. The first transformation converts scores to a range of 4–20 and the second transformation converts domain scores to a 0–100 scale. The domain scores show good content validity, discriminant validity and internal consistency [27]. Pomeroy et al. evaluated the 4 domains of the WHOQOL-BREF as valid and drew the conclusion that the questionnaire can be used to assess HRQOL in persons affected by PPS [28]. Since there is no overall score for the questionnaire, the authors created a reliable summed total score, which can be used as an ordinal estimate of HRQOL in individuals with PPS. Therefore, in this study we also used the summed total score and it is estimated as follows: The two domains "psychological health" and "social relationships" are combined to one new domain due to low reliability and calculated as for the original domains (by summing up the points in all items associated with "psychological health" and "social relationships"). Thereafter, the total score is estimated as the mean of this new domain and the original domains "physical health" and "environmental health".

6 Minute Walking Distance

In medical literature, numerous timed clinical functional assessments have been reported to assess to monitor the disease progression. The 6 minute walking distance (6MWD) test is one of the most popular clinical tests used for assessment of muscle function and fatigue in patients with neuromuscular disorders [29; 30]. It is a validated tool to measure the distance that an individual is able to walk over a total of 6 minutes on a hard, flat surface. The aim of the test is to walk as far as possible in 6 minutes.

Motor function measure

The motor function measure (MFM) is a validated quantitative scale used for assessment of motor abilities of both ambulant and non-ambulant patients with neuromuscular disorders [31]. It includes 32 items that evaluate three dimensions of motor performance, including specific motor functions, such as transfers and standing posture, proximal and axial motor function, and distal motor function. Each item is scored on a scale from 0 (does not initiate movement) to 3 (completes the item with a standard pattern). The items are scored and summed to comprise a total score involving all of the motor dimensions, where the maximum represents normal motor function (100%). In this study, the MFM total score was analysed.

Procedure

All consecutive patients attending the study centre who fulfilled the inclusion criteria were enrolled in the study. As we wished to obtain the best compliance in the functional assessments, the PROMs were filled in after the functional tasks. Data were collected at baseline and at 6 months follow-up assessment.

Data analysis

Descriptive statistics were calculated for the continuous variables of mean, standard deviation and for the categorical variables of frequencies and percentages. One sample t-tests were

performed to compare the HRQOL scores of patients with PPS to data from general German population [32]. Paired t-tests were used to assess the change over time between baseline and 6 months follow-up visit of the PROMs and functional measures. Furthermore, the association between PROMs and functional data were assessed using linear mixed effects models. The outcome variables were the WHOQOL-BREF total score, the SIPP-RS total value and IBM-FRS total value. The visit number was included as a fixed effect and participants as random effect. The MFM and 6MWD were included at the corresponding visit as additional covariates. The coefficient estimates (β) is reported together with 95% confidence intervals, the t and p values. Statistical analyses were performed using R, version 3.4.4.

Results

Characteristics of participants with PPS

A total of 27 participants with PPS (mean age = 65.48 years, SD = 4.80) had both baseline and follow-up data and were included in the analysis. Participants included 15 males (56%) and 12 females (44%). Regarding marital status at study start, 19 participants were married (70%), 3 were divorced (11%), 3 patients were single (11%), 1 was separated (4%) and 1 was widowed (4%). The highest education with greater representation was secondary school (n = 12, 44%), followed by university degree (n = 8, 30%), high school (n = 4, 15%), and PhD (n = 3, 11%).

Baseline data

A summary of baseline PROM scores and functional data are shown in Table 1. All clinical tests were performed safely without any major fall during the assessment.

Self-reported impairments related to PPS

The mean score of the self-reported impairments was 25.52 (SD 5.07) out of 52 points. The most frequent impairments (rated as 'quite a bit' or 'extremely') that the participants reported were: for example muscle fatigue (18 participants, 67%), muscle weakness (15 participants, 56%), muscle and/or joint pain during physical activity (7 participants, 26%), breathing difficulties during physical activity (7 participants, 26%), and sleep disturbances (7 participants, 26%).

Activities of daily living

The mean score of the activities of daily living was 33.89 (SD 3.75) out of 40. Seven participants (26%) reported limitations ("being unable to perform" or "requires assistance") in their ability to stand up from sitting position independently. Over 15% reported limitations in their ability to climb stairs and 3.7% reported limitations in their ability to walk.

HRQOL in patients with PPS in comparison to normative data

Table 2 shows the comparison of HRQOL between participants with PPS and normative data of general German population (n = 2073). Analysis revealed that participants with PPS reported significantly higher scores in the social relationships and the environmental health domains compared to general population (see Figure 1). The physical and the psychological domains in PPS patients however did not significantly differ from the general population.

Longitudinal data

Table 3 shows comparison between baseline and 6 months follow-up visit for the PROMs and functional data. The selected clinical outcome measures detected no significant change in physical function over the 6-months period (6MWD: t = 1.05, p = 0.30; MFM: t = 1.50, p = 0.14). The analysis of the HRQOL scores yielded a significant decrease between baseline and

6 months in the psychological domain (t = -2.10, p = 0.05). No significant change over time could be found for the total score (t = -1.83, p = 0.08), the physical (t = -1.17, p = 0.25), the social relationships (t = -0.95, p = 0.35) and the environmental domains (t = -1.02, p = 0.32). As shown in Figure 2, no statistically significant difference could be found between baseline and 6 months for patients' self-reported impairments related to PPS (t = -0.86, p = 0.40) and activities of daily living (t = -1.31, p = 0.20).

Association between PROMs and functional outcome measures

Linear mixed model analysis revealed a significant positive association between the IBM-FRS and the 6MWD (β = 0.02, 95% CI: 0.02;0.03, t = 6.88, p < 0.01), indicating that participants with PPS who were able to walk a further distance in 6 minutes more meters experienced less difficulties in activities in daily living. Moreover, a significant positive association was found between the IBM-FRS and the MFM (β = 0.25, 95% CI: 0.17;0.33, t = 6.69, p < 0.01), demonstrating that patients with PPS with poorer motor function experience reduced activities of daily living. The association of the IBM-FRS and the clinical outcome measures at baseline is presented in Figure 3.

Analysis revealed no significant association between the WHOQOL-BREF total score and the 6MWD (β = 0.01, 95% CI: -0.01;0.04, t = 1.19, p = 0.24) and the MFM (β = 0.11, 95% CI: -0.17;0.40, t = 0.77, p = 0.45) .

Both the 6MWD and the MFM did not correlate significantly with the SIPP-RS (6MWD: β = -0.01, 95% CI: -0.02;0.00, t = -1.35, p = 0.19; MFM: β = -0.04, 95% CI: -0.17;0.08, t = -0.68, p = 0.50).

Considering the change over time in PROMs, the analysis yielded no significant time effect for the WHOQOL-BREF total score when adjusting for the 6MWD (β = -2.46, 95% CI: -5.25;0.43, t = -1.73, p = 0.10) and the MFM (β = -2.51, 95% CI: -5.34;-0.42, t = -1.73, p =

0.10). Also, no significant time effect was detected for the SIPP-RS and IBM-FRS when adjusting for the 6MWD (SIPP-RS: β = -0.61, 95% CI: -2.01;0.76, t = -0.88, p = 0.39; IBM-FRS: β = -0.69, 95% CI: -1.70;0.36, t = -1.34, p = 0.19) and the MFM (SIPP-RS: β = -0.60, 95% CI: -1.98;0.77, t = -0.86, p = 0.40; IBM-FRS: β = -0.91, 95% CI: -2.07;0.25, t = -1.58, p = 0.13).

Discussion

The PPS is a condition that leads to a life-long disability, with a variety of impairments that can increase over time and affect a person's motor function, walking ability and quality of life. Our results indicate that participants revealed significantly higher HRQOL scores in the social relationships and environmental health than the general population; physical and psychological health did not significantly differ from general population. Patients with PPS reported significantly lower psychological health scores after 6 months compared to baseline, while no significant difference between baseline and 6 months in total HRQOL, self-reported impairments, activities in daily living and muscle function outcome measures could be found. Moreover, a significant positive association between activities and daily living and clinical outcomes was found.

Participants reported higher average HRQOL scores of social relationships and environmental health scores compared to general population. To our knowledge, these findings have not been reported before. In one study, 101 polio survivors reported normal mental scores including emotional and social functioning [11]. A possible explanation for our observation could be that the majority of our participants live with a partner and receive help and support from this person. Several studies reported that social support is important for people who have contracted a disease [33; 34]. Social support, patients' ability to manage stressors, as well as their ability to adjust to disability may minimize the importance of physical ability and therefore play an important role in maintaining mental health [35; 36].

Another possible explanation might be the relative low number of patients included in our study, thereby overestimating positive findings of individual patients.

Interestingly, our results revealed that patients with PPS reported comparable average HRQOL scores of physical and psychological health compared to healthy adults. Previous reports on patients with PPS suggest that physical limitations are the major contributing factor to the impaired HRQOL [4; 11; 20; 21; 37], therefore our result is inconsistent with previous literature. The domain physical health of the WHOQOL-BREF questionnaire incorporates the following facets: dependence on medicinal substances and medical aids, energy and fatigue, mobility, pain and discomfort, sleep and rest, work capacity, and activities of daily living. It is possible that these areas may not be very severely affected in the included participants with PPS. Another explanation could be that patients with PPS had been living with the effects of polio for many years, thus they had learnt to live with the changes caused by the disease. Coping strategies were developed and employed so they felt that they had a "good life" and their physical impairments did not affect their HRQOL [10; 36]. Regarding the psychological health, Jacob and Shapira reported in their study normal emotional functioning in patients with PPS which is in line with our finding [11] .

In this study, the participants were on average moderately affected by their impairments. The most often reported impairments (muscle fatigue, muscle weakness, muscle and/or joint pain during physical activity) are exemplary for people with PPS, therefore this finding is consistent results of recent studies [16; 38]. Few participants reported breathing difficulties during physical activity and sleep disturbances. These impairments have been shown to be more common in previous literature [39], which demonstrates that the degree of self-reported impairments in persons with PPS can vary considerably. Further, the most common self-reported limitations in their activities of daily living were the ability to stand up from sitting position independently, the ability to climb stairs and limitations in their ability to walk. These walking limitations in daily life are in agreement with previous studies measured

by other self-reported instruments [16; 38; 40] and emphasize the importance to assess several aspects of walking, not only walking distance and motor function.

Limited PROMs and physical function data are available on disease progression of PPS. The majority of studies so far used cross-sectional research designs measuring HRQOL at a single time point [4; 11; 20; 37]. In our study a significant decrease after the 6 months observation was only found for the HRQOL psychological health scores. No significant changes of self-reported impairments related to PPS and activities of daily living were found after 6 months follow-up. Neither an objective disease progression was found in the MFM or 6MWD. This is likely to the relative slow disease progression in PPS and a too short time span to detect changes in PROMs. Still, as HRQOL psychological health was declining even in a short observational period HRQOL assessments may be used in clinical trials to obtain additional information on disease evolution compared to self-reported and objectively assessed physical disability. Further longer lasting natural history studies are recommended to get more objective data on different aspects of PPS disease progression.

Another interesting finding we observed is that the activities of daily living measured by the IBM-FRS correlated well to the 6MWD and the MFM. In accordance, the IBM-FRS was shown to correlate to traditional measures of efficacy in muscle testing in inclusion body myositis [24]. A closer look at the individual items possibly explains why the IBM-FRS correlated so well with clinical muscle function outcomes, while the PPS condition specific questionnaire SIPP-RS did not. The IBM-FRS mainly focuses on muscle groups essential to the activities of daily living, such as handgrip and quadriceps function [41], while the SIPP-RS reflects also secondary symptoms such as sleep disturbances, memory difficulties, and mood swings that may not parallel to functional changes.

To the best of our knowledge, this study is the first that assessed the association of various PROMs and several objective motor function measures and, therefore, our findings cannot be compared with some of the existing studies. The majority of previous studies in

individuals with PPS have focused on the association between self-reported gait performance and a specific impairment. Bickerstaff et al. showed that self-reported physical mobility decline over 10 years in patients with PPS and reported that reduced quadriceps muscle strength could only explain to a small extent the proportion of variance of the decline in walking capacity [15]. In another study, knee muscle strength was found to be a weak to moderate predictor of gait speed and walking distance in patients with PPS [42]. This study, in which several PROMs were used, adds new knowledge and increases our understanding of how a variety of self-reported impairments in persons with PPS can impact walking and motor abilities. However, more research is needed to increase understanding of how these self-reported impairments are related to objectively measured walking and motor abilities. It is important for future studies to assess changes over time in physical function and PROM scores to capture minimally important differences and clinically meaningful changes in individuals with PPS.

Our study highlights the complexity of the relationship between functional measures and patient's perspective of disability measured by PROMs. In practice, the SIPP-RS and IBM-FRS can be a complement when walking ability and secondary impairments in persons with late effects of polio or other neurological diseases are evaluated. The rating scales are quick, inexpensive, easy to administer, and they do not require any special equipment or training. The IBM-FRS appear to be the most appropriate PROM of the ones used in this analysis for the PPS population, since it had the lowest burden and it was well correlated with the functional assessments. However, it is important to state that PROMs cannot replace traditional gait performance tests. Further studies on longer time frame and/or using other PROMs addressing changes in daily living activities, may help to elucidate to which extend the available PROMs are capable of mirroring the functional changes and/or eventually to identify new valuable tools.

353 This study has a number of important clinical implications. Since no curative
354 treatment is available for PPS, rehabilitation management is considered the mainstay of
355 treatment. Persons with PPS should be offered individually tailored rehabilitation programs
356 by a multi-professional team, which should primarily target participants' activity and
357 participation in society and involve great sensitivity to individual needs [43; 44]. As muscle
358 fatigue, muscle weakness, muscle and/or joint pain during physical activity and several
359 disabilities in activities of daily living such as stand up from sitting position, climb stairs and
360 walking ability are reported as most common impairments, this implies that rehabilitation
361 management should primarily focus on limiting the impact of these impairments. By reducing
362 impairments, walking ability is expected to improve and the risk of falls to decrease [45].
363 Also, prescribing proper orthoses and assistive devices may facilitate daily life activities [9].
364 Moreover, since persons with PPS have learned to disregard their impairments in order to
365 achieve an active life, they might have difficulty with adapting their lifestyle to their
366 decreasing abilities and psychological support might be indicated [46].

367 There are a number of important limitations of this analysis. A clear limitation of the
368 study is the small sample size, which decreases the statistical power of the study. Sample size
369 calculations for the study were based on the primary endpoint (6MWD) on the larger
370 randomised controlled trial. A major limitation of this study was that one of the inclusion
371 criteria was set to ensure that participants had a higher level of mobility (ability to walk 350m
372 in 6 minutes). Thus, this showed no major shift in health-related quality of life and motor
373 function. In future studies, patients with broader range of function (also lower functioning
374 patients) should be included. Although analysis corrected for baseline values was carried out,
375 it is possible that important covariates such as fatigue, comorbidities etc. that may have had an
376 impact were missed. Based on our data collected only from one site in Switzerland, the
377 generalizability of our findings is reduced. Another limitation is the short observation period
378 of 6 months. More research and long-term studies, including long-term follow-up visits (at

least one year or more), are needed to establish if the observed trends are stable over longer periods.

Conclusions

Self-reported impairments and activities of daily living overall HRQOL and muscle function outcomes remained stable during 6 months in patients with PPS. Lower psychological health at 6 months was found compared to baseline. Patients reported higher scores in the social relationships and environmental health domains of HRQOL in comparison to general population. Further, association of clinical muscle outcomes and PROMs revealed a strong association between the IBM-FRS and the 6MWD and the total MFM score. By limiting the impact of reported impairments and disabilities in activities of daily living, physical abilities may be improved. Interdisciplinary rehabilitation programs considering individual needs are needed and should primarily target participants' activity and participation in society.

List of abbreviations

6MWD: 6 minute walking distance

HRQOL: Health-related quality of life

IBM-FRS: Inclusion body myositis – functional rating scale

MFM: Motor function measurement

PPS: Post-polio syndrome

PROM: Patient-reported outcome measure

SIPP-RS: Self-reported impairments in persons with late effects of polio rating scale

WHOQOL-BREF: World health organization (WHO) quality of life abbreviated scale

Declaration section

Ethics Approval and Consent to Participate

Eligible subjects were included in the study only after providing written informed consent. Ethics approval has been obtained from the local Ethics Committee (EKNZ 2015-221) and the National Swiss Drug Agency (Swissmedic, Reference number: 2016DR2067).

Consent for publication

We confirm that (1) the authors of this manuscript had access to all study data, are responsible for all contents of the manuscript, and had authority over the preparation of the manuscript and the decision to submit the manuscript for publication and (2) all authors have read and approved the submission of this manuscript to the journal.

Availability of data and supporting materials

Data used in the analysis is available upon request from the corresponding author. Patient-level data remains confidential under patient data privacy regulations.

Competing Interests

DF is principle investigator for studies on spinal muscular atrophy sponsored by Hofmann-La Roche Ltd. There are no other activities related to commercial companies. The authors declare that they have no competing interests.

Funding

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Authors' Contribution

VG participated in the design of the study, acquired data and drafted the manuscript. PH, AO and SiS participated in the design of the study and acquired data. VG and PH participated in patient recruitment. DR, NR, and VG participated in the organization and the conduct of the study. SaS performed the statistical analysis. DR participated in the design of the study. PW revised the manuscript critically for important intellectual content. DF designed the study, analyzed data and drafted the manuscript. All authors read and approved the final manuscript.

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References

1. Alexander, J. P., Jr., Gary, H. E., Jr., & Pallansch, M. A. (1997). Duration of poliovirus excretion and its implications for acute flaccid paralysis surveillance: a review of the literature. J Infect Dis, 175 Suppl 1, S176-182.
2. Dalakas, M. C. (2006). Sporadic inclusion body myositis—diagnosis, pathogenesis and therapeutic strategies. Nat Rev Neurol, 2(8), 437.
3. Gonzalez, H., Olsson, T., & Borg, K. (2010). Management of postpolio syndrome. Lancet Neurol, 9(6), 634-642.
4. Kling, C., Persson, A., & Gardulf, A. (2000). The health-related quality of life of patients suffering from the late effects of polio (post-polio). J Adv Nurs, 32(1), 164-173.
5. Laffont, I., Julia, M., Tiffreau, V., Yelnik, A., Herisson, C., & Pelissier, J. (2010). Aging and sequelae of poliomyelitis. Ann Phys Rehabil Med, 53(1), 24-33.
6. Tiffreau, V., Rapin, A., Serafi, R., Percebois-Macadré, L., Supper, C., Jolly, D., & Boyer, F.-C. (2010). Post-polio syndrome and rehabilitation. Ann Phys Rehabil Med, 53(1), 42-50.

7. Halstead, L. S. (1998). Post-polio syndrome. Sci Am, 278(4), 42-47.
8. Wiechers, D. O., & Hubbell, S. L. (1981). Late changes in the motor unit after acute poliomyelitis. Muscle Nerve, 4(6), 524-528.
9. Koopman, F. S., Beelen, A., Gilhus, N. E., de Visser, M., & Nollet, F. (2015). Treatment for postpolio syndrome. Cochrane Libr.
10. Hansson, B., & Ahlstrom, G. (1999). Coping with chronic illness: a qualitative study of coping with postpolio syndrome. Int J Nurs Stud, 36(3), 255-262.
11. Jacob, & Shapira. (2010). Quality of life and health conditions reported from two post-polio clinics in Israel. J Rehabil Med, 42(4), 377-379.
12. Thoren-Jonsson, A. L., & Grimby, G. (2001). Ability and perceived difficulty in daily activities in people with poliomyelitis sequelae. J Rehabil Med, 33(1), 4-11.
13. Finch, L., Venturini, A., Trojan, D., & Lemoignan, J. (1995). Assessment of the Health Status in Post-Polio Syndrome Patients in Developing Outcomes for a Rehabilitation Programme: A Preliminary Report. Qual Life Res, 426-427.
14. Thoren-Jonsson, A. L., Hedberg, M., & Grimby, G. (2001). Distress in everyday life in people with poliomyelitis sequelae. J Rehabil Med, 33(3), 119-127.
15. Bickerstaffe, A., Beelen, A., & Nollet, F. (2015). Change in physical mobility over 10 years in post-polio syndrome. Neuromuscul Disord, 25(3), 225-230.
16. Winberg, C., Flansbjer, U. B., Rimmer, J. H., & Lexell, J. (2015). Relationship between physical activity, knee muscle strength, and gait performance in persons with late effects of polio. PM R, 7(3), 236-244.
17. Black, N. (2013). Patient reported outcome measures could help transform healthcare. BMJ, 346, f167.
18. Health, U. S. D. o., Human Services, F. D. A. C. f. D. E., Research, Health, U. S. D. o., Human Services, F. D. A. C. f. B. E., Research, Health, U. S. D. o., Human Services, F. D. A. C. f. D., & Radiological, H. (2006). Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes, 4, 79.
19. Studenski, S. (2009). Bradypedia: is gait speed ready for clinical use? : Springer.
20. Garip, Y., Eser, F., Bodur, H., Baskan, B., Sivas, F., & Yilmaz, O. (2017). Health related quality of life in Turkish polio survivors: impact of post-polio on the health related quality of life in terms of functional status, severity of pain, fatigue, and social, and emotional functioning. Rev Bras Reumatol, 57(1), 1-7.
21. On, A. Y., Oncu, J., Atamaz, F., & Durmaz, B. (2006). Impact of post-polio-related fatigue on quality of life. J Rehabil Med, 38(5), 329.
22. Schmidt, S., Gocheva, V., Zumbrunn, T., Rubino-Nacht, D., Bonati, U., Fischer, D., & Hafner, P. (2017). Treatment with L-citrulline in patients with post-polio syndrome: study protocol for a single-center, randomised, placebo-controlled, double-blind trial. Trials, 18(1), 116.
23. Brogardh, C., Lexell, J., & Lundgren-Nilsson, A. (2013). Construct validity of a new rating scale for self-reported impairments in persons with late effects of polio. PM R, 5(3), 176-181; quiz 181.
24. Jackson, C. E., Barohn, R. J., Gronseth, G., Pandya, S., Herbelin, L., & Muscle Study, G. (2008). Inclusion body myositis functional rating scale: a reliable and valid measure of disease severity. Muscle Nerve, 37(4), 473-476.
25. Amato, A. A., & Barohn, R. J. (2009). Inclusion body myositis: old and new concepts. J Neurol Neurosurg Psychiatry, 80(11), 1186-1193.
26. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. (1998). Psychol Med, 28(3), 551-558.
27. Skevington, S. M., Lotfy, M., & O'Connell, K. A. (2004). The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res, 13(2), 299-310.

28. Pomeroy, I. M., Tennant, A., & Young, C. A. (2013). Rasch analysis of the WHOQOL-BREF in post polio syndrome. J Rehabil Med, 45(9), 873-880.
29. Andersen, L. K., Knak, K. L., Witting, N., & Vissing, J. (2016). Two-and 6-minute walk tests assess walking capability equally in neuromuscular diseases. Neurology, 86(5), 442-445.
30. Montes, J., McDermott, M., Martens, W., Dunaway, S., Glanzman, A., Riley, S., Quigley, J., Montgomery, M., Sproule, D., & Tawil, R. (2010). Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. Neurology, 74(10), 833-838.
31. Bérard, C., Payan, C., Hodgkinson, I., Fermanian, J., & Group, M. C. S. (2005). A motor function measure scale for neuromuscular diseases. Construction and validation study. Neuromuscul Disord, 15(7), 463-470.
32. Angermeyer, M. C., Kilian, R., & Matschinger, H. (2000). WHOQOL-100, WHOQOL-BREF (WHO-QOL): Handbuch für die deutschsprachigen Version der WHO Instrumente zur Erfassung von Lebensqualität: Hogrefe.
33. Cobb, S. (1976). Social support as a moderator of life stress. Psychosom Med.
34. Kaplan, R. M., & Toshima, M. T. (1990). The functional effects of social relationships on chronic illnesses and disability. In Social support: An interactional view. (pp. 427-453). Oxford, England: John Wiley & Sons.
35. Pierini, D., & Stuifbergen, A. K. (2010). Psychological Resilience and Depressive Symptoms in Older Adults Diagnosed with Post-Polio Syndrome. Rehabil Nurs, 35(4), 167-175.
36. Stuifbergen, A. K., Seraphine, A., Harrison, T., & Adachi, E. (2005). An explanatory model of health promotion and quality of life for persons with post-polio syndrome. Soc Sci Med, 60(2), 383-393.
37. McNaughton, H., McPherson, K., Falkner, E., & Taylor, W. (2001). Impairment, disability, handicap and participation in post-poliomyelitis subjects. Int J Rehabil Res, 24(2), 133-136.
38. Brogårdh, C., & Lexell, J. (2015). How various self-reported impairments influence walking ability in persons with late effects of polio. NeuroRehabilitation, 37(2), 291-298.
39. Kalpakjian, C. Z., Toussaint, L. L., Klipp, D. A., & Forchheimer, M. B. (2005). Development and factor analysis of an index of post-polio sequelae. Disabil Rehabil, 27(20), 1225-1233.
40. Brogårdh, C., Flansbjer, U.-B., Espelund, C., & Lexell, J. (2013). Relationship between self-reported walking ability and objectively assessed gait performance in persons with late effects of polio. NeuroRehabilitation, 33(1), 127-132.
41. Cortese, A., Machado, P., Morrow, J., Dewar, L., Hiscock, A., Miller, A., Brady, S., Hilton-Jones, D., Parton, M., & Hanna, M. (2013). Longitudinal observational study of sporadic inclusion body myositis: implications for clinical trials. Neuromuscul Disord, 23(5), 404-412.
42. Flansbjer, U.-B., Brogårdh, C., & Lexell, J. (2013). Muscle strength is only a weak to moderate predictor of gait performance in persons with late effects of polio. NeuroRehabilitation, 33(3), 457-464.
43. Bruno, R. L., & Frick, N. M. (1991). The psychology of polio as prelude to post-polio sequelae: behavior modification and psychotherapy. Orthopedics, 14(11), 1185-1193.
44. Nätterlund, B., & Ahlström, G. (1999). Experience of social support in rehabilitation: a phenomenological study. J Adv Nurs, 30(6), 1332-1340.
45. Brogårdh, C., & Lexell, J. (2014). Falls, fear of falling, self-reported impairments, and walking limitations in persons with late effects of polio. PM R, 6(10), 900-907.
46. Nollet, F. (2003). Post-polio syndrome, Orphanet Encyclopedia.

553 **Tables**

554 Table 1. Summary of PROMs and clinical outcomes at baseline (n = 27).

	Mean (±SD)	Possible range
PROMs		
WHOQOL-BREF		
Total Score	77.90 (±10.61)	0-100
Physical health	72.09 (±14.99)	0-100
Psychological health	76.85 (±16.11)	0-100
Social relationships	78.70 (±13.54)	0-100
Environmental health	84.14 (±10.79)	0-100
SIPP-RS	25.52 (±5.07)	13-52
IBM-FRS	33.89 (±3.75)	0-40
Clinical outcomes		
6MWD	391.52 (±132.24)	
MFM	83.87 (±12.85)	0-100

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557 Table 2. Comparison of HRQOL scores among participants with PPS and healthy general
558 population from normative data.

	Participants with PPS *n* = 27	General population *n* = 2073	Difference (95% CI)	*t*	*p*
WHOQOL-BREF					
Physical health	72.09 (±14.99)	76.92 (±17.68)	-4.83 (-10.76, 1.10)	-1.67	0.11
Psychological health	76.85 (±16.11)	74.02 (±15.68)	2.83 (-3.54, 9.20)	0.91	0.37
Social relationships	78.70 (±13.54)	71.83 (±18.52)	6.87 (1.52, 12.23)	2.64	**0.01****
Environmental health	84.14 (±10.79)	70.38 (±14.17)	13.76 (9.50, 18.03)	6.63	**<0.01****

559 *p* significant values in bold. *$p \leq 0.05$, **$p \leq 0.01$ or above.

560 Table 3. Comparison between baseline and 6 months follow-up visit for PROMs and clinical

561 outcomes.

	Baseline Mean (±SD)	6 months Mean (±SD)	Difference between the means (95% CI)	*t*	*p*
PROMs					
WHOQOL-BREF					
Total Score	77.90 (±10.61)	75.26 (±12.62)	-2.64 (-5.60, 0.33)	-1.83	0.08
Physical health	72.09 (±14.99)	69.86 (±16.29)	-2.23 (-6.14, 1.68)	-1.17	0.25
Psychological health	76.85 (±16.11)	72.38 (±17.42)	-4.48 (-8.86, -0.09)	-2.10	**0.05***
Social relationships	78.70 (±13.54)	76.85 (±13.54)	-1.85 (-5.87, 2.17)	-0.95	0.35
Environmental health	84.14 (±10.79)	82.06 (±12.24)	-2.08 (-6.28, 2.12)	-1.02	0.32
SIPP-RS	25.52 (±5.07)	24.93 (±5.35)	-0.59 (-2.02, 0.83)	-0.86	0.40
IBM-FRS	33.89 (±3.75)	33.30 (±4.58)	-0.59 (-1.53, 0.34)	-1.31	0.20
Clinical outcomes					
6MWD	391.52 (±132.24)	401.85 (±148.10)	10.33 (-9.96, 30.63)	1.05	0.30
MFM	83.87 (±12.85)	85.46(±12.19)	1.58 (-0.58, 3.74)	1.50	0.14

p significant values in bold. *$p \leq 0.05$, **$p \leq 0.01$ or above.

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Figure captions

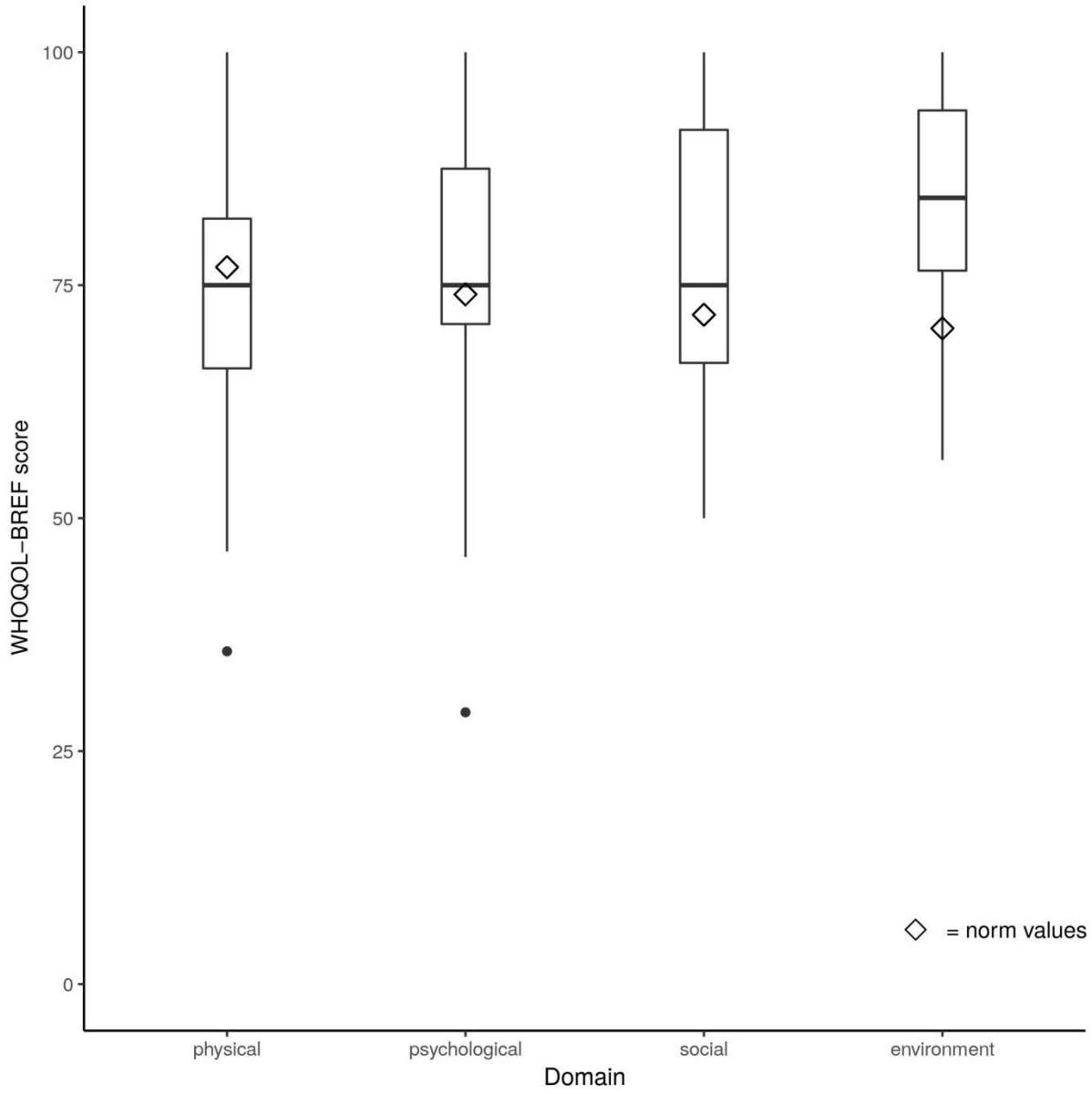
Figure 1. Distribution of the WHOQOL-BREF subscales at baseline of study participants compared to normative data.

Figure 2. Change over time for the SIPP-RS and the IBM-FRS.

Figure 3. The relationship between the IBM-FRS and the clinical outcomes at baseline. The grey surface represents the 95% CI.

571 **Figures**

572 Figure 1



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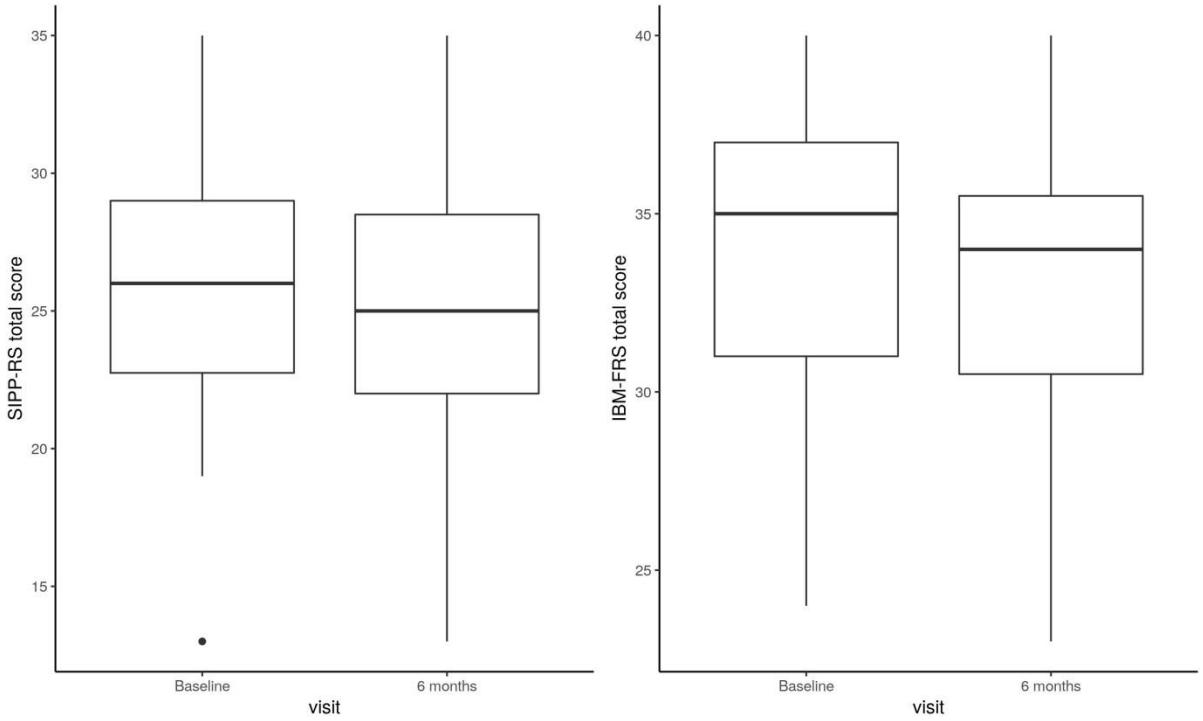
582 Figure 2



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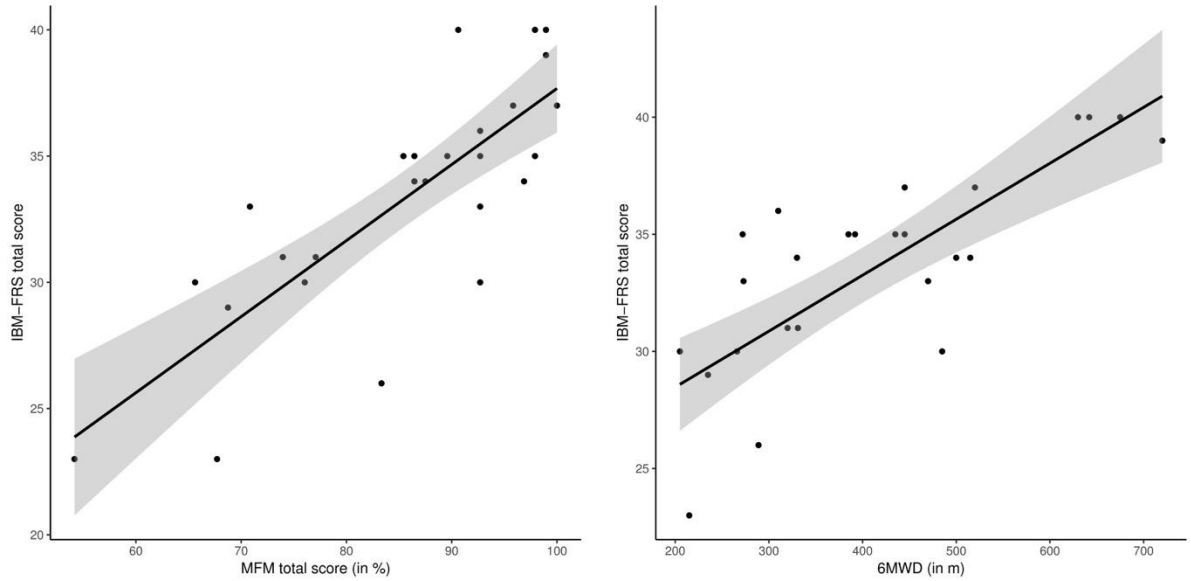
585 Figure 3



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2.2. Manuscript 2: Association between health-related quality of life and motor function in ambulant and non-ambulant Duchenne muscular dystrophy patients

Journal: Journal of Child Neurology – accepted

Authors: Gocheva V, Schmid S, Orsini AL, Hafner P, Schaedelin S , Rueedi N, Weber P, Fischer D

Abstract: This cross-sectional study assessed health-related quality of life (HRQOL) in ambulant and non-ambulant patients with Duchenne muscular dystrophy (DMD), and explored the association between HRQOL and clinically assessed motor function. The PedsQL™ Generic Core Scale and PedsQL™ Neuromuscular module were completed by 34 parent-child dyads. Association between PedsQL™ scores and overall motor abilities and the transfers and standing posture domain measured by motor function measure (MFM) were examined. Child self-reported and parent proxy-reported mean PedsQL™ scores for children with DMD were lower than those for healthy children for physical and psychosocial HRQOL. Fifty-six percent of patients reported clinically impaired psychosocial HRQOL scores. Several aspects of the generic and disease-specific HRQOL in patients with DMD were positively associated to overall motor function and transfers and standing posture domain. Associations remained stable when adjusted for age and corticosteroid use. The MFM is clinically meaningful in the context of a patient's day-to-day life.

Association between health-related quality of life and motor function in ambulant and non-ambulant Duchenne muscular dystrophy patients

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Abstract

This cross-sectional study assessed health-related quality of life (HRQOL) in ambulant and non-ambulant patients with Duchenne muscular dystrophy (DMD), and explored the association between HRQOL and clinically assessed motor function. The PedsQL™ Generic Core Scale and PedsQL™ Neuromuscular module were completed by 34 parent-child dyads. Association between PedsQL™ scores and overall motor abilities and the transfers and standing posture domain measured by motor function measure (MFM) were examined. Child self-reported and parent proxy-reported mean PedsQL™ scores for children with DMD were lower than those for healthy children for physical and psychosocial HRQOL. Fifty-six percent of patients reported clinically impaired psychosocial HRQOL scores. Several aspects of the generic and disease-specific HRQOL in patients with DMD were positively associated to overall motor function and transfers and standing posture domain. Associations remained stable when adjusted for age and corticosteroid use. The MFM is clinically meaningful in the context of a patient's day-to-day life.

Keywords Duchenne muscular dystrophy; health-related quality of life; Pediatric Quality of Life Inventory (PedsQL); clinical outcome measures; motor function

Introduction

Duchenne Muscular Dystrophy (DMD) is a genetic X-linked recessive disease with the second highest incidence considering all the hereditary diseases.[1] DMD affects 1 in 3600 to 6000 live male births.[2] Mutations in the dystrophin gene lead to the absence of the protein dystrophin, which leads to progressive muscle degeneration causing muscle weakness and resulting in loss of independent ambulation by the age of 13 years.[3]

Besides functional impairment, the impact of the disease on additional biopsychosocial aspects such as quality of life should not be underestimated. Regulatory authorities, researchers, and clinicians start to recognize the importance of health-related quality of life (HRQOL) measures in natural history and clinical trials. The impact of possible functional changes on daily living activities and more generally, on patients' quality of life is increasingly explored.[4, 5] HRQOL is a multidimensional construct, consisting at minimum of physical, psychological (including emotional and cognitive), and social health domains defined by the World Health Organization.[6, 7] The HRQOL is thought to be the best representation of patient perceptions concerning the impact of an illness and its treatment on their own functioning and well-being.[6, 7] A variety of age-appropriate instruments are given allowing the assessment of child and adolescent HRQOL by means of self- and parent-reports.[8] Wei et al. pointed out in their review that the Pediatric Quality of Life Inventory (PedsQL^{TM}) appears to be the most comprehensive and validated measure for clinical use and research in DMD patients.[9] The PedsQL^{TM} Generic Core Scale is the most widely used tool to assess generic quality of life in clinical studies. A specific module for neuromuscular disorders, the PedsQL^{TM} Neuromuscular Module, has been validated in DMD and spinal muscular atrophy.[10, 11] Several studies have reported the use of these instruments in DMD cohorts.[10, 12-16]

The reports on the HRQOL in DMD patients in previous studies are still controversial. Some researchers reported reduced HRQOL among DMD patients compared to healthy children both for parent-proxy report and child self-report[12-17], others have found no differences in the HRQOL between DMD patients and healthy controls except the physical domain of HRQOL.[18-21]

While many functional and strength-based performance tests quantify aspects of a clinically meaningful function (e.g. motor abilities), they do not directly assess the patient's HRQOL or participation in daily activities. Determining the impact of a disease on HRQOL and understanding the association of HRQOL to motor function can provide useful information for medical care, education, and welfare decision-making. However, until now the relationship between motor function and HRQOL in DMD patients is unclear. Additionally, research so far is often limited to only ambulant DMD patients.[14, 18, 22] A summary of previous literature investigating the association between HRQOL and functional outcomes is presented in Table 1. The aims of the study are to assess general and disease-specific HRQOL in ambulant and non-ambulant DMD patients, to compare general HRQOL data with normative data of healthy children, and to assess parent-child agreement. Further, we explore the association between HRQOL and clinical assessment of motor function in patients with DMD.

Methods

Participants

We performed an observational cross-sectional study of DMD patients who have participated in the past in two investigator-initiated clinical trials[23, 24] at the Division of Neuropediatrics, University Children's Hospital Basel. Former participants from both studies were invited to participate for the observational single visit 2.5 up to 5 years after completion of the clinical trial. Of the 48 former participants invited to participate 34 (71%) subjects, 33 boys and 1 girl, with molecular diagnosis of DMD and their respective caregivers agreed to participate and were included in this study. The age range of the patients who did not participate in this study was 10.2 to 14.9 years. Inclusion criteria for this study were being able to provide informed consent and comply with the study procedures. Children aged between 8.5 and 16 years were included. The study was approved by the local Ethics Committee (EKNZ 2017-01028). Informed consent was obtained from study participants and their parents.

The healthy children sample was derived from a normative sample of 9566 families previously collected by Varni and colleagues.[25] Healthy children are those children who were assessed either in physicians' offices during check-ups and/or whose parents did not report the presence of a chronic health condition. Data was obtained from the children and their caregivers. We used this normative sample in our study to compare the HRQOL child self- and parent proxy-reports of children with DMD to healthy peers.

Procedures

Patients were contacted by telephone and email and asked if they are willing to participate in the study. After obtaining an explanation of the study, subjects agreed to participate willingly and voluntarily by signing the informed consent or giving assent (children under the age of 11). During the visit at the hospital, each participant was assessed individually in rooms containing a mat, a stretcher, and the material required to answer the scales and questionnaires. Participants were evaluated by trained physical therapists. The MFM was used to assess the motor functional status.[26] HRQOL was assessed with the generic module PedsQL™ Generic Core Scale[27] and the disease-specific module PedsQL™ 3.0 Neuromuscular module.[11] Participants were allowed to take a short rest when necessary while answering the questionnaires. Each caregiver answered to the questionnaires while the participants were assessed with the MFM. Eighteen patients out of 34 had difficulties in getting to the hospital (mainly due to loss of ambulation) and received the questionnaires by mail and were interviewed by telephone about their current clinical status.

Measures

Generic Health-Related Quality of Life. Generic health-related quality of life was assessed with the PedsQL™ 4.0 Generic Core Scale (PedsQL™ GCS). The PedsQL™ 4.0 Generic Core Scale was developed to assess HRQOL in children and adolescents aged 2-18 years in both healthy and disease populations. [27] The PedsQL™ GCS contains 23 items across four domains: physical (8 items), social (5 items), emotional (5 items) and school (5 items) functioning. Items are linearly transformed to a 0-to-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0), so that higher scores indicate better HRQOL. Scale scores are computed as the sum of the items divided by the number of items that were answered.

To create a psychosocial health summary score, the mean is computed as the sum of the items divided by the number of items in the emotional, social, and school functioning scales. The PedsQL™ GCS is composed of parallel child self-report and parent proxy-report formats.

Disease-Specific Health-Related Quality of Life. Disease-specific health-related quality of life was assessed with the PedsQL™ 3.0 Neuromuscular Module (PedsQL™ NMM). The PedsQL™ 3.0 Neuromuscular module was developed specifically for use in neuromuscular diseases including spinal muscular atrophy (SMA) and DMD. [11] The measure contains 25 items across three domains: about my neuromuscular disease (17 items related to the disease process and associated symptomatology), communication (3 items related to the patient's ability to communicate with health care providers and others about his/her illness), and about my family resources (5 items related to family financial and social support systems). The format, instructions, Likert response scale, and scoring method for the PedsQL™ NMM are identical to the PedsQL™ GCS. Higher scores on the PedsQL™ NMM indicate lower problems, therefore better disease-specific HRQOL. The PedsQL™ NMM is composed of parallel child self-report and parent proxy-report formats. Both scales, the PedsQL™ GCS and the PedsQL™ NMM, have previously been found to be valid and reliable in paediatric patients with DMD.[10]

Motor Function. Motor function was assessed with the Motor Function Measure (MFM). The MFM is a validated quantitative scale used for assessment of motor abilities of both ambulant and non-ambulant patients with neuromuscular disorders. [26] It includes 32 items that evaluate three dimensions of motor performance, including specific motor functions, such as the "transfers and standing posture" as the first dimension (D1) of the MFM, the proximal and axial motor functions (second dimension of the MFM; D2), and the distal motor function (third dimension of the MFM; D3). Each item is scored on a scale from 0 (does not initiate movement) to 3 (completes the item with a standard pattern). The items are summed to comprise the overall motor function (MFM total score) involving all of the motor dimensions, where the maximum represents normal motor function (100%). In this study, we analysed

the MFM total score and its D1 subscore. D2 and D3 domains were not analyzed because they remain relatively stable at this disease stage and usually decline at more advanced disease stages.

Statistical Analysis

Because this was an observational study and did not test a predefined hypothesis, sample size was not dependent on a formal calculation. All subjects who performed the questionnaires were included in the analysis. Descriptive statistics were generated for demographic and clinical variables and reported as mean and SD values for continuous variables and frequencies/proportions for categorical variables. Mean PedsQL™ scale and total scores were calculated for the DMD self- and parent-proxy reports. One sample t-tests were used to investigate, if the PedsQL™ GCS scores of DMD patients differed from the scores of healthy peers from a normative sample collected by Varni and colleagues.[25] Subgroup analyses were performed, where the DMD patients were stratified by ambulation status (ambulant vs. non-ambulant). The proportion of patients with DMD who reported clinically significant PedsQL™ GCS subscores was calculated; the cut off score for "clinical significance" was defined as >1SD below the mean value of the healthy population sample mean.[28] Furthermore, the PedsQL™ scores were presented graphically. Thereby the mean and the 95 % confidence interval (CI) were shown. For the healthy norm sample, the CI was calculated from the SD and the number of patients reported in the literature assuming normal distribution. In order to assess parent-child agreement, intraclass correlation coefficients (ICCs) together with their 95% Cis, calculated using 999 bootstrap replicates, were calculated between PedsQL™ child self-report and parent proxy-report. [29] To this end the score was modelled in a mixed effects model using patient as random effect (one-way random-effects model). The variance due to difference between patients was divided by the total variance seen in the data. Therefore, the ICC indicates the percentage of total score variance attributable to the difference between patients. The ICC has a value between 0 and 1, where 1 would indicate that the inter-patient variance explains all the observed variance, and thus implies perfect agreement between parents and child. ICCs are designated as 0.40 for poor to fair agreement; 0.41 to 0.60 for moderate agreement; 0.61 to 0.80 for good agreement; and 0.81 to 1.00 for excellent agreement.[30] Furthermore, bivariate analysis using Spearman correlation was conducted to determine the association between

PedsQL™ and motor function was assessed. Subgroup analyses were conducted aiming to explore the association between PedsQL™ and the D1 score in ambulant and non-ambulant DMD patients, respectively. Correlation coefficients were interpreted as follows: 0 to 0.29 little to negligible correlation; 0.30 to 0.49 low correlation; 0.50 to 0.69 moderate correlation; 0.70 to 0.89 high correlation; and correlations ≥ 0.90 indicated a very high correlation.[23] No correlation for multiple testing was performed. Linear regression analyses (multivariate analysis) were conducted to determine the stability of the association between HRQOL and motor function when adjusted for age and corticosteroid use. For these analyses the following variables were entered into the equations simultaneously: child age, corticosteroid use (yes/no), MFM total score and D1 subscore separately, with each of the PedsQL™ scores GCS and NMM total scores for child self-report and parent proxy-report as the dependent variable. Data were analyzed using R. Significance was set at $p<.05$ for all statistical analyses.

Results

Sample Characteristics

Thirty three boys and one girl with DMD and their caregivers participated in the study. Demographic characteristics of the DMD sample and normative sample are shown in Table 2. The mean age of the participants was 11 years (range 9-14.1 years). Among all participants, 25 of 34 (73.5%) took corticosteroids (prednisone or deflazacort). 14 patients (41.2%) were ambulant, 20 were not able to walk 10m without assistance (58.8%). No patient needed assisted ventilation. Caregiver respondents included mothers (79.4%), fathers (17.6%) and other family members (2.9%). Most parents were married (73.5%). Most families lived in a rural neighborhood (58.8%), and did not participate in a DMD support group (67.7%).

Generic and Disease-Specific Health-Related Quality of Life in Duchenne Muscular Dystrophy Patients and Comparison to Healthy Sample

Descriptive statistics for the PedsQL™ GCS and NMM child self-report and parent proxy-report and comparisons with healthy children scores are shown in Table 3. Examining the PedsQL™ GCS subscores, patients and their parents rated the physical health with the lowest mean score (relating to the highest impairment) followed by social functioning, emotional functioning, and finally school functioning with the highest mean score (relating to the least impairment). The same pattern was seen in both subgroups of ambulant and non-ambulant patients (Table S1). Regarding disease-specific PedsQL™ NMM in Figure 1, participants indicated about my neuromuscular module with the highest score (relating to the least impairment), followed by about my family resources, and communication (relating to the highest impairment). Parents rated about my neuromuscular module with the highest score (relating to the least impairment), followed by communication, and about my family resources.

As shown in Figure 2, DMD patients revealed significantly lower scores in all subscores, both for parent-proxy report and child self-report, compared to the normative values of healthy children ($p<0.01$). The largest difference in mean scores for the DMD patients compared to healthy children is seen in the physical health and the smallest in the school functioning. Subgroup analyses revealed that child self-report and parent-proxy report of non-ambulant DMD patients display significantly lower scores in all subscores compared to the normative values of healthy children ($p<0.01$). The same pattern was detected for ambulant DMD patients, with exception for child self-report emotional functioning ($p=0.07$) and school functioning ($p=0.08$) that did not differ significantly from normative data.

By self-report, 55.9% of all patients had a psychosocial health summary score below 66.03, the cut off point for significantly impaired HRQOL in the general pediatric population.[28] Noticeably, 64.7% of the patients had a social score below the cut off point of 66.61. As reported by parents, 60.6 % of the children with DMD had psychosocial health summary scores below 64.38, the cut off score for significantly impaired psychosocial HRQOL. [28]

Parent-Child Concordance of Health-Related Quality of Life

In light of observed differences between the perceptions of children and their parents, ICCs were examined for each of the PedsQL™ GCS and NMM scales. As shown in Table 4, the majority of ICCs for the PedsQL™ GCS indicated poor to moderate parent-child agreement for the general HRQOL. For the PedsQL™ NMM, the majority of the ICCs were of good agreement, indicating that parent and children tend to agree well in their evaluation for the disease-specific HRQOL. The greatest overall agreement was found on the PedsQL™ NMM communication scale.

Correlation between the Subscales of Health-Related Quality of Life and Motor Function

The mean of the MFM total score was 65% (SD=18.96) and the D1 subscore 31% (SD=32.40). As expected, the subscores D2 and D3 were only mildly impaired at this disease stage (D2: M=87.85; SD=13.41; D3:M=88.69; SD=10.98) and were therefore excluded from the analysis.

PedsQL™ child self-report

As shown in Table 5, the correlation between the PedsQL™ GCS total score showed moderate positive correlation with the MFM total score ($r=0.59$, $p=0.02$) and high positive correlation with the D1 score ($r=0.73$, $p<0.01$), indicating that higher generic HRQOL could be seen in patients with better motor function and better standing and transfer abilities. A high positive correlation between the domain physical health and the MFM total score ($r=0.79$, $p<0.01$) and the D1 score ($r=0.88$, $p<0.01$) was found, which shows that patients with DMD, who have better overall motor function as well as standing and transfer abilities, perceive their physical health as better. A moderate positive correlation exists between psychosocial and social functioning compared to the D1 subscore (psychosocial: $r=0.51$, $p=0.04$; social: $r=0.53$, $p=0.03$), indicating that lower psychosocial and social health could be seen in patients with worsening ability to stand and transfer on their own.

For the PedsQL™ NMM, a moderate positive correlation was found between the total score and the MFM total score ($r=0.57$, $p=0.03$) and the D1 subscore ($r=0.65$, $p<0.01$), indicating that better general

motor function and their standing and transfer abilities are associated with higher disease-specific HRQOL in DMD patients. In accordance, we found a moderate positive correlation between the about my neuromuscular disease domain and the MFM total score (r=0.56, p=0.032) and the D1 (r=0.56, p=0.031). Additionally, a moderate to high correlation between about my family resources domain and the MFM total (r=0.60, p=0.019) and the D1 subscore (r=0.70, p<0.01) existed, indicating that poorer motor function could be seen in patients with worsening family financial and social support system resources. All the other correlations were not significant.

Subgroup analysis for ambulant patients revealed high positive correlation between the PedsQL™ GCS total score and the MFM total score (r=0.77, p=0.02) and the D1 score (r=0.74, p=0.02) (Table S2). Also, the domain physical health correlated with the MFM total score (r=0.80, p<0.01) and the D1 score (r=0.79, p=0.01). No significant correlations were found for non-ambulant patients.

PedsQL™ parent proxy-report

For the PedsQL™ GCS, a high positive correlation between physical health and the MFM total score (r=0.81, p<0.01) as well as the D1 subscore (r=0.86, p<0.01) exists, indicating that parents perceive a higher patients' physical health in patients with better motor function and ability of stand and transfer. Similarly, for the PedsQL™ NMM, a moderate positive correlation was found between the total score and the D1 subscore (r=0.57, p=0.02). Additionally, a moderate correlation exists between the about my neuromuscular disease domain, the about my family resources and the D1 subscore (neuromuscular: r=0.54, p=0.03, family resources: r=0.50, p=0.048). All the other correlations were not significant. Correlations of the specific subscales of the PedsQL™ GCS and NMM and motor function derived from the MFM are shown in Table 5. In figure 3, the association between the PedsQL™ GCS physical health and MFM total score as well as D1 subscore for both parent proxy-report and child self-report are presented.

Subgroup analysis for ambulant patients revealed a high positive correlation between the PedsQL™ GCS physical health domain and the MFM total score (r=0.82, p<0.01) and the D1 score (r=0.75, p=0.02). The PedsQL™ GCS physical health indicated high negative correlation with the MFM total

(r=-0.89, p=0.04) in non-ambulant patients, showing that parents of non-ambulant patients who have high overall motor function evaluate their physical health as poor. Moreover, a high negative correlation was found between the PedsQL^{TM} NMM total score and the MFM total score (r=-0.79, p=0.05), indicating that better general motor function is associated with lower parents rated disease-specific HRQOL in non-ambulant patients.

Table 6 presents multivariate analysis only for the D1 subscore, since the D1 score revealed higher correlations with HRQOL scores than the MFM total score in the univariate analysis. Significant associations between PedsQL^{TM} and MFM total score from the univariate analysis retained their independent significance in the multivariate analyses, when adjusted for age and corticosteroid use. Results of the multivariate analysis which had the PedsQL^{TM} GCS total score (child self-report) as the dependent variable and the D1 score, age and corticosteroid use as the independent variables yielded that the D1 score contributed significantly to the regression model (β=0.42, CI: 0.21;0.62, p<0.01), when adjusted for age and corticosteroid use. Similarly, for the PedsQL^{TM} NMM total score child self-report and parent proxy-report, the D1 score was found to be significantly contributor to the regression model (child self-report: β=0.43, CI: 0.09;0.55, p=0.01; parent proxy-report: β=0.36, CI: 0.09;0.63, p=0.01).

Discussion

This cross-sectional study demonstrated several moderate to high correlations between different aspects of generic and disease-specific HRQOL in DMD patients and their functional motor function. The aim of this study was not to duplicate previous reports on HRQOL in DMD or their correlation with different demographic data, but to establish the value of the PedsQL^{TM} in assessing HRQOL in relation to possible functional changes of the MFM. As expected, the physical health correlated with the MFM and its standing and transfer subdomain both on child self-report and parent-proxy report. This finding is in line with previous study results including different functional outcomes.[14, 22, 31]To the best of our knowledge, this is the first observational study to show a significant association between

the self-reported psychosocial health, the social functioning score, and the standing and transfer functional score of the MFM. A possible explanation for this could be that due to the progressive physical weakness experienced by DMD children, their ability to participate in a variety of physical and social activities is limited. Children may miss out on the opportunity to maintain relationships and participate in social activities, where wheelchair access is not given.[32] Further, periods in which disease severity increases (e.g. losing the ability to stand and to transfer, becoming wheelchair dependent) may be associated with experiencing more emotional difficulties such as feeling anxious or depressed.

At a variance with previous studies [14, 18, 31], we also used the PedsQL™ NMM, which was developed specifically for the use in neuromuscular diseases and has previously been found to be valid and reliable in DMD .[10] Notably, its use did not appear to increase the level of significance compared to the general module except for the family resources domain that correlated better with the functional motor function in the children's questionnaire. Poorer patients' motor function was associated with worsening of family financial and social support system resources. Therefore, families are overburdened by the illness and by the responsibilities of caring for their child that they are more likely to experience chronic emotional stress because of overcommitment, family conflict, and the demands of caring for their child with complex medical needs.[33, 34] Other problems that are frequently addressed are the social isolation and financial considerations of the families which also may be a burden.[35-37] Another explanation could be that the socio-economic status of the family may have an influence on the HRQOL, so that children with chronic disease from lower socio-economic backgrounds experience reduced HROQL compared with their wealthier counterparts independent of the neurological course of the disease.[38]

The subgroup of ambulant patients reported that their generic HRQOL and their physical health correlated with the MFM and its standing and transfer subdomain. While parents of ambulant patients reported that their physical health is positively associated with the overall motor function, in non-ambulant patients this association was negative, indicating that parents rate the physical health of non-ambulant patients who have better overall motor function as poor. A possible explanation for this

finding may be that since in general parents' ratings tend to be lower than patient self-reports, parents may underrate the HRQOL of non-ambulant patients and patients may have already adapted to their physical difficulties while their parents still have not.

It is important to note that the statistically significant positive correlation between generic and disease-specific HRQOL and the standing and transfer subdomain of the MFM obtained in the bivariate analysis was also observed in the multivariate analysis, when adjusted for age and corticosteroid use. Previous findings indicated no significant effects of corticosteroids on PedsQL™ measures in DMD patients confirming our findings.[14] This is the first study to describe a significant association between different aspects of the HRQOL such as psychosocial health, social functioning, family resources, and functional outcome measures. Since previous studies examined only ambulant DMD patients [14, 18, 22], we included both ambulant and non-ambulant DMD patients. This may reveal different results because of neglect of the natural disease progression. In one study, the PedsQL™ GCS generic physical functioning score and the PedsQL™ NMM about my neuromuscular disease score were significantly different in full-time wheelchair users versus part-time/full-time ambulatory patients.[10] However, it is important to note that our results are to be interpreted with caution as only 16 participants (47%) performed the MFM and the separate patient groups stratified by ambulation status were very small.

Consistent with results of previous studies [10, 12, 14-16], our findings reflect that the HRQOL of children with DMD is considerably affected in the physical and psychosocial domain compared to healthy peers. An impaired psychosocial health was detected in more than half of the children. These data confirm previous findings showing that between 30% and 50% of DMD boys have psychosocial problems.[15, 39, 40] A possible explanation could be that younger children with DMD may not have developed effective coping strategies yet and therefore still have difficulties adjusting emotionally to living with the disorder. Several studies found a trend toward improved psychosocial functioning with advancing age, indicating that adolescents with DMD tend to report better psychosocial functioning than younger affected individuals.[15, 40] Additionally, confrontation with the consequences of the disease (such as increased physical complaints, wheelchair dependency etc.) can be associated with

362 emotional difficulties.[41] Noticeably, the social functioning was found to be the second most impaired
363 domain. More than sixty percent of the participants reported significantly impaired social functioning.
364 This finding supports previous studies that suggested that children with DMD score significantly
365 worse on the Social Problems scale than either unaffected siblings or children with cerebral palsy,
366 independent of their cognitive abilities or motor impairment.[42] This may be due to the fact that
367 children with DMD appear to have mild difficulties in matching facial affects suggesting that they
368 may lack the subtle social perception skills which are necessary for optimal interpersonal integration.
369 Hendriksen and colleagues found that functioning in peer relations was decreased with increasing
370 age.[40] It is essential to identify those children who show early signs of social adjustment difficulties to
371 initiate behavioral counselling services such as social-skills training in expedient manner as secondary
372 and tertiary preventive interventions.[43] Subgroup analyses indicated that ambulant and non-ambulant
373 patients and their parents rated the HRQOL as lower compared to healthy peers in all domains, apart
374 from the finding that ambulant patients rated their reported emotional and school functioning as
375 comparable to healthy peers. However, it is important to note that this finding is to be interpreted with
376 caution as the ambulant patients group consisted of only 14 participants.

377 Our findings suggest that parents generally rated their child's HRQOL lower than children
378 themselves did, which has been consistently observed in DMD patients and across a number of other
379 pediatric chronic illnesses.[10, 15, 31, 44] This difference tends to be greater in the psychosocial domains
380 than in the physical domain. There are a number of possible explanations for this observation: children
381 may have adapted better to their illness than their parents have, and parents may not always have the
382 most accurate assessment of their child's emotional state. In addition, parents' own worries and fears
383 about their child's disease may influence their assessment of their child's HRQOL. Until now, few
384 studies included both child-self reports and parent proxy-reports about HRQOL in DMD and
385 investigated the level of agreement between children's self-reports and parents' reports. Poor to
386 moderate parent-child agreement was found for the PedsQL™ GCS and good parent-child agreement
387 for the PedsQL™ NMM. In studies that used the PedsQL™ GCS, we could replicate the findings
388 revealing that only the school domain had moderate concordance, while other domains had poor
389 concordance.[10, 15, 31] Taken together, the data suggests that DMD patients and their parents tend to

agree better on disease-specific HRQOL aspects that on general HRQOL. Evaluating both children's and parents' perspectives regarding HRQOL should be the standard for routine assessment in clinical practice and clinical trials for children with neuromuscular disorders because their different perspectives potentially provide different unique information.

This study documented association between different aspects of patient-reported generic and disease-specific HRQOL and clinician-measured motor abilities. This lent support to the concept that the commonly used MFM is "clinically meaningful" in the context of a patient's day-to-day-life. In the present study we observed that several aspects of HRQOL in patients with DMD (specifically the physical health, psychosocial health, social functioning etc.) are positively related to motor function. Further studies on longer time frame may help to explain the complexity of the relationship between HRQOL and functional performances. McDonald and colleagues concluded that the Pediatric Outcomes Data Collection Instrument (PODCI) is more sensitive to DMD disease progression than the PedsQL™.[14] Future studies should include additional tools measuring HRQOL, such as the PODCI and/or specific questionnaires addressing changes in activity of daily living.

There are a number of important limitations of this analysis. This study only included one cross-sectional assessment; therefore longitudinal studies are needed in order to confirm the association between motor function and patient-reported HRQOL. Although both global and disease-specific HRQOL were correlated with the functional status of the patients, other factors (e.g. socioeconomic status etc.) may also influence HRQOL. Another limitation is that the association between HRQOL and motor function was adjusted for age and corticosteroid use, which is only possible to a limited extent due to the study's small sample size. It will be important to replicate these findings in a larger sample. Moreover, all included patients participated already in a clinical trial which may bias the results. Since the motor function was performed in less severely affected DMD patients, a selection bias can be assumed for the estimated motor function.

List of abbreviations

CI – Confidence Interval

DMD – Duchenne Muscular Dystrophy

HRQOL – Health-Related Quality of Life

ICC - Intraclass Correlation Coefficient

MFM – Motor Function Measure

PedsQL™ - Pediatric Quality of Life Inventory

PODCI - Pediatric Outcomes Data Collection Instrument

Disclosure section

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Author Contributions

VG participated in the design of the study, acquired data and drafted the manuscript. PH, AO and SiS participated in the design of the study and acquired data. VG and NR participated in patient recruitment. NR and VG participated in the organization and the conduct of the study. SaS performed the statistical analysis. PW revised the manuscript critically for important intellectual content. DF designed the study, analysed data and drafted the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

DF is principle investigator for studies on spinal muscular atrophy sponsored by Hofmann-La Roche Ltd. There are no other activities related to commercial companies. All authors declare that they have no conflict of interest.

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Ethical approval

Ethics approval has been obtained from the local Ethics Committee (EKNZ 2017-01028). All the research meets the ethical guidelines, including adherence to the legal requirements of the study country.

References

1. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010;9(1): 77-93.
2. Mendell JR, Shilling C, Leslie ND, et al. Evidence-based path to newborn screening for Duchenne muscular dystrophy. *Ann Neurol*. 2012;71(3): 304-13.
3. Hoffman EP, Brown RH and Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell*. 1987;51(6): 919-28.
4. Acquadro C, Berzon R, Dubois D, et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001. *Value Health*. 2003;6(5): 522-31.
5. Mendell JR, Csimma C, McDonald CM, et al. Challenges in drug development for muscle disease: a stakeholders' meeting. *Muscle Nerve*. 2007;35(1): 8-16.
6. Food and Administration D. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. *Fed Regist*. 2009;74(235): 65132-3.
7. Organization WH. World health organization constitution. *Basic documents*. 1948;1: 22.
8. Solans M, Pane S, Estrada MD, et al. Health-related quality of life measurement in children and adolescents: a systematic review of generic and disease-specific instruments. *Value Health*. 2008;11(4): 742-64.
9. Wei Y, Speechley K and Campbell C. Health-Related Quality of Life in Children with DuchenneMuscular Dystrophy: A Review. *J Neuromuscul Dis*. 2015;2(3): 313-24.
10. Davis SE, Hynan LS, Limbers CA, et al. The PedsQL™ in Pediatric Patients with Duchenne Muscular Dystrophy: Feasibility, Reliability, and Validity of the Pediatric Quality of Life Inventory Neuromuscular Module and Generic Core Scales. *J Clin Neuromuscul Dis*. 2010;11(3): 97-109.
11. Iannaccone ST, Hynan LS, Morton A, Buchanan R, Limbers CA and Varni JW. The PedsQL™ in pediatric patients with spinal muscular atrophy: Feasibility, reliability, and validity of the pediatric quality of life inventory™ generic core scales and neuromuscular module. *Neuromuscul Dis*. 2009;19(12): 805-12.
12. Bendixen RM, Senesac C, Lott DJ and Vandenborne K. Participation and quality of life in children with Duchenne muscular dystrophy using the International Classification of Functioning, Disability, and Health. *Health Qual Life Outcomes*. 2012;10(1): 1.
13. Landfeldt E, Lindgren P, Bell CF, et al. Health-related quality of life in patients with Duchenne muscular dystrophy: a multinational, cross-sectional study. *Dev Med Child Neurol*. 2016;58(5): 508-15.

14. McDonald CM, McDonald DA, Bagley A, et al. Relationship between clinical outcome measures and parent proxy reports of health-related quality of life in ambulatory children with Duchenne muscular dystrophy. *J Child Neurol*. 2010;25(9): 1130-44.
15. Uzark K, King E, Cripe L, et al. Health-related quality of life in children and adolescents with Duchenne muscular dystrophy. *Pediatrics*. 2012;130(6): e1559-66.
16. Wei Y, Speechley KN, Zou G and Campbell C. Factors associated with Health-Related Quality of Life in children with Duchenne muscular dystrophy. *J Child Neurol*. 2016;31(7): 879-86.
17. Baiardini I, Minetti C, Bonifacino S, et al. Quality of life in Duchenne muscular dystrophy: the subjective impact on children and parents. *J Child Neurol*. 2011;26(6): 707-13.
18. Henricson E, Abresch R, Han JJ, et al. The 6-minute walk test and person-reported outcomes in boys with duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year. *PLoS currents*. 2013;5.
19. Kohler M, Clarenbach CF, Böni L, Brack T, Russi EW and Bloch KE. Quality of life, physical disability, and respiratory impairment in Duchenne muscular dystrophy. *Am J Respir Crit Care Med*. 2005;172(8): 1032-6.
20. Opstal SHv, Jansen M, van Alfen N and de Groot IJ. Health-related quality of life and its relation to disease severity in boys with Duchenne muscular dystrophy: satisfied boys, worrying parents—a case-control study. *J Child Neurol*. 2014;29(11): 1486-95.
21. Simon VA, Resende MBD, Simon MA, Zanoteli E and Reed UC. Duchenne muscular dystrophy: quality of life among 95 patients evaluated using the Life Satisfaction Index for Adolescents. *Arq Neuropsiquiatr*. 2011;69(1): 19-22.
22. Messina S, Vita GL, Sframeli M, et al. Health-related quality of life and functional changes in DMD: A 12-month longitudinal cohort study. *Neuromuscul Disord*. 2016;26(3): 189-96.
23. Hafner P, Bonati U, Erne B, et al. Improved Muscle Function in Duchenne Muscular Dystrophy through L-Arginine and Metformin: An Investigator-Initiated, Open-Label, Single-Center, Proof-Of-Concept-Study. *PLoS One*. 2016;11(1): e0147634.
24. Hafner P, Bonati U, Rubino D, et al. Treatment with L-citrulline and metformin in Duchenne muscular dystrophy: study protocol for a single-centre, randomised, placebo-controlled trial. *Trials*. 2016;17(1): 389.
25. Varni JW, Limbers CA and Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL™ 4.0 Generic Core Scales. *Health Qual Life Outcomes*. 2007;5(1): 43.
26. Bérard C, Payan C, Hodgkinson I, Fermanian J and Group MCS. A motor function measure scale for neuromuscular diseases. Construction and validation study. *Neuromuscul Disord*. 2005;15(7): 463-70.
27. Varni JW, Seid M and Rode CA. The PedsQL™: measurement model for the pediatric quality of life inventory. *Med Care*. 1999;37(2): 126-39.
28. Varni JW, Burwinkle TM, Seid M and Skarr D. The PedsQL™* 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;3(6): 329-41.
29. Streiner D and Norman G. Health measurement scales: a practical guide to their development and use 4 edition Oxford University Press. *New York*. 2008.
30. Fleiss JL, Levin B and Paik MC. *Statistical methods for rates and proportions*. John Wiley & Sons; 2013.
31. Bray P, Bundy AC, Ryan MM, North KN and Everett A. Health-related quality of life in boys with Duchenne muscular dystrophy: agreement between parents and their sons. *J Child Neurol*. 2010;25(10): 1188-94.
32. Read J, Kinali M, Muntoni F, Weaver T and Garralda ME. Siblings of young people with Duchenne muscular dystrophy--a qualitative study of impact and coping. *Eur J Paediatr Neurol*. 2011;15(1): 21-8.
33. Buchanan DC, LaBarbera CJ, Roelofs R and Olson W. Reactions of families to children with Duchenne muscular dystrophy. *Gen Hosp Psychiatry*. 1979;1(3): 262-9.

34. Thompson RJ, Jr., Zeman JL, Fanurik D and Sirotkin-Roses M. The role of parent stress and coping and family functioning in parent and child adjustment to Duchenne muscular dystrophy. *J Clin Psychol*. 1992;48(1): 11-9.
35. Bothwell J, Dooley J, Gordon K, MacAuley A, Camfield P and MacSween J. Duchenne muscular dystrophy—parental perceptions. *Clin Pediatr*. 2002;41(2): 105-9.
36. Carnevale FA, Alexander E, Davis M, Rennick J and Troini R. Daily living with distress and enrichment: the moral experience of families with ventilator-assisted children at home. *Pediatrics*. 2006;117(1): e48-e60.
37. Yılmaz O, Yıldırım SA, Öksüz C, Atay S and Turan E. Mothers' depression and health-related quality of life in neuromuscular diseases: Role of functional independence level of the children. *Pediatr Int*. 2010;52(4): 648-52.
38. Didsbury MS, Kim S, Medway MM, et al. Socio-economic status and quality of life in children with chronic disease: A systematic review. *J Paediatr Child Health*. 2016;52(12): 1062-9.
39. Darke J, Bushby K, Le Couteur A and McConachie H. Survey of behaviour problems in children with neuromuscular diseases. *Eur J Paediatr Neurol*. 2006;10(3): 129-34.
40. Hendriksen JG, Poysky JT, Schrans DG, Schouten EG, Aldenkamp AP and Vles JS. Psychosocial adjustment in males with Duchenne muscular dystrophy: psychometric properties and clinical utility of a parent-report questionnaire. *J Pediatr Neuropsychol*. 2009;34(1): 69-78.
41. Snow WM, Anderson JE and Jakobson LS. Neuropsychological and neurobehavioral functioning in Duchenne muscular dystrophy: a review. *Neurosci Biobehav Rev*. 2013;37(5): 743-52.
42. Hinton VJ, Nereo NE, Fee RJ and Cyrulnik SE. Social behavior problems in boys with Duchenne muscular dystrophy. *J Dev Behav Pediatr*. 2006;27(6): 470-6.
43. Colvin MK, Poysky J, Kinnett K, et al. Psychosocial Management of the Patient With Duchenne Muscular Dystrophy. *Pediatrics*. 2018;142(Supplement 2): S99-S109.
44. Upton P, Lawford J and Eiser C. Parent–child agreement across child health-related quality of life instruments: a review of the literature. *Qual Life Res*. 2008;17(6): 895.

565 Tables:

566 Table 1. Summary of studies investigating HRQOL and functional outcomes in DMD

Citation	Study design; DMD sample characteristics [N, mean age, (age range)]; ambulation status	HRQOL measures used	Functional outcome measures used	Major findings
14	Cross-sectional; [52; 8.4 years; (4-17)]; only ambulant patients included	PedsQL™ GCS and PODCI Only parent-report	Vignos functional grade, quantitative knee extension strength, timed functional performance measures, and gait velocity	Parents reported significantly lower HRQOL scores in both measures compared to controls.The physical function domain of the PedsQL and of PODCI correlated with age and clinical measures of strength.
18	Longitudinal; [24; 7.9 years; (4-12)]; only ambulant patients included	PedsQL™ GCS and PODCI Only parent-report	6 minute walk test, 10-meter run/walk velocity	Parents reported significantly lower total and physical function domains of PedsQL and PODCI compared to controls. PODCI domain scores are more strongly correlated with functional outcomes than PedsQL. Decline in PODCI score but not PedsQL were significantly correlated with decline in 6 minute walk test.
22	Longitudinal; [98; 8.4 years; (5-13)]; only ambulant patients included	PedsQL™ GCS, PedsQL™ NMM and PedsQL ™ Multidimensional Fatigue Scale Child and parent report	6 minute walk test, North Star Ambulatory Assessment, 10-meter run/walk velocity and Gowers test	At baseline, the PedsQL inventories correlated with almost all the functional measures. Significant decrease between baseline and 12 months on the child-self report PedsQL GCS, in parallel with the decrement in the functional outcome measures. Correlation between the 12 month changes on the PedsQL inventories and functional measures were almost all negligible. Similar results were obtained on the Parent Proxy-Report.

31	Cross-sectional; [35; 12.5 years; (9-17)]; ambulant and non-ambulant patients included	PedsQL™ GCS Child and parent report	Vignos scale and Brooke scale	Poor to moderate agreement between children and parents on HRQOL was found. Self-reports revealed a strong relationship between the disease progression (Vignos scale) and PedsQL physical domain; however, disease stage was not related to psychosocial domains. Physical functioning differed significantly between patients receiving corticosteroids and patients not receiving corticosteroids. Psychosocial health did not differ between the two groups.

567

568 Table 2. Demographic characteristics in DMD sample and normative sample.

Characteristics	DMD sample	DMD sample (with MFM)	Normative sample
Age, Mean (SD)	11.0 (3.1)	9.9 (4.1)	9.8 (3.2)
Age Range, y	9.0-14.1	9.0-13.4	5.0-18.1
Gender			
Male, n (%)	33 (97.1%)	15 (93.8%)	2836 (51.5%)
Female, n (%)	1 (2.9%)	1 (6.2%)	2671 (48.5%)
Corticosteroid use	25 (73.5%)	13 (81.3%)	-

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571 Table 3. PedsQL™ GCS and PedsQL™ NMM for child self-report and parent proxy-report for DMD

572 sample and comparisons with healthy children scores

	Child self-report			Parent proxy-report		
	DMD	Healthy		DMD	Healthy	
	Mean (SD) N=34	Mean (SD) N= 5480	p	Mean (SD) N=34	Mean (SD) N=9430	p
PedsQL™ GCS Total Score	54.66 (15.23)	83.84 (12.65)	<0.01	49.34 (13.07)	82.70 (15.40)	<0.01
Physical Health	33.03 (23.35)	87.53 (13.50)	<0.01	29.65 (18.56)	84.48 (19.51)	<0.01
Psychosocial Health	66.38(13.96)	81.87 (14.09)	<0.01	59.15 (14.45)	81.65 (15.22)	<0.01
Emotional Functioning	66.97 (17.89)	79.33 (18.15)	<0.01	59.88 (19.64)	81.31 (16.50)	<0.01
Social Functioning	61.03 (18.02)	85.15 (16.76)	<0.01	53.67 (17.53)	83.70 (19.43)	<0.01
School Functioning	71.73 (15.51)	81.12 (16.45)	<0.01	64.58 (17.64)	78.83 (19.59)	<0.01
PedsQL™ NMM Total Score	70.01 (15.67)	-	-	64.95 (16.86)	-	-
About my Neuromuscular Disease	71.44 (16.92)	-	-	67.16 (17.97)	-	-
Communication	62.37 (28.95)	-	-	66.41 (31.28)	-	-
About our Family Resources	70.23 (20.40)	-	-	57.12 (24.46)	-	-

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574

575 Table 4. Intraclass Correlations (ICC) between patient self-report and parent proxy-report on

576 PedsQL™ GCS and PedsQL™ NMM for DMD sample

Scale	Parent-Child Agreement ICC [1]	95% CI
PedsQL™ GCS		
Total Score	0.47	0.13;0.55
Physical Health	0.77	0.55;0.82
Psychosocial Health	0.36	0.08;0.47
Emotional Functioning	0.38	0.00;0.48
Social Functioning	0.31	0.02;0.37
School Functioning	0.54	0.22;0.63
PedsQL™ NMM		
Total Score	0.65	0.44;0.73
About my Neuromuscular Disease	0.64	0.42;0.74
Communication	0.81	0.66;0.85
About Our Family Resources	0.62	0.39;0.69

[1]ICCs are designated as ≤ 0.40, poor to fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, good agreement; and 0.81 to 1.00, excellent agreement.

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578

579 Table 5. Correlation Coefficients (r and 95% Confidence Intervals) between PedsQL™ Child Self- and

580 Parent Proxy-Report and MFM.

	MFM total score	MFM D1 score
Child self-report		
PedsQL™ GCS Total Score	**0.59* (0.17;1.06)**	**0.73** (0.42;1.09)**
Physical Health	**0.79** (0.55;1.09)**	**0.88** (0.74;1.06)**
Psychosocial Health	0.39 (-0.13;0.94)	**0.51* (0.09;0.97)**
Emotional Functioning	0.22 (-0.29;0.75)	0.28 (-0.17;0.72)
Social Functioning	0.40 (-0.14;0.97)	**0.53* (0.12;0.98)**
School Functioning	0.08 (-0.54;0.71)	0.20 (-0.36;0.75)
PedsQL™ NMM Total Score	**0.57* (0.14;1.02)**	**0.65** (0.27;1.09)**
About my Neuromuscular Disease	**0.56* (0.21;0.94)**	**0.56* (0.19;0.98)**
Communication	-0.01 (-0.52;0.53)	0.10 (-0.40;0.62)
About Our Family Resources	**0.60* (0.21;1.02)**	**0.70** (0.42;1.04)**
Parent proxy-report		
PedsQL™ GCS Total Score	0.22 (-0.30;0.81)	0.27 (-0.21;0.77)
Physical Health	**0.81** (0.51;1.08)**	**0.86** (0.73;1.05)**
Psychosocial Health	-0.07 (-0.66;0.54)	0.00 (-0.57;0.57)
Emotional Functioning	-0.19 (-0.80;0.38)	-0.10 (-0.66;0.44)
Social Functioning	-0.04 (-0.66;0.57)	0.04 (-0.55;0.63)
School Functioning	-0.18 (-0.78;0.39)	-0.10 (-0.64;0.47)
PedsQL™ NMM Total Score	0.40 (-0.08;0.91)	**0.57* (0.24;0.95)**

About my Neuromuscular Disease	0.40 (-0.06;0.92)	**0.54* (0.20;0.93)**
Communication	0.11 (-0.43;0.65)	0.25 (-0.24;0.71)
About Our Family Resources	0.37 (-0.05;0.84)	**0.50* (0.16;0.90)**

Significant p values are in bold. * $p<0.05$, ** $p<0.01$ or above.

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582

583 Table 6. Summary of regression analyses for the impact of different variables on generic and disease-

584 specific HRQOL in DMD patients

Instruments	Variables	β (SE)	95% CI	p
PedsQL GCS ™ Total Score	D1	0.42 (0.09)	0.21;0.62	<0.01
(child self-report)	Corticosteroid use	-6.11 (7.30)	-22.02;9.80	0.42
	Child age	1.25 (2.02)	-3.14;5.65	0.55
PedsQL GCS ™ Total Score	D1	0.21 (0.13)	-0.08;0.49	0.14
(parent proxy-report)	Corticosteroid use	-6.26 (11.66)	-31.93;19.41	0.60
	Child age	2.93 (2.91)	-3.48;9.33	0.34
PedsQL NMM ™ Total Score	D1	0.32 (0.11)	0.09;0.55	0.01
(child self-report)	Corticosteroid use	-7.92 (9.48)	-28.80;12.95	0.42
	Child age	1.68 (2.37)	-3.53;6.89	0.49
PedsQL NMM ™ Total Score	D1	0.36 (0.12)	0.09;0.63	0.01
(parent proxy-report)	Corticosteroid use	-6.63 (9.73)	-27.82;14.56	0.51
	Child age	1.52 (2.69)	-4.33;7.37	0.58

585 β:=Regression coefficient; SE= Standard error.

586

Table S1 Subgroup analyses for PedsQL™ GCS of ambulant and non-ambulant DMD sample and comparisons with healthy children scores

	Child self-report			Parent proxy-report		
	DMD	Healthy		DMD	Healthy	
Ambulant patients	N= 14	N= 5480		N=14	N=9430	
PedsQL™ GCS Total Score	65.23 (15.37)	83.84 (12.65)	<0.01	52.66 (12.53)	82.70 (15.40)	<0.01
Physical Health	52.46 (21.02)	87.53 (13.50)	<0.01	43.08 (18.60)	84.48 (19.51)	<0.01
Psychosocial Health	68.93 (14.41)	81.87 (14.09)	<0.01	57.80 (13.84)	81.65 (15.22)	<0.01
Emotional Functioning	68.57 (20.42)	79.33 (18.15)	0.07	60.38 (18.98)	81.31 (16.50)	<0.01
Social Functioning	64.64 (17.70)	85.15 (16.76)	<0.01	49.29 (19.10)	83.70 (19.43)	<0.01
School Functioning	73.57 (14.85)	81.12 (16.45)	0.08	65.36 (16.23)	78.83 (19.59)	<0.01
Non-ambulant patients	N= 20	N= 5480		N=20	N=9430	
PedsQL™ GCS Total Score	48.66 (12.21)	83.84 (12.65)	<0.01	46.90 (13.25)	82.70 (15.40)	<0.01
Physical Health	19.43 (13.11)	87.53 (13.50)	<0.01	19.20 (9.99)	84.48 (19.51)	<0.01

Psychosocial Health	64.59 (13.73)	81.87 (14.09)	<0.01	60.15 (15.18)	81.65 (15.22)	<0.01
Emotional Functioning	65.79 (16.27)	79.33 (18.15)	<0.01	59.54 (20.60)	81.31 (16.50)	<0.01
Social Functioning	58.50 (18.26)	85.15 (16.76)	<0.01	56.91 (16.02)	83.70 (19.43)	<0.01
School Functioning	70.44 (16.20)	81.12 (16.45)	<0.01	64.01 (19.03)	78.83 (19.59)	<0.01

Table S2 Correlation Coefficients (r and 95% Confidence Intervals) between PedsQL™ Child Self- and Parent Proxy-Report and MFM for ambulant vs. non-ambulant patients.

	Ambulant patients (N=14)		Non-ambulant patients (N=20)	
	MFM total score	MFM D1 score	MFM total score	MFM D1 score
Child self-report				
PedsQL™ GCS Total Score	**0.77* (0.49;1.12)**	**0.74* (0.47;1.11)**	-0.58 (-1.38;0.13)	-0.28 (-1.09;0.60)
Physical Health	**0.80** (0.51;1.28)**	**0.79** (0.50;1.19)**	-0.38 (-1.21;0.39)	-0.10 (-1.02;0.68)
Psychosocial Health	0.61 (0.07;1.05)	0.59 (0.12;1.17)	-0.46 (-1.57;0.29)	-0.17 (-1.08;0.59)
Emotional Functioning	0.66 (0.21;1.22)	0.62 (0.19;1.04)	-0.61 (-1.43;0.05)	-0.23 (-1.15;0.70)

Social Functioning	0.63 (0.30;1.04)	0.65 (0.28;1.13)	0.16 (-0.78;1.19)	0.68 (0.20;1.18)
School Functioning	0.07 (-0.86;0.85)	0.07 (-0.79;0.79)	-0.52 (-1.30;0.16)	-0.29 (-1.08;0.49)
PedsQL™ NMM Total Score	0.47 (-0.12;1.16)	0.40 (-0.24;1.13)	-0.14 (-1.36;0.88)	0.29 (-0.69;1.27)
About my Neuromuscular Disease	0.38 (-0.27;1.12)	0.32 (-0.27;0.89)	0.03 (-1.01;1.23)	0.21 (-0.86;1.33)
Communication	-0.14 (-0.82;0.59)	-0.19 (-0.88;0.48)	-0.32 (-1.31;0.74)	-0.03 (-1.01;0.70)
About Our Family Resources	0.58 (0.05;1.06)	0.53 (0.05;1.12)	-0.37 (-1.48;0.68)	0.06 (-1.14;1.11)
Parent proxy-report				
PedsQL™ GCS Total Score	0.30 (-0.27;1.02)	0.22 (-0.29;0.78)	-0.35 (-1.42;0.61)	-0.15 (-1.31;0.85)
Physical Health	**0.82** (0.58;1.17)**	**0.75** (0.36;1.28)**	**-0.89* (-1.08;-0.69)**	-0.46 (-1.44;0.61)
Psychosocial Health	0.18 (-0.46;0.78)	0.11 (-0.46;0.88)	-0.21 (-1.36;0.76)	0.09 (-0.76;0.95)
Emotional Functioning	0.25 (-0.50;1.12)	0.18 (-0.55;0.99)	-0.70 (-1.67;0.05)	-0.51 (-1.28;0.05)
Social Functioning	0.23 (-0.42;0.93)	0.19 (-0.53;1.05)	-0.03 (-1.11;1.03)	0.32 (-0.50;1.25)
School Functioning	-0.15 (-0.94;0.48)	-0.22 (-0.92;0.54)	-0.21 (-1.47;0.80)	0.09 (-0.79;1.00)
PedsQL™ NMM Total Score	0.3 (-0.31;0.92)	0.26 (-0.41;0.85)	**-0.79* (-1.26;-0.27)**	-0.28 (-1.22;0.57)
About my Neuromuscular Disease	0.34 (-0.26;0.91)	0.29 (-0.26;0.91)	-0.68 (-1.35;-0.11)	-0.17 (-1.02;0.74)
Communication	-0.09 (-0.98;0.77)	-0.20 (-0.87;0.68)	-0.67 (-1.23;-0.17)	-0.47 (-1.13;0.14)

About Our Family Resources	0.20 (-0.51;0.93)	0.19 (-0.57;0.95)	0.09 (-0.97;1.07)	0.52 (-0.23;1.20)

587 Figure legends

588

589 Figure 1. PedsQL^{TM} NMM subscores for parent proxy-report and child self-report for the DMD

590 sample. Thereby, the mean and the 95 % confidence interval (CI) are shown.

591 Figure 2. PedsQL^{TM} GCS subscores for child self-report and parent proxy-report for the DMD sample

592 compared to the HC sample. Thereby, the mean and the 95 % confidence interval (CI) are shown.

593 Figure 3. Correlations between PedsQL^{TM} physical health score and functional measures for child self-

594 (A and B) and parent proxy-report (C and D).

595

Figure 1.

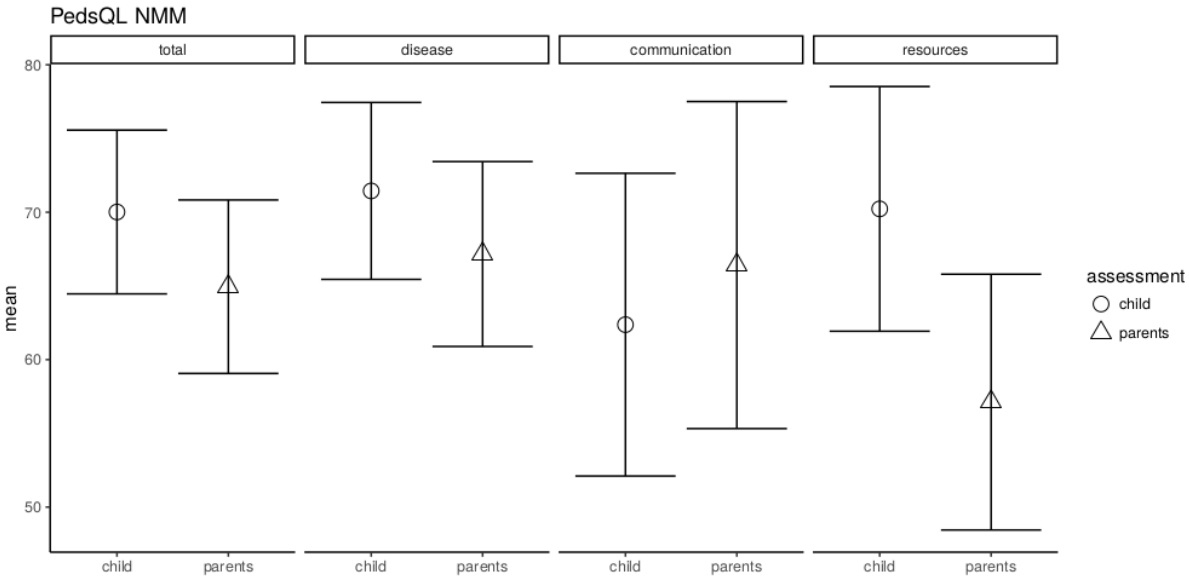
PedsQL NMM
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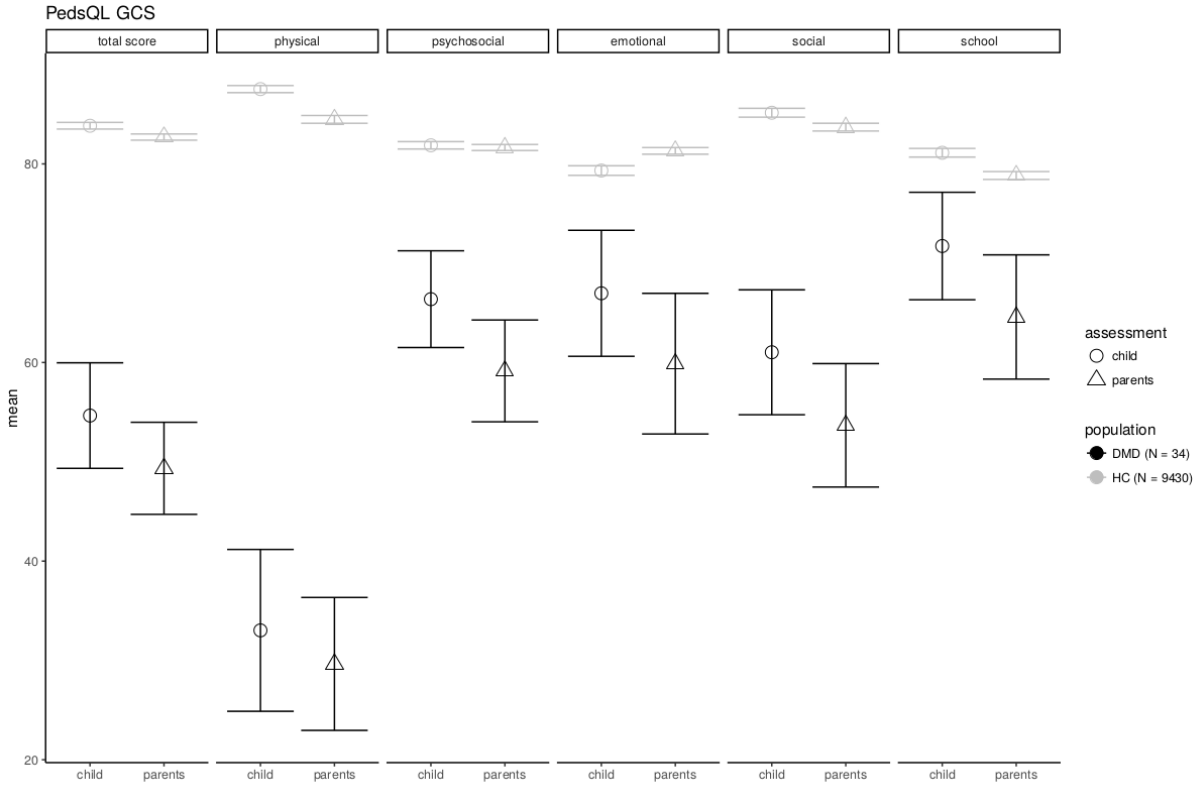
Figure 2.


PedsQL GCS
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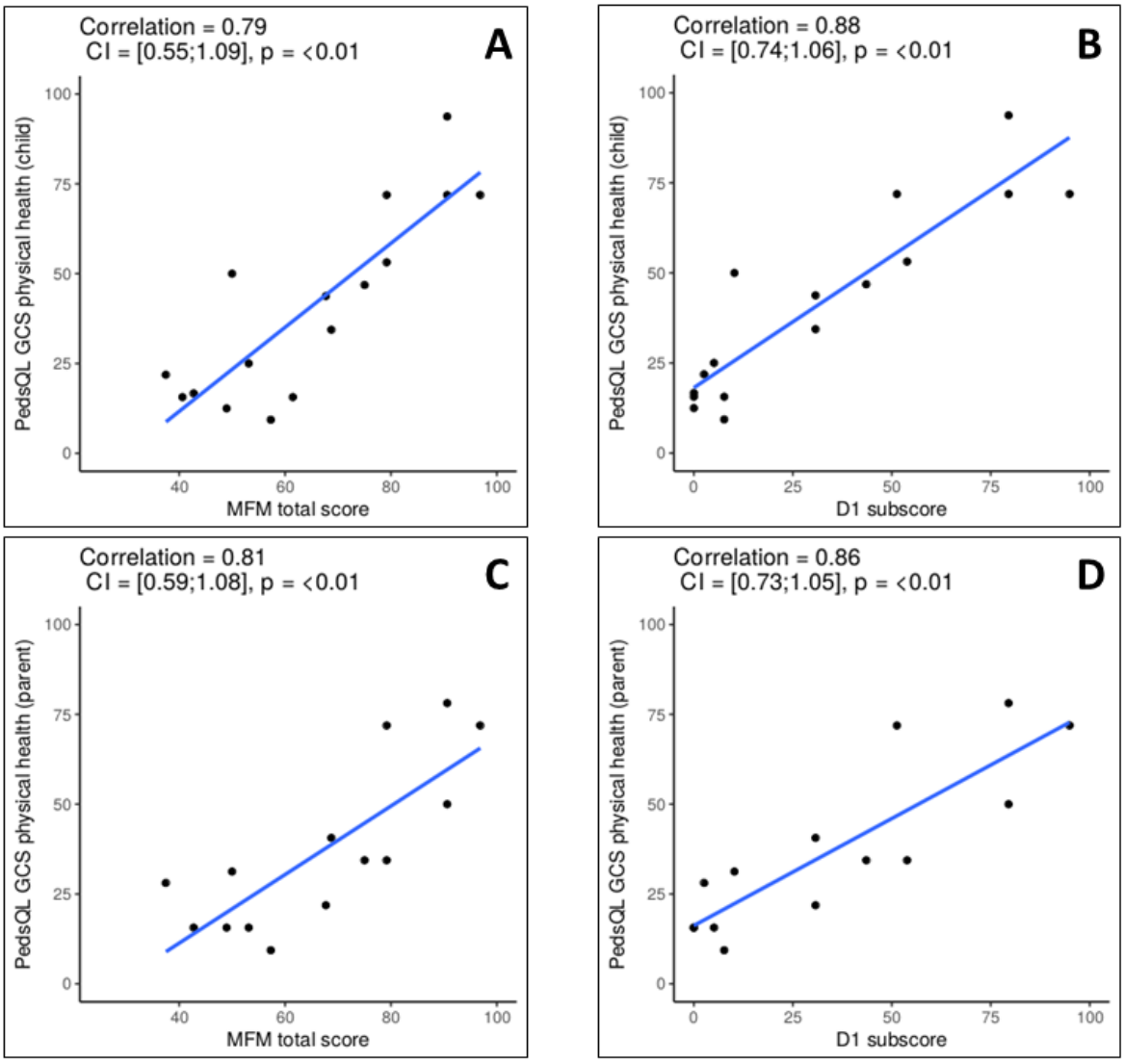
parents
population
DMD (N = 34)
HC (N = 9430)

Figure 3.


Correlation = 0.79
CI = [0.55;1.09], p = <0.01
A
PedsQL GCS physical health (child)
MFM total score
Correlation = 0.88
CI = [0.74;1.06], p = <0.01
B
PedsQL GCS physical health (child)
D1 subscore
Correlation = 0.81
CI = [0.59;1.08], p = <0.01
C
PedsQL GCS physical health (parent)
MFM total score
Correlation = 0.86
CI = [0.73;1.05], p = <0.01
D
PedsQL GCS physical health (parent)
D1 subscore

2.3. Manuscript 3: Psychosocial adjustment and parental stress in Duchenne Muscular Dystrophy

Journal: European Journal of Pediatric Neurology – submitted

Authors: Gocheva V, Schmid S, Orsini AL, Hafner P, Schaedelin S , Weber P, Fischer D

Abstract: Objective: The primary aim of this cross-sectional study was to assess psychosocial adjustment of children with Duchenne Muscular Dystrophy (DMD); the second aim was to explore its possible association to parental stress.

Methods: 34 children with DMD, 9-14.1 years of age, and their parents were included in the study. Caregivers completed the Child Behavior Checklist (CBCL), the Psychosocial Adjustment and Role Skills Scale III (PARS-III) and the Parenting Stress Index–Short Form (PSI-SF). Patients older than 11 years completed the Youth Self Report (YSR). Regression analyses including parental stress, socio-demographic and disorder-related factors were performed to determine how these aspects influence the psychosocial adjustment in children with DMD.

Results: Depending on the measure, 15% to 47% of children with DMD were found to be psychosocially “at risk” for emotional and behavioural problems. Half of the caregivers experienced very high parenting stress. Moreover, the two aspects parent-child dysfunctional interaction and difficult child scores were associated to psychosocial adjustment. Regression analyses showed that both parental stress and participation in a DMD support group are related to the psychosocial adjustment.

Conclusions: The PARS-III represents a more suitable instrument assessing psychosocial adjustment in DMD, since compared to the CBCL it excludes physiological symptoms regarding chronic diseases. Decreased parents’ stress levels and participation in a DMD support group positively contributed to good psychosocial

adjustment. A family-centered approach is crucial for interventions in order to improve the psychosocial adjustment of these children and their families even while living with the significant burdens associated with DMD.

Psychosocial adjustment and parental stress in Duchenne Muscular Dystrophy

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Running title: Psychosocial adjustment and parental stress in DMD

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Keywords: Duchenne muscular dystrophy, psychosocial adjustment, parental stress, CBCL, PARS-III, PSI-SF

1. Introduction

A major issue for children with chronic medical conditions and physical disability is to cope with the challenges of their chronic disease.[1] Chronically ill or physically disabled individuals are at a much greater risk of significant psychosocial maladjustment, internalizing problems and somatic complaints compared to healthy peers.[2, 3] Research has shown a high risk of maladjustment in neurological disorders and those involving motor functioning.[4] For those who must cope with a progressively disabling, terminal illness like Duchenne Muscular Dystrophy (DMD), the psychosocial adjustment process is even more complicated.

DMD is the most common, inherited childhood neuromuscular disorder affecting mainly boys with an estimated incidence of 1:3600 to 6000 among new-born males.[5] It is characterised by a progressive muscle loss, which results in muscle weakness. The impact of the disease can begin as early as age 3, with an impact upon practices of daily life.[6] Gait loss and functional dependence typically occur in the second decade of life.[5] Up to date, the disease has no cure and life expectancy is limited. Death generally occurs by the third decade of life, usually caused by extreme muscle weakness that leads to respiratory or cardiac failure.[5] In view of the devastating outcome of DMD, most attention has been directed toward improving muscle function and structure. However, this perspective neglects the social, psychological, and emotional needs of patients with DMD since they not only face inevitable deterioration of physical functioning, but also become susceptible to emotional and behavioural problems.[7]

At present, there are relatively few studies examining the psychosocial adjustment in DMD and findings concerning psychosocial adjustment are equivocal. Early research indicates that between 30% and 50% of children with DMD reported psychosocial maladjustment and behavioural problems.[7-9] More precisely, symptoms of depression and anxiety, social isolation, and social problems have been reported.[10-12] In contrast, newer

research found no indication of decreased psychosocial adjustment or behavioural problems among DMD boys compared to normative data and other chronic medical conditions.[13, 14] Understanding what may contribute to the psychosocial adjustment among children with DMD is a valuable and necessary information to ensure each child has the best possible quality of life and adjustment to the disease.

DMD may have implications on the psychosocial well-being of the children and their families. Caregivers of children with DMD must not only deal with the stressors most families with chronically ill children encounter, but also the additional stressors associated with one family member's progressively disabling and terminal disorder. Research indicates that the majority of caregivers of children with DMD report higher levels of psychological stress than parents of healthy children or of children affected by other chronic diseases.[15-19] Providing care to a child with DMD is a heavy physical and emotional burden [20], with factors such as difficulty in accessing adequate and timely health services and managing everyday difficulties were found to contribute to the burden.[21] Moreover, parents of children with DMD were reported to have a higher probability of having a major depressive episode than general population.[15] Landfeldt et al. revealed that half of the 700 investigated DMD caregivers of children with DMD report being moderately or extremely anxious or depressed.[22] Another study found that parents of boys with DMD exhibited great psychological stress and decreased enjoyment of life.[23] Moreover, parents reported increased difficulty in discussing death issues with their children, which only contributed further to the children's feelings of isolation.[7] Most of the parents expressed significant feelings of guilt, and thus were unable to cope appropriately with their grief or help their children cope with theirs. These previous results highlight the association of parental factors to psychosocial functioning of children with DMD and suggest that parental stress may contribute to the psychological adjustment of

children with DMD, whereas good parental functioning predicts better psychosocial adjustment.

Accordingly, the current study had the following objectives: (1) to examine the psychosocial adjustment/functioning in children with DMD; (2) to measure parental stress in caregivers of children with DMD and (3) to assess the association between the psychosocial adjustment of children with DMD and parental stress as well as the influence of other sociodemographic and disorder-related factors.

2. Materials and methods

2.1. Participants

This observational cross-sectional study was performed with children with DMD who have participated in the past in two investigator-initiated clinical trials [24, 25] at the Division of Neuropediatrics, University Children's Hospital Basel. Former participants from both studies were invited to participate for the observational single visit 2.5 up to 5 years after completion of the clinical trial. Inclusion criteria were child age between 8.5 and 16 years, and being able to provide informed consent and comply with the study procedures. Of the 48 former participants, 34 (71%) subjects, 33 boys and 1 girl, with molecular diagnosis of DMD and their respective caregivers agreed to participate and were included in this study.

2.2.Procedures

Patients were contacted by telephone and email and asked if they are willing to participate in the study. After obtaining an explanation of the study, subjects agreed to participate willingly and voluntarily by signing the informed consent during a study visit at the hospital. All assessments were done by a trained medical doctor and appointments were scheduled at the hospital. All caregivers completed the following questionnaires: the Child Behavior Checklist 6-18, the Psychosocial Adjustment and Role Skills Scale III and the Parenting Stress Index –

Short Form. Further, caregivers answered questions regarding their child's current state of health (disease-specific questions) and other sociodemographic questions. Patients older than 11 years completed the Youth Self Report 11-18.

When families had difficulties to get to the hospital (mainly due to loss of ambulation of the child), they were sent a cover letter, consent form, and return envelope. Families who agreed to participate returned their signed consent forms to the investigators. After signing the consent forms, families received the questionnaires with a return envelope. Additionally, a trained medical doctor called each family to arrange a phone interview in order to clarify questions regarding the questionnaires, assess patient's current state of health and answer sociodemographic and disease-specific questions.

2.3. Measures

2.3.1. Psychosocial adjustment

The level of psychosocial adjustment was assessed by the Child Behavior Checklist 6-18 (CBCL), the Youth Self Report 11-18 (YSR), and the Psychosocial Adjustment and Role Skills Scale (PARS-III).

The CBCL [26] is a widely used 118-item questionnaire assessing behavioural, emotional, and social problems. Parents rate, on a 0 (never) to 2 (very much) scale, how often their child engages in each behaviour. The CBCL includes 8 syndrome scales (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behaviour, and Aggressive Behaviour) and two broadband scales (Internalizing Problems and Externalizing Problems), and a Total Problem scale. Internalizing Problems are problems that are primarily within the individual and include Anxious/Depressed, Withdrawn/Depressed and Somatic Complaints, while Externalizing Problems are problems that mainly involve conflict with other people and their expectations for the child and include Rule-Breaking and Aggressive Behaviour subscales. Higher scores

on the CBCL indicate more adjustment problems. The CBCL yields T scores (M = 50, SD = 10), which are derived from a comparison of the individual's score with the appropriate normative group, based upon gender and age. The YSR [26] is a self-report version of the CBCL questionnaire that is addressed to children and adolescents aged 11-18 years.

The PARS-III [27] is a brief parent-completed measure of psychosocial adjustment. All 28 items use a 4-point interval rating scale, ranging from 1= "never or rarely" to 3= "always". The PARS-III includes 6 psychosocial subscales (Peer Relations, Dependency, Hostility, Productivity, Anxiety/Depression, and Withdrawal) and a Total Score. Higher scores indicate better adjustment.[27] In the original study by Walker and colleagues conducted with 450 children with a variety of chronic medical conditions, the reliability (coefficient α) of the total summary score was .88 overall, with subscales ranging from .70 to .80.[27] Construct validity of the six subscales was supported by principal component factor analysis and concurrent validity was adequate, as supported by significant correlations in the expected directions with the CBCL.[26]

2.3.2. Parental Stress

Parental stress was assessed by the Parenting Stress Index – Short Form (PSI-SF). The PSI-SF [28] is a 36-items self-reported questionnaire developed from the perspective that the stress which a parent experiences is a function of characteristics of both the child and the parent, as well as their unique style of interaction. It includes a Total score and 3 subscales: Parental Distress (emotional distress in the parenting role), Parent-Child Dysfunctional Interaction (problematic parent-child interactions), and Difficult Child (problematic child behaviour or demands). The items of the scale range from 1 (strongly disagree) to 5 (strongly agree). Higher scores indicate greater levels of parenting stress.[28] Raw scores above 33 on the Parental Distress and Difficult Child subscales and above 27 on the Parent-Child Dysfunctional Interaction subscale are considered as clinically elevated. Raw Total score

above 90 indicates clinically significant high level of stress scores.[28] The PSI-SF includes a "defensive responding" scale, indicated by low scores on seven items from the parental distress scale, and indicates the degree to which parents may deny or minimize problems. A score lower than 11 on the defensive responding scale is considered "defensive" and the PSI-SF protocol's validity is therefore questionable. Test-retest reliability of the PSI-SF total score and the subscales ranges from .68 to .85. Internal consistency (alpha) for the short form total score and subscales ranges from .80 to .91.[28]

2.3.3. Sociodemographic and disorder-related measures

Sociodemographic and disorder-related informations were collected through a questionnaire developed by the investigators. Questions addressed items pertaining to the child's diagnosis, physical function (age, ambulation status, and corticosteroids use), marital status of caregivers and participation in a DMD support group.

2.4. Statistical analysis

Descriptive statistics were generated for demographic and clinical variables and were reported as mean and SD values for continuous variables and frequencies for categorical variables. Psychosocial adjustment level in the DMD population was calculated by frequencies of clinical syndrome and broadband scales. According to ASEBA Multicultural Manual, as measured by the CBCL and YSR, we considered clinical range scores corresponding to T > 69 for the syndrome scales, and T > 63 for the Internalizing, Externalizing, and Total Problems Scales. Pearson correlation examined the relationship between the CBCL Total Problem Scales and the PARS-III Total score. One-sample t-tests were performed to compare parental stress level, measured by the PSI-SF, in parents of children with DMD to norm mean subscale scores reported by the scale's authors (n = 800 parents of children at well-child clinic visits).[29] For these analyses all participants were included as potential defensive responders were included in the normative sample as well. Six per cent of the parents had a range of

scores indicating defensive responding. Pearson correlations examined the relationship between psychosocial adjustment of the children and parental stress. Linear regression analyses were conducted on data from DMD participants to determine the relative contributions of other variables to psychosocial adjustment. For these analyses each of the three psychosocial adjustment (measured by CBCL, YSR and PARS-III) total scores was included as the dependent variable. Parental stress (PSI-SF total score) and child age were used as independent variables. In a second step, the models were refit each time adding one of the following variables: ambulation status, corticosteroid use, support group participation, and marital status of caregivers. These analyses were explorative analyses, results have thus to be interpreted as hypothesis generating and not confirmatory. P values should be interpreted as a continuous measure of evidence against the corresponding null-hypothesis and not as confirmatory. No correction for multiple testing was performed. Data were analysed using R. Significance was set at $p<.05$ for all statistical analyses.

3. Results

3.1. Patients' and caregivers' characteristics

Table 1 presents the main sociodemographic, parental and patients' illness data. The mean age of the DMD participants was 11.6 years (SD: 1.34, range 9-14.1 y). Among all participants, 25 of 34 (73.53%) were taking corticosteroids (prednisone or deflazacort). 14 patients (41.20%) were ambulant, 20 were not able to walk 10m without assistance (58.80%). Many patients visited a school for physically handicapped children (41.18%). No patient needed assisted ventilation. Caregivers' mean age was 44.44 years (SD: 6.28, range 36–57.58 y). Caregivers were primarily mothers (73.53%). The majority of the parents were married (73.53%). Ten families participated in a DMD support group (29.41%).

3.2. Psychosocial adjustment

The CBCL syndrome and broadband scales T values (mean and SD) are reported in Figure 1 and 2. In addition, to ensure that the behavioural outcome data were "clinically relevant", T values above the clinical cut-off (T value up to 69 for the syndrome scales and 63 for the broadband scales) were reported. According to the „clinically significant" range scores for the CBCL Total score presented by the ASEBA Multicultural Manual, 46.88% of the children with DMD had significantly elevated scores as rated by the caregivers. Moreover, 56.25% had elevated Internalizing Problems and 25% had elevated Externalizing Problems. Examination of the YSR self-reports revealed that 21.74% rated to have significantly elevated Total score. Moreover, 30.43% reported Internalizing Problems and 4.35% Externalizing Problems. Figure 1 shows that parents T values were higher than self-reports for all syndrome scales except for the Thought Problems.

Data from the PARS-III Total score ranged from 50 to 103 (mean: 83.09; SD: 11.65). According to the clinical cut-off for the Total score[13], 5 patients out of 34 (14.71%) were identified as being at risk for having adjustment problems. Pearson correlation showed a significant high correlation between the PARS-III Total score and the CBCL Total score (r=-0.82), indicating that both measures correlate well.

3.3. Parental stress

Parental stress, as measured by the PSI-SF, revealed a mean Total score of 91.67 (SD 20.41), with scores ranging from 53 to 148. Table 2 demonstrates that caregivers of children with DMD reported significantly greater PSI-SF Total score compared to the normative sample's mean (p<0.01). Moreover, mean scores of parental distress (p =0.01), parent-child dysfunctional interaction score (p <0.01), and difficult child score (p <0.01) in caregivers of children with DMD were significantly greater compared to the normative sample. Further, 50.0 % of the caregivers had PSI-SF Total scores greater than or equal to the 90th percentile.

This rate differs substantially from the comparison norms of parents of healthy children (10 %) reported by the PSI-SF's author.[30]

3.4.Association between psychosocial adjustment in children with DMD and parental stress

Table 3 illustrates the association between parental stress and patients' psychosocial adjustment assessed by Pearson correlations. There was a strong correlation between PSI-SF Total score and the CBCL Internalizing Problems (r=0.72), CBCL Total score (r =0.72) and moderate correlations with the CBCL Externalizing Problems (r =0.64), the PARS Total score (r =-0.59), and the subscores Withdrawal (r =-0.58), Anxiety/Depression (r =-0.57), and Hostility (r =-0.52). PSI-SF Parent-Child Dysfunctional Interaction scale revealed significant high correlations with the CBCL Externalizing Problems (r =0.72) and Total score (r =0.71), and moderate correlations with CBCL Internalizing Problems (r =0.68), PARS Total Score (r =-0.62), Anxiety/Depression (r =-0.62), Hostility (r =-0.60), and Withdrawal (r =-0.59). PSI-SF Difficult Child scale showed significant high correlations with the PARS Total score (r =-0.71), Anxiety/Depression scale (r =-0.71), and the CBCL Total score (r =0.82), and Internalizing (r =0.82) and Externalizing Problems (r =0.82). Moderate correlations were found between PSI-SF Difficult Child scale and PARS Hostility (r =-0.64), Withdrawal (r =-0.53), YSR Total score (r =0.53) and Externalizing Problems (r =0.54).

Regression model analyses were performed to examine the effects of the following variables on the psychosocial adjustment in children with DMD: parental stress, child age, ambulation status, corticosteroid use, marital status of caregivers and DMD support group participation (see Table 4). The estimates of the PSI-SF Total score were adjusted for age. All other estimates were adjusted for age and the PSI-SF Total score. Significant contributors to the psychosocial adjustment measured by the PARS-III and CBCL were next to the total parental stress also the participation in a DMD support group (B= –.23 and 9.57; p <0.01 and

<.01, respectively). For the self-reports, no significant contributors to the psychosocial adjustment were found.

4. Discussion

The present study investigated psychosocial adjustment in children with DMD and its possible association to parental stress as well to other sociodemographic and disorder-related factors. Our investigation of sociodemographic variables showed that most caregivers are mothers of DMD children and the majority are married. Very few caregivers participated in a DMD support group.

Based on the CBCL, 47% of the included children were found to be psychosocially "at risk" for emotional and behavioural problems. In our cohort, caregivers reported a high prevalence of internalizing and externalizing problems, 56% and 25% respectively. This finding indicates that rates of psychosocial adjustment problems are increased in DMD, which is in accordance with previous publications[31-33]. Additionally, it is noteworthy that self-perception among many children is more positive than what their caregivers indicated. Based on the YSR self-reports, 21.74% of the children rated to have overall high psychosocial adjustment problems while their parents reported higher rates. An explanation of these discrepancies may be that factors such as mental state and level of stress may also influence parents' accounts of their children's problems.[34] Distressed or depressed parents may have a lower tolerance of frustration and regard their children as more of a burden and subsequently report more behavioural problems.[35] In contrast to the CBCL, based on the PARS-III only 15% of children with DMD were identified as being at risk for having adjustment problems. Hendriksen et al. examined psychosocial functioning in a large cohort of boys with DMD using the PARS-III and reported comparable rates of psychosocial adjustment and indicated that patients with DMD are not at a significantly greater risk of psychosocial difficulties than

those with other paediatric chronic medical conditions such as seizure disorders, cystic fibrosis and cerebral palsy. [13]

Most of former studies investigating psychosocial adjustment in children with DMD so far have used the CBCL, which represents the gold standard of screening and detecting psychopathology in children and adolescents; however, it may not be the most suitable instrument measuring psychosocial functioning in children with a chronic physical illness. Since the CBCL includes a range of items that may be overly sensitive to illness-related variables (items related to somatic complaints), the reliance on the CBCL when assessing psychosocial adjustment in DMD may over-represent psychosocial maladjustment in DMD or mislabel normal behaviour as pathological resulting in false positives.[13] Therefore, in this study we included also the PARS-III. The strength of the questionnaire is that it excludes items based on physiological symptoms (e.g. aches and pains and fatigue), which are part of the chronic disease, and therefore represents a more suitable instrument assessing psychosocial adjustment in children with chronic illnesses. [27]

As compared to the normative sample, caregivers of children with DMD reported greater parental stress. In our study, half of the caregivers had very high parenting stress – defined here as Total score of 90 or more in a general population sample, where 10% reported very high stress. This means that very high parenting stress among families with a child with DMD is five times more common than in a general population sample. These findings indicate that, indeed, caregivers of children with DMD experience greater stress than a healthy normative group, which is consistent with results of previous studies.[15-19] In particular, the parental stress is related to their children, in that the children's behaviour and interactions with them are more stressful for caregivers of children with DMD than for caregivers of healthy children.

Moderate to high correlations were found between parental stress and psychosocial adjustment levels measured by both the CBCL and PARS-III. A closer look at the associations demonstrated that mainly the parent-child dysfunctional interaction and difficult child subscores correlate with aspects of the psychosocial adjustment (CBCL: Externalizing Problems, Internalizing Problems; PARS-III: Anxiety/Depression, Hostility and Withdrawal). However, the correlations between parental stress and psychosocial adjustment were all negligible. This result indicates that parental stress largely depends on the child's behavioural functioning as well as practical aspects of caring for the child, rather than stress independent from the parent-child interaction. It may be that the experience of having a chronically ill child has more global effects. Therefore, the additional stress leads to an overall lower stress tolerance in these parents, which can lead to poorer parenting skills and coping mechanisms. [18]

Finally, and most importantly, the regression analyses indicated that psychosocial adjustment level in children with DMD is strongly associated with the intensity of parental stress and the participation in a DMD support group. Those findings suggest that parental stress related to parent-child interaction and the participation in a support group is more salient to psychosocial outcomes than the influence of disease progression.

This study has clinical implications for health-care professionals and families with children affected by DMD. Clinicians who care for patients with DMD should assess psychosocial adjustment/functioning regularly through the use of screening measures such as the PARS-III. [36] If concerns of psychosocial maladjustment are identified, a structured or semi-structured interview based on clinical evaluation is needed to accurately assess psychopathology so that a more intensive psychiatric service may be warranted. Further, family variables have been shown to protect against maladjustment in cases of chronic illness and in adverse environments. [37] Parents, who are supportive, involved, and have positive

attitudes increase a stress-resilient outcome in their children. [38] Among families living with DMD, family functioning has been shown to be positively associated with child's outcome. [17] Therefore, a family-centered approach that recognizes the family as central to the child's health may be helpful including comprehensive support not only for the affected child but also for the family for example with the participation in a parent-to-parent support group. [39]

If there is reason to believe that a lack of psychosocial adjustment to life with a muscle disorder is a significant contributor to distress, psychological interventions directed at improving acceptance may be an optimal first-line treatment. For example, Acceptance and Commitment Therapy (ACT), a cognitive-behavioural model of disease self-management with acceptance as the central component, aims specifically to improve an individual's ability to persist with or to adopt behaviour patterns in line with deeply held values. [40] In the context of a muscle disorder, a key process in improving adjustment might be helping someone find new ways of expressing personal values despite functional limitations, while accepting both of those limitations and the negative thoughts and feelings they are likely to have. ACT might be applied to address the issues of distress, nonadherence to treatments, pain, and fatigue in people with muscle disorders. [41]

These results should be regarded as preliminary and with some limitations in mind. Firstly, we did not have a control group, whereas other studies have compared DMD patients with their siblings or with patients who have other neuromuscular diseases. Secondly, even though the sample size is appropriate for a monocentric study, it is relatively low for the range of age and clinical phenomenology. Using self-reported questionnaires in general may lead to an under/overestimation of the true rate of psychosocial maladjustment in this special clinical population. Therefore, patients that are above the clinical cut-off should be evaluated by clinically structured interviews to detect the rate of emotional and behavioural problems. Since caregivers were predominantly female, the generalisability of results is restricted.

373 Future research should include other factors which may influence the psychosocial adjustment
374 such as the cognitive functioning of the child. In addition, future studies should use
375 longitudinal designs to investigate how key variables change over critical time periods.

376 ## 5. Conclusions

377 In the present study, psychosocial adjustment in 34 children with DMD and stress among
378 their caregivers were assessed. Our data indicate that depending on different measures
379 between 15% and 47% of children with DMD exhibited psychosocial adjustment problems.
380 Additionally, it is noteworthy that self-perception among children with DMD was more
381 positive than what their caregivers imagine. Further, half of the caregivers of children with
382 DMD experienced very high parenting stress. Low parental stress along with the participation
383 in a DMD support group were contributory factors to better psychosocial adjustment of
384 children with DMD. A family-centered approach for interventions is needed in order to
385 improve the psychosocial adjustment of these children and their families.

386 ## Declarations

387 ### Ethics approval and consent to participate

388 Eligible subjects were included in the study only after providing written informed consent.
389 Ethics approval has been obtained from the local Ethics Committee (EKNZ 2017-01028).

390 ### Consent for publication

391 We confirm that (1) the authors of this manuscript had access to all study data, are responsible
392 for all contents of the manuscript, and had authority over the preparation of the manuscript
393 and the decision to submit the manuscript for publication and (2) all authors have read and
394 approved the submission of this manuscript to the journal.

395 ### Availability of data and material

Data used in the analysis is available upon request from the corresponding author. Patient-level data remains confidential under patient data privacy regulations.

Competing interests

DF is principle investigator for studies on spinal muscular atrophy sponsored by Hofmann-La Roche Ltd. There are no other activities related to commercial companies. The authors declare that they have no competing interests.

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Authors' contributions

VG participated in the design of the study, acquired data and drafted the manuscript. PH, AO and SiS participated in the design of the study and acquired data. VG and NR participated in patient recruitment. NR and VG participated in the organization and the conduct of the study. SaS performed the statistical analysis. PW revised the manuscript critically for important intellectual content. DF designed the study, analysed data and drafted the manuscript. All authors read and approved the final manuscript.

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Authors' information

Not applicable

Highlights

- 15% to 47% of children with DMD exhibit psychosocial adjustment problems.
- Half of caregivers of children with DMD report very high levels of stress.
- Decreased parents' stress positively contribute to good psychosocial adjustment.
- Support group participation positively contribute to good psychosocial adjustment.

References

1. Eiser C. Psychological effects of chronic disease. *J Child Psychol Psychiatry.* 1990; 31: 85-98.
2. Gartstein MA, Short AD, Vannatta K, Noll RB. Psychosocial adjustment of children with chronic illness: an evaluation of three models. *J Dev Behav Pediatr.* 1999; 20: 157-63.
3. Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. *J Child Psychol Psychiatry.* 1998; 39: 29-46.
4. Hysing M, Elgen I, Gillberg C, Lundervold AJ. Emotional and behavioural problems in subgroups of children with chronic illness: results from a large-scale population study. *Child Care Health Dev.* 2009; 35: 527-33.
5. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 2010; 9: 77-93.
6. Bendixen RM, Senesac C, Lott DJ, Vandenborne K. Participation and quality of life in children with Duchenne muscular dystrophy using the International Classification of Functioning, Disability, and Health. *Health Qual Life Outcomes.* 2012; 10: 43.
7. Polakoff RJ, Morton AA, Koch KD, Rios CM. The psychosocial and cognitive impact of Duchenne's muscular dystrophy *Semin Pediatr Neurol*: Elsevier; 1998: 116-23.
8. Firth M, Gardner-Medwin D, Hosking G, Wilkinson E. Interviews with parents of boys suffering from Duchenne muscular dystrophy. *Dev Med Child Neurol.* 1983; 25: 466-71.
9. Leibowitz D, Dubowitz V. Intellect and behaviour in Duchenne muscular dystrophy. *Dev Med Child Neurol.* 1981; 23: 577-90.
10. Fitzpatrick C, Barry C, Garvey C. Psychiatric disorder among boys with Duchenne muscular dystrophy. *Dev Med Child Neurol.* 1986; 28: 589-95.
11. Hinton VJ, Nereo NE, Fee RJ, Cyrulnik SE. Social behavior problems in boys with Duchenne muscular dystrophy. *J Dev Behav Pediatr* 2006; 27: 470-76.
12. Livneh H, Antonak RF. Review of research on psychosocial adaptation to neuromuscular disorders: I. Cerebral palsy, muscular dystrophy, and Parkinson's disease. *J Soc Behav Pers.* 1994; 9: 201.
13. Hendriksen JG, Poysky JT, Schrans DG, et al. Psychosocial adjustment in males with Duchenne muscular dystrophy: psychometric properties and clinical utility of a parent-report questionnaire. *J Pediatr Psychol.* 2009; 34: 69-78.
14. Hendriksen JG, Vles JS. Are males with Duchenne muscular dystrophy at risk for reading disabilities? *Pediatr Neurol.* 2006; 34: 296-300.
15. Abi Daoud MS, Dooley JM, Gordon KE. Depression in parents of children with Duchenne muscular dystrophy. *Pediatr Neurol.* 2004; 31: 16-9.
16. Chen JY, Chen SS, Jong YJ, Yang YH, Chang YY. A comparison of the stress and coping strategies between the parents of children with Duchenne muscular dystrophy and children with a fever. *J Pediatr Nurs.* 2002; 17: 369-79.
17. Chen JY, Clark MJ. Family function in families of children with Duchenne muscular dystrophy. *Fam Community Health.* 2007; 30: 296-304.
18. Nereo NE, Fee RJ, Hinton VJ. Parental stress in mothers of boys with Duchenne muscular dystrophy. *J Pediatr Psychol.* 2003; 28: 473-84.
19. Thompson RJ, Jr., Zeman JL, Fanurik D, Sirotkin-Roses M. The role of parent stress and coping and family functioning in parent and child adjustment to Duchenne muscular dystrophy. *J Clin Psychol.* 1992; 48: 11-9.
20. Boyer F, Drame M, Morrone I, Novella JL. Factors relating to carer burden for families of persons with muscular dystrophy. *J Rehabil Med.* 2006; 38: 309-15.
21. Parker D, Maddocks I, Stern LM. The role of palliative care in advanced muscular dystrophy and spinal muscular atrophy. *J Paediatr Child Health.* 1999; 35: 245-50.

22. Landfeldt E, Lindgren P, Bell CF, et al. Quantifying the burden of caregiving in Duchenne muscular dystrophy. *J Neurol.* 2016; 263: 906-15.
23. Witte RA. The psychosocial impact of a progressive physical handicap and terminal illness (Duchenne muscular dystrophy) on adolescents and their families. *Br J Med Psychol.* 1985; 58 (Pt 2): 179-87.
24. Hafner P, Bonati U, Erne B, et al. Improved Muscle Function in Duchenne Muscular Dystrophy through L-Arginine and Metformin: An Investigator-Initiated, Open-Label, Single-Center, Proof-Of-Concept-Study. *PLoS One.* 2016; 11: e0147634.
25. Hafner P, Bonati U, Rubino D, et al. Treatment with L-citrulline and metformin in Duchenne muscular dystrophy: study protocol for a single-centre, randomised, placebo-controlled trial. *Trials.* 2016; 17: 389.
26. Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev.* 2000; 21: 265-71.
27. Walker DK, Stein RE, Perrin EC, Jessop DJ. Assessing psychosocial adjustment of children with chronic illnesses: a review of the technical properties of PARS III. *J Dev Behav Pediatr.* 1990; 11: 116-21.
28. Abidin RR, Abidin RR. *Parenting Stress Index (PSI)*: Pediatric Psychology Press Charlottesville, VA; 1990.
29. Parkes J, Caravale B, Marcelli M, Franco F, Colver A. Parenting stress and children with cerebral palsy: a European cross-sectional survey. *Dev Med Child Neurol.* 2011; 53: 815-21.
30. Abidin R. Manual for the parenting stress index. *Odessa, FL: Psychological Assessment Resources.* 1995.
31. Darke J, Bushby K, Le Couteur A, McConachie H. Survey of behaviour problems in children with neuromuscular diseases. *Eur J Paediatr Neurol.* 2006; 10: 129-34.
32. Hendriksen JG, Vles JS. Neuropsychiatric Disorders in Males With Duchenne Muscular Dystrophy: Frequency Rate of Attention-Deficit Hyperactivity Disorders (ADHD), Autism Spectrum Disorder, and Obsessive–Compulsive Disorder. *J Child Neurol.* 2008.
33. Ricotti V, Mandy WP, Scoto M, et al. Neurodevelopmental, emotional, and behavioural problems in Duchenne muscular dystrophy in relation to underlying dystrophin gene mutations. *Dev Med Child Neurol.* 2016; 58: 77-84.
34. Berg-Nielsen TS, Vika A, Dahl AA. When adolescents disagree with their mothers: CBCL-YSR discrepancies related to maternal depression and adolescent self-esteem. *Child Care Health Dev.* 2003; 29: 207-13.
35. Seiffge-Krenke I, Kollmar F. Discrepancies between mothers' and fathers' perceptions of sons' and daughters' problem behaviour: a longitudinal analysis of parent-adolescent agreement on internalising and externalising problem behaviour. *J Child Psychol Psychiatry.* 1998; 39: 687-97.
36. Colvin MK, Poysky J, Kinnett K, et al. Psychosocial Management of the Patient With Duchenne Muscular Dystrophy. *Pediatrics.* 2018; 142: S99-S109.
37. Fee RJ, Hinton VJ. Resilience in children diagnosed with a chronic neuromuscular disorder. *J Dev Behav Pediatr.* 2011; 32: 644-50.
38. Condly SJ. Resilience in children: A review of literature with implications for education. *Urban Educ.* 2006; 41: 211-36.
39. Meleski DD. Families with chronically ill children. *Am J Nurs.* 2002; 102: 47-54.
40. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behav Res Ther.* 2006; 44: 1-25.
41. Graham CD, Simmons Z, Stuart SR, Rose MR. The potential of psychological interventions to improve quality of life and mood in muscle disorders. *Muscle Nerve.* 2015; 52: 131-6.

529 **Tables**

530 Table 1 Sociodemographic, parental and children's illness data.

	N (%) or Mean (SD)
Patients (*N*=34)	
Age	11.6 years (SD 1.34)
Males/Females	33 (97.10%)/ 1 (2.90%)
Non-ambulant	20 (58.80%)
Corticosteroids (current therapy)	25 (73.53%)
Education type patients	
School for physically handicapped	14 (41.18%)
Primary school	9 (26.47%)
Secondary school	7 (20.59%)
Other	3 (8.82%)
Unknown	1 (2.94%)
Caregiver *(N*=34)	
Age	44.44 years (SD 6.28)
Mother	27 (79.41%)
Father	6 (17.65%)
Other	1 (2.94%)
Marital Status	
Married	25 (73.53%)
Divorced	4 (11.77%)
Living with partner	2 (5.88%)
Single	1 (2.94%)
Separated	1 (2.94%)
Unknown	1 (2.94%)
Participation in DMD support group	10 (29.41%)

531

532

533 Table 2. Significant association between parental stress in DMD sample compared to norms

534 of parents of healthy children

	DMD sample (*N*=33)	General population[1] (*N*=800)	
	Mean (SD)	Mean (SD)	*p*
PSI-SF			
Total Score	91.67 (20.41)	71.00 (15.40)	<0.01**
Parental Distress	30.76 (9.44)	26.40 (7.20)	0.01**
Parent-Child Dysfunctional Interaction	28.09 (6.77)	18.70 (4.80)	<0.01**
Difficult Child	32.82 (7.38)	26.00 (6.70)	<0.01**

535 Note: Significant at the acceptable level of *p<0.05, **p<0.01.

536 [1]Parkes, Caravale, Marcelli, Franco, Colver [29]

537

538 Table 3. Pearson correlation between psychosocial adjustment and parental stress

	PSI Total Score		Parental distress		Parent-child dysfunctional interaction		Difficult child	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
PARS								
Total Score	-0.59	<0.01**	-0.20	0.27	-0.62	<0.01**	-0.71	<0.01**
Peers Relations	-0.20	0.26	-0.10	0.60	-0.15	0.42	-0.20	0.27
Dependency	-0.23	0.20	-0.04	0.81	-0.33	0.06	-0.31	0.08
Hostility	-0.52	<0.01**	-0.11	0.55	-0.60	<0.01**	-0.64	<0.01**
Productivity	-0.39	0.03*	-0.17	0.35	-0.31	0.08	-0.47	<0.01**
Anxiety/Depression	-0.57	<0.01**	-0.26	0.14	-0.62	<0.01**	-0.71	<0.01**
Withdrawal	-0.58	<0.01**	-0.37	0.04*	-0.59	<0.01**	-0.53	<0.01**
CBCL								
Total Score	0.72	<0.01**	0.32	0.08	0.71	<0.01**	0.82	<0.01**
Internalizing Problems	0.74	<0.01**	0.43	0.01**	0.68	<0.01**	0.82	<0.01**
Externalizing Problems	0.64	<0.01**	0.18	0.32	0.72	<0.01**	0.77	<0.01**
YSR								
Total Score	0.46	0.03*	0.35	0.10	0.40	0.06	0.53	<0.01**
Internalizing Problems	0.28	0.20	0.29	0.17	0.17	0.43	0.33	0.13
Externalizing Problems	0.44	0.04	0.22	0.31	0.41	0.05*	0.54	<0.01**

Note: Significant at the acceptable level of *p<0.05, **p<0.01.

539

540

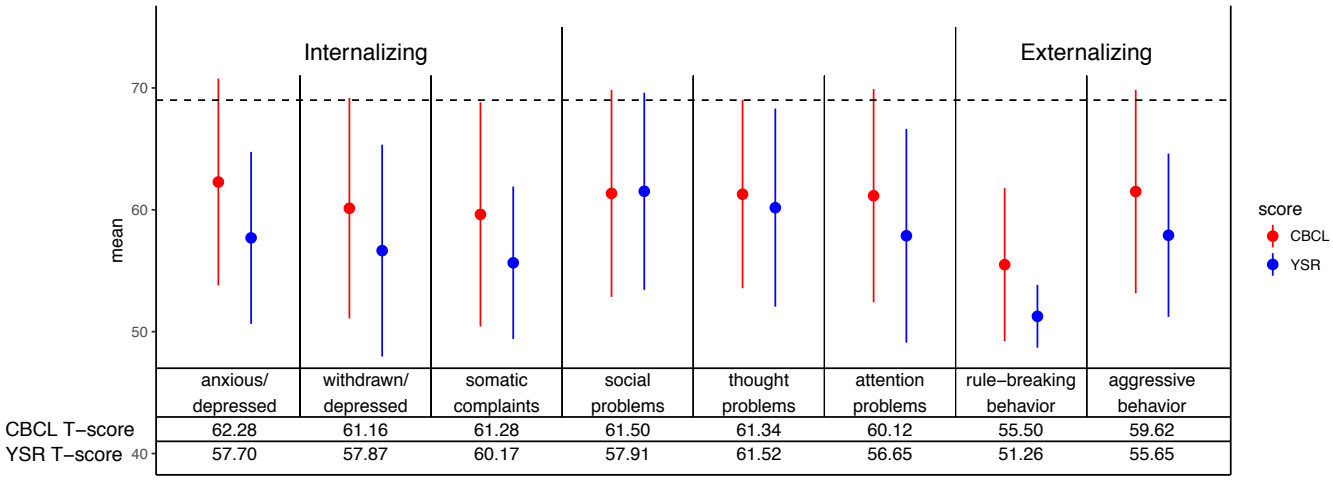
541 Table 4. Multiple regression models of factors influencing psychosocial adjustment to DMD.
542 Each line indicates the estimate from a separate model. The estimate for "parental stress" is
543 adjusted for the patients' age. All other estimates are adjusted for the patients' age and
544 parental stress.

	PARS-III		CBCL		YSR	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Parental stress (PSI-SF total score)	-0.23 (-0.40;-0.06)	<0.01	0.74 (0.38;1.10)	<0.01	0.41 (-0.02;0.84)	0.06
Marital status	5.60 (-5.09;16.29)	0.29	-7.57 (-30.45;15.30)	0.50	-4.89 (-28.97;19.19)	0.68
Ambulation status	1.80 (-5.76; 9.36)	0.63	-2.28 (-18.36;13.80)	0.77	-2.19 (-21.90;17.52)	0.82
Corticosteroid use	2.03 (-6.14;10.20)	0.62	-1.14 (-19.27;17.00)	0.90	5.83 (-14.89;26.55)	0.56
Support group participation	9.57 (2.61;16.53)	<0.01	-18.97 (-33.91;-4.04)	0.02	-7.78 (-29.11;13.56)	0.46

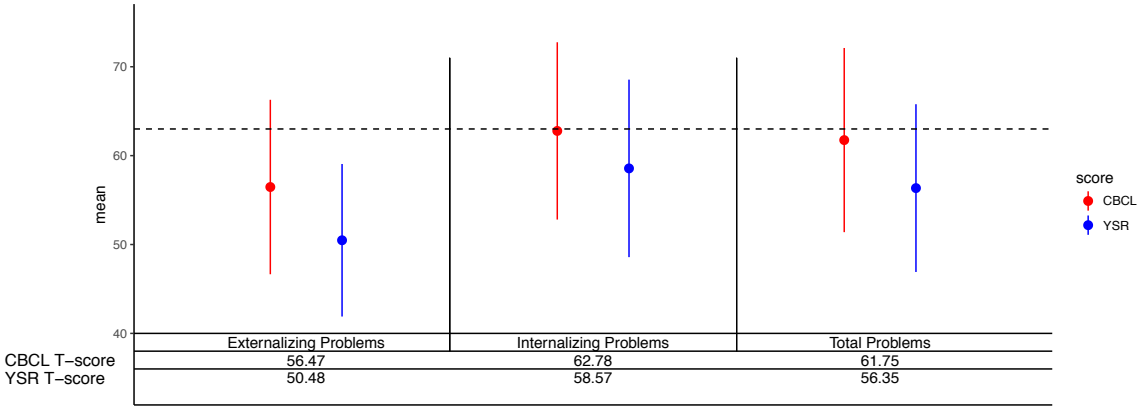
545 Note: *B* (regression coefficient unstandardized), 95 % CI (confidence interval).
546

Figures

Figure 1 Mean and standard deviations of CBCL and YSR T scores of syndrome scales.



551 Figure 2 Mean and standard deviations of CBCL and YSR T scores of broadband scales



552

3. Discussion

The aim of the present PhD thesis is to explore relevant psychological outcomes in two NMDs. First, a prospective observational study in patients with PPS was performed investigating HRQOL, self-reported impairments related to PPS and activities of daily living during 6 months and their association with clinical muscle function outcomes.

Second, we performed a cross-sectional study investigating the HRQOL in ambulant and non-ambulant patients with DMD and its association to motor function.

Third, we investigated the psychosocial adjustment in children with DMD and assessed its association to parental stress and other sociodemographic and disorder-related items.

These three studies provide a brief overview of relevant psychological outcomes in patients with PPS and DMD.

3.1. Patient-reported outcomes in post-polio syndrome

The first publication focuses on various PROMs and its association to objectively assessed physical function in patients with PPS. In our study, patients with PPS were moderately affected by their impairments. Muscle fatigue, muscle weakness, and muscle and/or joint pain during physical activity were the most reported impairments of the included patients. These impairments have been consistently reported as exemplary for patients with PPS in recent studies (Brogårdh & Lexell, 2015; Winberg, Flansbjer, Rimmer, & Lexell, 2015). The ability to stand up from sitting position independently, the ability to climb stairs and limitations in their ability to walk were the most common reported limitations considering their activities of daily living, which is in agreement with previous studies measured by self-reported instruments (Brogårdh, Flansbjer, Espelund, & Lexell, 2013; Brogårdh & Lexell, 2015; Winberg et al., 2015).

Rehabilitation management should concentrate on ways primary targeting and improving these impairments. Diminishing impairments is expected to improve walking ability and reduce the risk of falling (Brogardh & Lexell, 2014). Furthermore, prescribing effective technical aids and assistive devices (e.g. proper orthoses) may facilitate daily life activities and improve accessibility of public transport and leisure activities (Koopman et al., 2015).

Our results show that patients with PPS reported higher HRQOL scores in the social relationships and environmental health domain in comparison to general population, which has not been reported by other studies so far. Moreover, comparable HRQOL scores of the physical and psychological health were found for patients with PPS and healthy adults. This finding is inconsistent with previous literature, since former studies investigating patients with PPS refer to the physical limitations as the major contributing factor to the impaired HRQOL (Garip et al., 2017; Jacob & Shapira, 2010; Kling et al., 2000; McNaughton, McPherson, Falkner, & Taylor, 2001; On, Oncu, Atamaz, & Durmaz, 2006). We believe that the small sample size does not allow an extensive investigation of the HRQOL in comparison to general population, therefore the relative low number of patients included in our study may thereby overestimate positive findings of individual patients.

Further, no decrease in overall HRQOL, self-reported impairments related to PPS, activities of daily living and muscle function outcomes during 6 months in the affected individuals was found. This is likely due to the relatively slow disease progression of PPS and a time span being too short to detect changes in PROMs (Laffont et al., 2010). However, after 6 months patients reported lower psychological health scores compared to baseline. As the psychological health declined during the short observational study period, this finding highlights the added value of including HRQOL assessments also in clinical trials to obtain additional information on disease evolution.

Our results reveal an association between the activities of daily living measured by the IBM-FRS and the clinical outcome measures (6 Minute Walking Test and Motor Function Measure). This is in line with the findings of Jackson et al. indicating that the IBM-FRS correlates to traditional measures of efficacy in muscle testing in inclusion body myositis (Jackson et al., 2008). This finding provides evidence that the IBM-FRS is an appropriate rating scale when assessing impairments in activities of daily living as well as walking ability in patients with late effects of polio. However, it should be noted that self-reported measures cannot replace traditional gait performance tests. Further investigations are needed to increase the understanding of how the included PROMs are related to objectively measured physical function. Individuals affected by PPS should be offered individually tailored rehabilitation interventions conducted by a multi-professional team primarily targeting participants' activity and participation in society, that involve a great sensitivity to individual needs (Natterlund & Ahlstrom, 1999).

In this study it is important to underline that only participants with a high level of mobility (patients able to walk 350m in 6 minutes) were included. In future studies, also patients with lower level of mobility should be included.

3.2. Association between health-related quality of life and motor function in DMD

The second study explores the association between HRQOL and motor function in ambulant and non-ambulant children with DMD. Our results revealed moderate to high associations between different aspects of generic and disease-specific HRQOL and the motor function. The physical health correlated with the overall motor abilities as well as the standing and transfer posture domain both on child self-report and parent-proxy report, which is in line with previous study results including different functional outcomes (Bray, Bundy, Ryan, North, & Everett, 2010; McDonald et al., 2010; Messina

et al., 2016). Specifically, this is the first observational study reporting a significant association between the self-reported psychosocial health as well as the social functioning domain and the standing and transfer posture domain of the MFM. We believe that due to the progressive physical weakness of the affected children, their ability to take part in physical and social activities is very limited and therefore they have increasingly difficulties to maintain relationships and participate in activities, where wheelchair access is not given (Read, Kinali, Muntoni, Weaver, & Garralda, 2011). Also, as the disease progresses (e.g. losing the ability to stand and to transfer, becoming wheelchair dependent) children may experience more emotional difficulties such as feeling anxious or depressed.

This is the first study to describe a significant association between the family resources domain of the disease-specific HRQOL and motor function in the children's questionnaire, indicating that poorer patients' motor function is associated with worsening of family financial and social support system resources. Caregivers which are overburdened by the responsibilities of caring for their chronically ill child are more likely to experience chronic emotional stress (Chen & Clark, 2007; Nereo et al., 2003), which may contribute to social isolation (Bothwell et al., 2002; Yilmaz, Yildirim, Oksuz, Atay, & Turan, 2010). Also, the socio-economic status of the family may have an impact on the HRQOL, so that chronically ill children coming from a lower socio-economic background experience a deterioration in the HRQOL compared with their wealthier peers with better socio-economic conditions independent of the neurological course of the disease (Didsbury et al., 2016).

Another important finding is that the multivariate analysis confirmed the significant correlations obtained in the bivariate analysis between the generic and the disease-

specific HRQOL domains and the overall motor abilities as well as the standing and transfer posture domain, when adjusted for age and corticosteroid use.

Consistent with previous study findings (Bendixen, Senesac, Lott, & Vandenborne, 2012; Davis et al., 2010; McDonald et al., 2010; Uzark et al., 2012; Wei et al., 2016), this study reflects that the HRQOL of children affected by DMD have considerable limitations in the physical and psychosocial domain compared to healthy peers. More than half of the children with DMD reported an impaired psychosocial health, which confirms previous findings reporting that boys with DMD have increased levels of psychosocial problems (Darke et al., 2006; Hendriksen et al., 2009; Uzark et al., 2012).

In this study it is important to underline that we included both ambulant and non-ambulant patients with DMD, since previous studies examined mainly ambulant patients (Henricson et al., 2013; McDonald et al., 2010; Messina et al., 2016). This may reveal different results because neglecting the natural disease progression. Moreover, it is important to note that our results are to be interpreted with caution as only 47% of the participants performed the motor function measure.

3.3. Psychosocial adjustment in DMD

The third study investigates psychosocial adjustment in children with DMD and its possible association to parental stress as well to other sociodemographic and disorder-related factors.

Our results show that based on different instruments measuring psychosocial adjustment different levels of psychosocial maladjustment were detected. Based on the Child Behavior Checklist (CBCL), almost half of the patients with DMD were found to be psychosocially at risk for emotional and behavioural problems. This finding indicates increased rates of psychosocial adjustment problems in DMD, which is in line

with previous study results (Darke et al., 2006; Hendriksen & Vles, 2008; Ricotti et al., 2016). In contrast, measuring the psychosocial adjustment with the Psychosocial Adjustment and Role Skills Scale (PARS-III) revealed that only 15% of the affected children were identified as being at risk for emotional and behavioural problems.

The measure most widely used for the assessment of psychosocial adjustment in children with DMD in former studies is the CBCL representing the gold standard of screening and detecting psychopathology in children and adolescents. However, the CBCL may not represent the most suitable instrument for children with a chronic physical conditions since it includes a range of items that may be overly sensitive to illness-related variables, especially items related to somatic complaints. Therefore, when assessing psychosocial adjustment in DMD the use of the CBCL may over-represent psychosocial maladjustment or mislabel normal behaviour as pathological resulting in false positives (Hendriksen et al., 2009). In contrast, the PARS-III excludes items based on physiological symptoms, which are part of the chronic medical condition, and therefore is a more suitable tool for the assessment of psychosocial adjustment in children with chronic medical conditions.

In our study, half of the caregivers reported very high parenting stress compared to a general population sample, where only 10% of the parents reported very high stress. Thus, our finding indicates that very high parenting stress is five times more common among families caring for a child with DMD than in a general population sample. This is in line with previous reports on higher stress level in caregivers of children with DMD compared to healthy normative group (Abi Daoud, Dooley, & Gordon, 2004; Chen, Chen, Jong, Yang, & Chang, 2002; Chen & Clark, 2007; Nereo et al., 2003).

Moreover, parental stress domains demonstrated moderate to high correlations with the psychosocial adjustment in children with DMD. Specifically, mainly the difficult child

and the parent-child dysfunctional interaction subscores correlated with domains of the psychosocial adjustment. In contrast, the correlations between parental stress and psychosocial adjustment were negligible. This finding reveals that parental stress largely depends on the behavioural functioning of the affected child as well as practical aspects of caring for the child, rather than on parental stress independent from the parent-child interaction. The experience of caring for a chronically ill child may have a more global impact, so that additional stress contributes to an overall lower stress tolerance in these caregivers, resulting in poorer parenting skills and coping mechanisms (Nereo et al., 2003).

Finally, the regression analyses demonstrated that the psychosocial adjustment level in children affected by DMD is strongly associated with the intensity of parental stress and the participation in a DMD support group. This findings indicate that the participation in a support group and parental stress associated to parent-child interaction are more salient to emotional and behavioural outcomes than the impact of disease progression.

3.4. Limitations and further directions

Due to the exploratory nature of the present work, it is important to highlight the limitations of the investigated studies and suggest possible improvements for future works on psychological outcomes in NMD populations.

First of all the small sample size of the studies is a major limitation when generalizing findings to other patients with PPS and DMD. Furthermore, two of the studies had cross-sectional design; therefore longitudinal studies are needed to confirm the reported associations over a longer time and to investigate how key variables change over critical time. A further limitation is the lack of control group and comparison to normative sample data of healthy peers. Future studies should include an age and

gender–matched healthy control population and/or populations including individuals with different chronic medical conditions.

Moreover, we controlled the results for some confounding variables (e.g. age, corticosteroid use). However future research should include further factors which may influence different psychological outcomes (e.g. socioeconomic status, cognitive functioning) of patients with NMD.

As the included psychological outcomes can be measured with different instruments, to some extend it is difficult to compare our results to those of other studies. Furthermore, in one of the included studies the patients had already participated in a clinical trial which may bias the results. Since the motor function was performed in less severely affected individuals with PPS, a selection bias can be assumed for the estimated motor function. Moreover, in the second study only half of the patients with DMD were able to perform the motor function measure. Therefore, multicentre studies investigating patients with a broad range of motor function abilities should be encouraged.

4. Conclusion

Limitations in physical function are associated with limitations in activities of daily living and HRQOL in patients with PPS and DMD. While not all patients with NMDs report decreased HRQOL or psychosocial adjustment problems, it is recommended to integrate psychosocial management into the multidisciplinary management of the neuromuscular disease. Moreover, primary care clinicians who care for patients with NMDs may be the first clinicians to identify psychosocial concerns. Therefore, it is recommended to screen regularly for impairments of the HRQOL and psychosocial functioning in the neuromuscular clinic. If concerns are identified, more intensive psychiatric services may be warranted (Colvin et al., 2018). Based on the present work,

interdisciplinary rehabilitation programs considering individual needs of persons with late effects of polio should be developed and primarily target participants' activity and participation in society. Furthermore, in patients with DMD a family-centered approach for interventions is needed to be developed in order to improve the HRQOL and psychosocial adjustment of the affected children and their families. Further, the participation in a disease-specific support group should be recommended by clinicians.

References

Abi Daoud, M. S., Dooley, J. M., & Gordon, K. E. (2004). Depression in parents of children with Duchenne muscular dystrophy. *Pediatr Neurol, 31*(1), 16-19. doi:10.1016/j.pediatrneurol.2004.01.011

Baj, A., Colombo, M., Headley, J. L., McFarlane, J. R., Liethof, M.-a., & Toniolo, A. (2015). Post-poliomyelitis syndrome as a possible viral disease. *Int J Infect Dis, 35*, 107-116. doi:10.1016/j.ijid.2015.04.018

Barlow, J. H., & Ellard, D. R. (2006). The psychosocial well-being of children with chronic disease, their parents and siblings: an overview of the research evidence base. *Child Care Health Dev, 32*(1), 19-31. doi:10.1111/j.1365-2214.2006.00591.x

Bendixen, R. M., Senesac, C., Lott, D. J., & Vandenborne, K. (2012). Participation and quality of life in children with Duchenne muscular dystrophy using the International Classification of Functioning, Disability, and Health. *Health Qual Life Outcomes, 10*, 43. doi:10.1186/1477-7525-10-43

Black, N. (2013). Patient reported outcome measures could help transform healthcare. *BMJ, 346*, f167. doi:10.1136/bmj.f167

Bothwell, J. E., Dooley, J. M., Gordon, K. E., MacAuley, A., Camfield, P. R., & MacSween, J. (2002). Duchenne muscular dystrophy--parental perceptions. *Clin Pediatr (Phila), 41*(2), 105-109. doi:10.1177/000992280204100206

Bray, P., Bundy, A. C., Ryan, M. M., North, K. N., & Everett, A. (2010). Health-related quality of life in boys with Duchenne muscular dystrophy: agreement between parents and their sons. *J Child Neurol, 25*(10), 1188-1194. doi:10.1177/0883073809357624

Brogårdh, C., Flansbjer, U.-B., Espelund, C., & Lexell, J. (2013). Relationship between self-reported walking ability and objectively assessed gait performance in persons with late effects of polio. *NeuroRehabilitation, 33*(1), 127-132. doi:10.3233/NRE-130936

Brogardh, C., & Lexell, J. (2014). Falls, fear of falling, self-reported impairments, and walking limitations in persons with late effects of polio. *PM R, 6*(10), 900-907. doi:10.1016/j.pmrj.2014.04.010

Brogårdh, C., & Lexell, J. (2015). How various self-reported impairments influence walking ability in persons with late effects of polio. *NeuroRehabilitation, 37*(2), 291-298. doi:10.3233/NRE-151261

Bushby, K., Finkel, R., Birnkrant, D. J., Case, L. E., Clemens, P. R., Cripe, L., . . . Group, D. M. D. C. C. W. (2010). Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol, 9*(1), 77-93. doi:10.1016/S1474-4422(09)70271-6

Chen, J. Y., Chen, S. S., Jong, Y. J., Yang, Y. H., & Chang, Y. Y. (2002). A comparison of the stress and coping strategies between the parents of children with Duchenne muscular dystrophy and children with a fever. *J Pediatr Nurs, 17*(5), 369-379. doi:10.1053/jpdn.2002.123525

Chen, J. Y., & Clark, M. J. (2007). Family function in families of children with Duchenne muscular dystrophy. *Fam Community Health, 30*(4), 296-304. doi:10.1097/01.FCH.0000290542.10458.f8

Colvin, M. K., Poysky, J., Kinnett, K., Damiani, M., Gibbons, M., Hoskin, J., . . . Weidner, N. (2018). Psychosocial Management of the Patient With Duchenne

Muscular Dystrophy. *Pediatrics, 142*(Suppl 2), S99-S109. doi:10.1542/peds.2018-0333L
Conference, I. H. (2002). Constitution of the World Health Organization. 1946. *Bulletin of the World Health Organization, 80*(12), 983.
Darke, J., Bushby, K., Le Couteur, A., & McConachie, H. (2006). Survey of behaviour problems in children with neuromuscular diseases. *Eur J Paediatr Neurol, 10*(3), 129-134. doi:10.1016/j.ejpn.2006.04.004
Davis, E., Waters, E., Mackinnon, A., Reddihough, D., Graham, H. K., Mehmet-Radji, O., & Boyd, R. (2006). Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. *Dev Med Child Neurol, 48*(4), 311-318. doi:10.1017/S0012162206000673
Davis, S. E., Hynan, L. S., Limbers, C. A., Andersen, C. M., Greene, M. C., Varni, J. W., & Iannaccone, S. T. (2010). The PedsQL™ in Pediatric Patients with Duchenne Muscular Dystrophy: Feasibility, Reliability, and Validity of the Pediatric Quality of Life Inventory Neuromuscular Module and Generic Core Scales. *J Clin Neuromuscul Dis, 11*(3), 97-109. doi:10.1097/CND.0b013e3181c5053b
de Ridder, D., Geenen, R., Kuijer, R., & van Middendorp, H. (2008). Psychological adjustment to chronic disease. *Lancet, 372*(9634), 246-255. doi:10.1016/S0140-6736(08)61078-8
Didsbury, M. S., Kim, S., Medway, M. M., Tong, A., McTaggart, S. J., Walker, A. M., . . . Wong, G. (2016). Socio-economic status and quality of life in children with chronic disease: A systematic review. *J Paediatr Child Health, 52*(12), 1062-1069. doi:10.1111/jpc.13407
Firth, M., Gardner‐Medwin, D., Hosking, G., & Wilkinson, E. (1983). Interviews with parents of boys suffering from Duchenne muscular dystrophy. *Dev Med Child Neurol, 25*(4), 466-471. doi:10.1111/j.1469-8749.1983.tb13791.x
Fitzpatrick, C., Barry, C., & Garvey, C. (1986). Psychiatric disorder among boys with Duchenne muscular dystrophy. *Dev Med Child Neurol, 28*(5), 589-595. doi:10.1111/j.1469-8749.1986.tb03900.x
Garip, Y., Eser, F., Bodur, H., Baskan, B., Sivas, F., & Yilmaz, O. (2017). Health related quality of life in Turkish polio survivors: impact of post-polio on the health related quality of life in terms of functional status, severity of pain, fatigue, and social, and emotional functioning. *Rev Bras Reumatol Engl Ed, 57*(1), 1-7. doi:10.1016/j.rbre.2014.12.006
Hendriksen, J. G., Poysky, J. T., Schrans, D. G., Schouten, E. G., Aldenkamp, A. P., & Vles, J. S. (2009). Psychosocial adjustment in males with Duchenne muscular dystrophy: psychometric properties and clinical utility of a parent-report questionnaire. *J Pediatr Psychol, 34*(1), 69-78. doi:10.1093/jpepsy/jsn067
Hendriksen, J. G., & Vles, J. S. (2006). Are males with Duchenne muscular dystrophy at risk for reading disabilities? *Pediatr Neurol, 34*(4), 296-300. doi:10.1016/j.pediatrneurol.2005.08.029
Hendriksen, J. G., & Vles, J. S. (2008). Neuropsychiatric Disorders in Males With Duchenne Muscular Dystrophy: Frequency Rate of Attention-Deficit Hyperactivity Disorders (ADHD), Autism Spectrum Disorder, and Obsessive–Compulsive Disorder. *J Child Neurol*. doi:10.1177/0883073807309775
Henricson, E., Abresch, R., Han, J. J., Nicorici, A., Goude Keller, E., de Bie, E., & McDonald, C. M. (2013). The 6-Minute Walk Test and Person-Reported Outcomes in Boys with Duchenne Muscular Dystrophy and Typically Developing Controls: Longitudinal Comparisons and Clinically-Meaningful

Changes Over One Year. *PLoS Curr, 5*. doi:10.1371/currents.md.9e17658b007eb79fcd6f723089f79e06
Hinton, V. J., Nereo, N. E., Fee, R. J., & Cyrulnik, S. E. (2006). Social behavior problems in boys with Duchenne muscular dystrophy. *J Dev Behav Pediatr, 27*(6), 470-476. doi:10.1097/00004703-200612000-00003
Houwen-van Opstal, S. L., Jansen, M., van Alfen, N., & de Groot, I. J. (2014). Health-related quality of life and its relation to disease severity in boys with Duchenne muscular dystrophy: satisfied boys, worrying parents--a case-control study. *J Child Neurol, 29*(11), 1486-1495. doi:10.1177/0883073813506490
Hullmann, S. E., Wolfe-Christensen, C., Ryan, J. L., Fedele, D. A., Rambo, P. L., Chaney, J. M., & Mullins, L. L. (2010). Parental overprotection, perceived child vulnerability, and parenting stress: a cross-illness comparison. *J Clin Psychol Med Settings, 17*(4), 357-365. doi:10.1007/s10880-010-9213-4
Hysing, M., Elgen, I., Gillberg, C., & Lundervold, A. J. (2009). Emotional and behavioural problems in subgroups of children with chronic illness: results from a large-scale population study. *Child Care Health Dev, 35*(4), 527-533. doi:10.1111/j.1365-2214.2009.00967.x
Jackson, C. E., Barohn, R. J., Gronseth, G., Pandya, S., Herbelin, L., & Muscle Study, G. (2008). Inclusion body myositis functional rating scale: a reliable and valid measure of disease severity. *Muscle Nerve, 37*(4), 473-476. doi:10.1002/mus.20958
Jacob, & Shapira. (2010). Quality of life and health conditions reported from two post-polio clinics in Israel. *J Rehabil Med, 42*(4), 377-379. doi:10.2340/16501977-0515
Katirji, B., Kaminski, H. J., & Ruff, R. L. (2013). *Neuromuscular disorders in clinical practice*: Springer Science & Business Media.
Ke, Q., Zhao, Z. Y., Mendell, J. R., Baker, M., Wiley, V., Kwon, J. M., . . . Gatheridge, M. A. (2019). Progress in treatment and newborn screening for Duchenne muscular dystrophy and spinal muscular atrophy. *World J Pediatr*. doi:10.1007/s12519-019-00242-6
Kling, C., Persson, A., & Gardulf, A. (2000). The health-related quality of life of patients suffering from the late effects of polio (post-polio). *J Adv Nurs, 32*(1), 164-173. doi:10.1046/j.1365-2648.2000.01412.x
Koopman, F. S., Beelen, A., Gilhus, N. E., de Visser, M., & Nollet, F. (2015). Treatment for postpolio syndrome. *Cochrane Libr*.
Laffont, I., Julia, M., Tiffreau, V., Yelnik, A., Herisson, C., & Pelissier, J. (2010). Aging and sequelae of poliomyelitis. *Ann Phys Rehabil Med, 53*(1), 24-33. doi:10.1016/j.rehab.2009.10.002
Landfeldt, E., Lindgren, P., Bell, C. F., Guglieri, M., Straub, V., Lochmuller, H., & Bushby, K. (2016). Quantifying the burden of caregiving in Duchenne muscular dystrophy. *J Neurol, 263*(5), 906-915. doi:10.1007/s00415-016-8080-9
Leibowitz, D., & Dubowitz, V. (1981). Intellect and behaviour in Duchenne muscular dystrophy. *Dev Med Child Neurol, 23*(6), 577-590. doi:10.1111/j.1469-8749.1981.tb02039.x
Livneh, H., & Antonak, R. F. (1994). Review of research on psychosocial adaptation to neuromuscular disorders: I. Cerebral palsy, muscular dystrophy, and Parkinson's disease. *J Soc Behav Pers, 9*(5), 201.
Lo, J. K., & Robinson, L. R. (2018). Post-polio syndrome and the late effects of poliomyelitis: Part 2. treatment, management, and prognosis. *Muscle Nerve, 58*(6), 760-769. doi:10.1002/mus.26167

McDonald, C. M., McDonald, D. A., Bagley, A., Sienko Thomas, S., Buckon, C. E., Henricson, E., . . . Sussman, M. D. (2010). Relationship between clinical outcome measures and parent proxy reports of health-related quality of life in ambulatory children with Duchenne muscular dystrophy. *J Child Neurol, 25*(9), 1130-1144. doi:10.1177/0883073810371509

McNaughton, H., McPherson, K., Falkner, E., & Taylor, W. (2001). Impairment, disability, handicap and participation in post-poliomyelitis subjects. *Int J Rehabil Res, 24*(2), 133-136. doi:10.1097/00004356-200106000-00006

Mendell, J. R., Csimma, C., McDonald, C. M., Escolar, D. M., Janis, S., Porter, J. D., . . . Howell, R. R. (2007). Challenges in drug development for muscle disease: a stakeholders' meeting. *Muscle Nerve, 35*(1), 8-16. doi:10.1002/mus.20686

Mendell, J. R., Shilling, C., Leslie, N. D., Flanigan, K. M., al-Dahhak, R., Gastier-Foster, J., . . . Weiss, R. B. (2012). Evidence-based path to newborn screening for Duchenne muscular dystrophy. *Ann Neurol, 71*(3), 304-313. doi:10.1002/ana.23528

Messina, S., Vita, G. L., Sframeli, M., Mondello, S., Mazzone, E., D'Amico, A., . . . Mercuri, E. (2016). Health-related quality of life and functional changes in DMD: A 12-month longitudinal cohort study. *Neuromuscul Disord, 26*(3), 189-196. doi:10.1016/j.nmd.2016.01.003

Morrison, B. M. (2016). Neuromuscular Diseases. *Semin Neurol, 36*(5), 409-418. doi:10.1055/s-0036-1586263

Natterlund, B., & Ahlstrom, G. (1999). Experience of social support in rehabilitation: a phenomenological study. *J Adv Nurs, 30*(6), 1332-1340. doi:10.1046/j.1365-2648.1999.01211.x

Nereo, N. E., Fee, R. J., & Hinton, V. J. (2003). Parental stress in mothers of boys with Duchenne muscular dystrophy. *J Pediatr Psychol, 28*(7), 473-484. doi:10.1093/jpepsy/jsg038

Nierse, C. J., Abma, T. A., Horemans, A. M., & van Engelen, B. G. (2013). Research priorities of patients with neuromuscular disease. *Disabil Rehabil, 35*(5), 405-412. doi:10.3109/09638288.2012.694964

On, A. Y., Oncu, J., Atamaz, F., & Durmaz, B. (2006). Impact of post-polio-related fatigue on quality of life. *J Rehabil Med, 38*(5), 329. doi:10.1080/16501970600722395

Passamano, L., Taglia, A., Palladino, A., Viggiano, E., D'Ambrosio, P., Scutifero, M., . . . Politano, L. (2012). Improvement of survival in Duchenne Muscular Dystrophy: retrospective analysis of 835 patients. *Acta Myol, 31*(2), 121-125.

Piccininni, M., Falsini, C., & Pizzi, A. (2004). Quality of life in hereditary neuromuscular diseases. *Acta Neurol Scand, 109*(2), 113-119. doi:10.1046/j.1600-0404.2003.00185.x

Polakoff, R. J., Morton, A. A., Koch, K. D., & Rios, C. M. (1998). *The psychosocial and cognitive impact of Duchenne's muscular dystrophy.* Paper presented at the Semin Pediatr Neurol.

Ravens-Sieberer, U., Erhart, M., Wille, N., Wetzel, R., Nickel, J., & Bullinger, M. (2006). Generic health-related quality-of-life assessment in children and adolescents: methodological considerations. *Pharmacoeconomics, 24*(12), 1199-1220. doi:10.2165/00019053-200624120-00005

Read, J., Kinali, M., Muntoni, F., Weaver, T., & Garralda, M. E. (2011). Siblings of young people with Duchenne muscular dystrophy--a qualitative study of impact and coping. *Eur J Paediatr Neurol, 15*(1), 21-28. doi:10.1016/j.ejpn.2010.07.006

Reid, D. T., & Renwick, R. M. (2001). Relating familial stress to the psychosocial adjustment of adolescents with Duchenne muscular dystrophy. *Int J Rehabil Res, 24*(2), 83-93. doi:10.1097/00004356-200106000-00001

Ricotti, V., Mandy, W. P., Scoto, M., Pane, M., Deconinck, N., Messina, S., . . . Muntoni, F. (2016). Neurodevelopmental, emotional, and behavioural problems in Duchenne muscular dystrophy in relation to underlying dystrophin gene mutations. *Dev Med Child Neurol, 58*(1), 77-84. doi:10.1111/dmcn.12922

Thoren-Jonsson, A. L., & Grimby, G. (2001). Ability and perceived difficulty in daily activities in people with poliomyelitis sequelae. *J Rehabil Med, 33*(1), 4-11.

Trojan, D. A., & Cashman, N. R. (2005). Post-poliomyelitis syndrome. *Muscle Nerve, 31*(1), 6-19. doi:10.1002/mus.20259

Uzark, K., King, E., Cripe, L., Spicer, R., Sage, J., Kinnett, K., . . . Varni, J. W. (2012). Health-related quality of life in children and adolescents with Duchenne muscular dystrophy. *Pediatrics, 130*(6), e1559-1566. doi:10.1542/peds.2012-0858

Vita, G., Vita, G. L., Musumeci, O., Rodolico, C., & Messina, S. (2019). Genetic neuromuscular disorders: living the era of a therapeutic revolution. Part 2: diseases of motor neuron and skeletal muscle. *Neurol Sci*. doi:10.1007/s10072-019-03764-z

Vuillerot, C., Hodgkinson, I., Bissery, A., Schott-Pethelaz, A.-M., Iwaz, J., Ecochard, R., . . . Berard, C. (2010). Self-perception of quality of life by adolescents with neuromuscular diseases. *J Adolesc Health, 46*(1), 70-76. doi:10.1016/j.jadohealth.2009.05.005

Wei, Y., Speechley, K. N., Zou, G., & Campbell, C. (2016). Factors Associated With Health-Related Quality of Life in Children With Duchenne Muscular Dystrophy. *J Child Neurol, 31*(7), 879-886. doi:10.1177/0883073815627879

WHO. (2019). Retrieved from https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/

Winberg, C., Flansbjer, U. B., Rimmer, J. H., & Lexell, J. (2015). Relationship between physical activity, knee muscle strength, and gait performance in persons with late effects of polio. *PM R, 7*(3), 236-244. doi:10.1016/j.pmrj.2014.09.005

Yilmaz, O., Yildirim, S. A., Oksuz, C., Atay, S., & Turan, E. (2010). Mothers' depression and health-related quality of life in neuromuscular diseases: role of functional independence level of the children. *Pediatr Int, 52*(4), 648-652. doi:10.1111/j.1442-200X.2010.03094.x

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Publication list

Gocheva, V., Schmidt, S., Orsini, AL., Hafner, P., Schaedelin, S., Weber, P., & Fischer, D. (2019) Psychosocial adjustment and parental stress in Duchenne Muscular Dystrophy. *European Journal of Pediatric Neurology. (Manuscript accepted for publication 16.09.2019)*

Gocheva, V., Hafner, P., Orsini, AL., Schmidt, S., Schaedelin, S., Rueedi, N., Rubino-Nacht, D., Weber, P., & Fischer, D. (2019) Health-related quality of life, self-reported impairments and activities of daily living in relation to muscle function in post-polio syndrome. *Journal of patient-reported outcomes. (Manuscript submitted for publication)*

Gocheva, V., Schmidt, S., Orsini, AL., Hafner, P., Schaedelin, S., Rueedi, N., Weber, P., & Fischer, D. (2019) Association Between Health-Related Quality of Life and Motor Function in Ambulant and Nonambulant Duchenne Muscular Dystrophy Patients. *Journal of Child Neurology. 0883073819865681.*

Nagy, S., Schmidt, S., Hafner, P., Klein, A., Rubino-Nacht, D., **Gocheva, V**., O. Bieri, O., Vuillerot, C., Bonati, U., & Fischer, D. (2019). Measurements of Motor Function and Other Clinical Outcome Parameters in Ambulant Children with Duchenne Muscular Dystrophy. *JoVE (Journal of Visualized Experiments),* (143), e58784.

Schmidt, S., Hafner, P., Klein, A., Rubino-Nacht, D., **Gocheva, V.,** Schroeder, J., Naduvilekoot Devasia, A., Zuesli, S., Bernert, G., Laugel, V., Bloetzer, C., Steinlin, M., Capone, A., Gloor, M., Tobler, P., Haas, T., Bieri , O., T. Zumbrunn, T., Fischer, D., & Bonati, U. (2018). Timed function tests, motor function measure, and quantitative thigh muscle MRI in ambulant children with Duchenne muscular dystrophy: A cross-sectional analysis. *Neuromuscular disorders*, 28(1), 16-23.

Gocheva, V., Hund-Georgiadis, M., & Hediger, K. (2018). Effects of animal-assisted therapy on concentration and attention span in patients with acquired brain injury: A randomized controlled trial. Neuropsychology, 32(1), 54.

Schmidt, S., **Gocheva, V.,** Zumbrunn, T., Rubino-Nacht, D., Bonati, U., Fischer, D., & Hafner, P. (2017). Treatment with L-citrulline in patients with post-polio syndrome: study protocol for a single-center, randomised, placebo-controlled, double-blind trial. *Trials*, 18(1), 116.

Hafner, P., Bonati, U., Rubino, D., **Gocheva, V.,** V., Zumbrunn, T., Gueven, N., & Fischer, D. (2016). Treatment with L-citrulline and metformin in Duchenne muscular dystrophy: study protocol for a single-centre, randomised, placebo-controlled trial. *Trials*, 17(1), 389.