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Fatigue in Children and Adolescents with Duchenne Muscular Dystrophy

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Abstract

Fatigue was recently reported to be the largest predictor of poor health-related quality of life (HRQOL) in children and adolescents with Duchenne muscular dystrophy (DMD). The objectives of this thesis were to describe fatigue from patients' and parents' perspectives and to explore associations of patient characteristics with fatigue in children and adolescents with DMD using a multicentre cross-sectional study design. Eligible patients and their parents were identified via the Canadian Neuromuscular Disease Registry and received mailed paper questionnaires. Children and adolescents with DMD experienced greater fatigue compared to healthy controls from published data. Fatigue was a significant issue in children and adolescents with DMD across all disease stages. Sleep disturbance symptoms, depressive symptoms and functional ability were associated with fatigue. Physical activity level was not associated with fatigue. These findings warrant future research aimed at understanding the determinants of fatigue and developing therapeutic strategies to reduce fatigue and improve HRQOL.

Keywords: Duchenne muscular dystrophy, children, adolescents, fatigue

Dedication

To my parents.

Thank you for instilling in me a love for education and learning.

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List of Abbreviations

ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
BMD	Becker muscular dystrophy
CNDR	Canadian Neuromuscular Disease Registry
CES-DC	Center for Epidemiological Studies Depression Scale for Children
CBT	Cognitive Behavioural Therapy
DMD	Duchenne muscular dystrophy
DMDSAT	Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool
EDMD	Emery-Dreifuss muscular dystrophy
ENMC	European Neuromuscular Centre
FSHD	Facioscapulohumeral muscular dystrophy
HRQOL	Health-related quality of life
LGMD	Limb-Girdle muscular dystrophy
MFS	Multidimensional Fatigue Scale
NIV	Non-invasive ventilation
NSAA	North Star Ambulatory Assessment
PAQ-C/A	Physical Activity Questionnaire for Children and Adolescents
PedsQL™	Pediatric Quality of Life Inventory™
QOL	Quality of life
RCT	Randomized controlled trial
6MWT	Six-minute walk test
SDSC	Sleep Disturbance Scale for Children
SMA	Spinal muscular atrophy
SBMA	Spinal and bulbar muscular atrophy
SMN	Survival motor neuron

Chapter 1

1 Introduction

1.1 Thesis Overview

Duchenne muscular dystrophy (DMD) is the most common and severe form of childhood muscular dystrophy, with an estimated incidence of 1 in 3600–6000 live male births. DMD is an X-linked recessive disease caused by the absence of or defect in the sarcolemmal protein dystrophin, ultimately resulting in progressive muscle degeneration and loss of independent ambulation by 13 years of age. Additional musculoskeletal, respiratory and cardiac complications emerge in patients as DMD advances. There is no cure for DMD. Current therapeutic strategies aim to improve quality of life [1]. In a recent study published by our group, fatigue was reported to be the largest predictor of poor health-related quality of life (HRQOL) in children and adolescents with DMD, from both patients' and caregivers' perspectives [2,3]. Fatigue is frequent and disabling in adults with neuromuscular disorders, but not well characterized in children and adolescents with neuromuscular disorders, including DMD [4]. Fatigue may be a modifiable factor, which makes it a particularly important construct to study fully [5]. However, the pathogenesis of fatigue in neuromuscular disorders is poorly understood and consequently, evidence regarding the efficacy of non-pharmacological and pharmacological interventions for the prevention and management of fatigue in patients with neuromuscular disorders is limited and inconsistent [6,7]. To our knowledge, no studies have explored factors associated with fatigue in children, adolescents or adults with DMD. Consequently, inferences from the study of fatigue in other neuromuscular disorders and childhood chronic health conditions, and a more clinically informed conceptualization of fatigue in DMD were required during

the formulation of the thesis objectives. Identifying fatigue when present and understanding the determinants of fatigue may facilitate the development of therapeutic strategies to effectively reduce fatigue, and subsequently improve HRQOL in children and adolescents with DMD. The aim of this thesis was to describe fatigue and to identify factors associated with fatigue in children and adolescents with DMD, using a multi-centre cross-sectional survey study design. The current chapter provides background knowledge on fatigue and DMD, a proposed model of fatigue in children and adolescents with DMD, and objectives of this thesis. Subsequent chapters provide a comprehensive literature review on fatigue in DMD and related neuromuscular disorders (Chapter 2), followed by the methods (Chapter 3), results (Chapter 4), and discussion (Chapter 5).

1.2 Fatigue

The feeling of fatigue is a universal phenomenon and can be a normal response to physical and mental stress. However, fatigue is a frequent complaint secondary to physical or psychiatric illnesses, and is consistently associated with decreased quality of life and functioning across patient populations [8–11]. Fatigue may be acute and come on suddenly or be experienced more chronically. In the case of neuromuscular disorders, it is generally chronic, however, acute episodes of worsened fatigue may occur and be severely disabling [12]. Fatigue is among the most disabling symptoms in adult neuromuscular disorders, but not well studied in paediatric neuromuscular disorders [4,5]. This is worrisome because fatigue has different implications in children compared with adults. Fatigue may limit children's participation in age-related recreational and school activities, and consequently delay physical, cognitive, language, social and emotional development, which are already problematic in children and adolescents with DMD [4,13]. In clinical practice, fatigue is

recognized as a common symptom of paediatric chronic health conditions, including neurologic disorders (cerebral palsy, multiple sclerosis, fibromyalgia, epilepsy and traumatic brain injury), cancer, postural orthostatic tachycardia syndrome, juvenile idiopathic arthritis, diabetes, inflammatory bowel disease and obesity [14]. However, data on the mechanisms and management of fatigue in paediatric chronic health conditions are limited, with most studies focusing on children with cancer [15].

A major challenge in studying fatigue is the lack of a commonly accepted definition. Many studies fail to explicitly define fatigue, possibly due to the assumption that the term is known to all. Among studies that have defined fatigue, there is a considerable range of definitions [9,16]. Differences in reported prevalence of fatigue in neuromuscular disorders may be due to different definitions and assessment methods [17]. In 2011, an expert workshop was organized by the European Neuromuscular Centre (ENMC) to achieve a consensus on the definition of fatigue in neuromuscular disorders, and to discuss possible interventions. The definition of fatigue proposed by the ENMC workshop reads "Subjective or experienced fatigue is a lack of energy or the existence of weakness or exhaustion—mentally, physically or both." [17]. In addition to subjective fatigue, the term physiological fatigue or fatigability often appears in the body of literature relating to fatigue in neuromuscular disorders. Physiological fatigue or fatigability refers to difficulty maintaining physical or mental activity at a desired level and, in the case of physical fatigability, appears to be related to muscle weakness. Physiological fatigability occurs in a short period of time, while subjective fatigue may persist over several days to weeks. Subjective fatigue and physiological fatigability are not necessarily correlated. Figure 1.1 describes a conceptual model of fatigue in neuromuscular disorders. Subjective fatigue and

physiological fatigability both have a physical and mental component [16]. Subjective fatigue is assessed using self-reported or parent proxy-reported questionnaires, which can be unidimensional or multidimensional [8,14,16,17]. Physiological fatigability is assessed objectively in a laboratory setting, using exercise protocols for physical fatigability and reaction time protocols for mental fatigability [9,16]. Physical fatigability can originate at the level of the central nervous system (upper motor neuron) or peripheral nervous system (lower motor neuron, neuromuscular junction or muscle) [18,19].

The focus of this thesis is subjective fatigue. Subjective fatigue often overlaps with sleep disturbance symptoms, such as excessive daytime sleepiness, or depressive symptoms. Fatigue, sleep disturbance symptoms and depressive symptoms can occur independently or co-exist and exacerbate one another in chronic health conditions. It is important to distinguish fatigue from these other entities, as clear definitions in the research and clinical realms are critical to accurately describe and measure these constructs, such that interventions can be more specifically targeted to achieve satisfactory outcomes [4,19]. Fatigue implies mental or physical exhaustion, independent of exertion or amount of sleep, whereas excessive daytime sleepiness implies a problem with the sleep-wake cycle [4]. Depression is characterized by a general lack of interest in daily activities that are normally enjoyed. However, this motivational component is unaffected in fatigue. Fatigue may be disease-related or induced by medical interventions [8]. Understanding the contributors to and factors associated with fatigue in paediatric DMD is essential for comprehending this complex symptom, and for ultimately developing effective therapeutic strategies for reducing fatigue. Additionally, it is important to differentiate between disease-related and treatment-induced fatigue. With the surge of novel therapeutics for DMD under

development and clinical investigation, it is important for fatigue to be assessed both as a potential marker of efficacy, given that an effective new therapy might reduce fatigue as it improves motor function, or as a possible adverse effect when documenting safety concerns. Moreover, the value of patient-reported outcomes in understanding the impact and efficacy of a treatment is increasingly being recognized by regulatory authorities, such as the U.S. Food and Drug Administration [20].

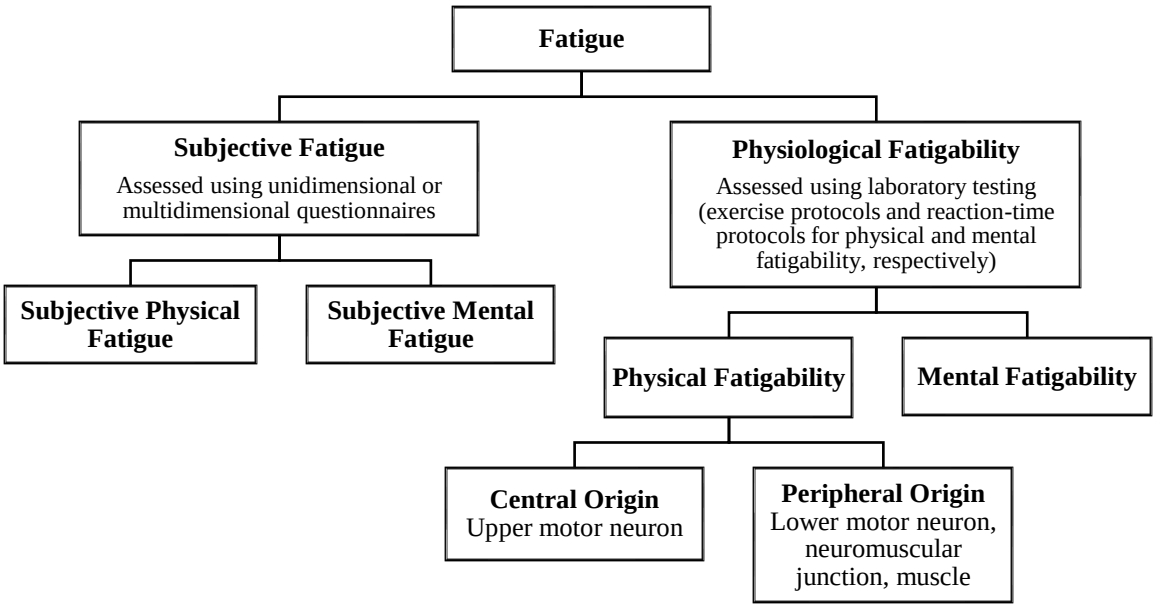

Figure 1.1. A conceptual model of fatigue in neuromuscular disorders. Adapted from Lou. Phys Med Rehabil Clin N Am. 2012;23:11–22.

1.3 Duchenne Muscular Dystrophy

1.3.1 Epidemiology

DMD is the most common form of inherited muscle disease in childhood [21]. A systematic review and meta-analysis of population-based prevalence and incidence estimates of DMD was recently conducted [22]. The pooled prevalence of DMD was 4.78 (95% CI: 1.94, 11.81) per 100,000 males worldwide. Among paediatric populations, the

prevalence was 12.57 (95% CI: 9.04, 17.46) per 100,000 males worldwide. Meta-analysis was not performed on incidence estimates due to limited data and study heterogeneity. The incidence of DMD ranged from 10.71 to 27.78 per 100,000 live born males per year worldwide between the years 1986–1997. Prevalence and incidence studies of DMD were limited to North American, European, African and Asian populations. However, the majority of data was collected from European populations [22]. The incidence rate in the Canadian population is estimated to be 1 per 3,600–4,700 live born males per year and has remained relatively stable over time between the years 1969–2008 [23,24].

1.3.2 Pathogenesis

As an X-linked recessive disease, DMD primarily affects males. However, approximately 8% of female carriers present with muscle weakness to some extent and are designated as manifesting carriers [25]. DMD is caused by mutations in the *DMD* gene at locus Xp21.2, which codes for the sarcolemmal protein dystrophin [26]. The *DMD* gene contains 79 exons and seven promoters, which generate protein isoforms expressed in various tissues [27]. The majority of cases are caused by deletions (~68%), followed by small point mutations (~20%) and duplications (~11%), which disrupt the reading frame or generate a premature stop codon in the protein-coding region of the *DMD* gene [28,29]. Consequently, the production of non-functional or truncated protein leads to dystrophin deficiency in skeletal and cardiac muscle, as well as other tissues where dystrophin isoforms are expressed, such as smooth muscle, brain, retina and kidney [30]. Normally, dystrophin interacts with integral membrane proteins to form the dystrophin-glycoprotein complex, which connects the inner cytoskeleton of skeletal and cardiac muscle fibres to the extracellular matrix. The primary function of the dystrophin-glycoprotein complex is

to stabilize the plasma membrane, protecting the muscle fibre from contraction-induced damage. In addition to a structural role, the dystrophin-glycoprotein complex is hypothesized to have a role in cellular signal transduction. In DMD, the absence of or defect in dystrophin ultimately results in progressive muscle degeneration and additional clinical manifestations that may contribute to fatigue [27,30–32].

1.3.3 Onset and Diagnosis

Children are typically diagnosed with DMD at 4–5 years of age, when their physical ability diverges noticeably from their peers [28]. However, the diagnosis may be suspected earlier due to delayed developmental motor or intellectual milestones [1,33]. Delayed speech development is reported in 50–70% of children with DMD and may precede concerns related to delayed motor development and muscle weakness. Although onset is before school age in most cases, occasionally, a diagnosis is not made until 8–9 years of age [34]. Weakness of pelvic girdle muscles results in a broad-based waddling gait, and difficulty standing from a supine or sitting position, climbing stairs, running and jumping [35,36]. Affected children also present with enlargement of the calf muscles during early stages of the disease. Muscle enlargement is primarily due to excess adipose and fibrous connective tissue and is therefore termed pseudohypertrophy [34]. In addition to abnormal muscle function discovered during the medical history and physical examination, suspicion of DMD may be triggered after the detection of elevated serum creatinine kinase or transaminases (amino and alanine aminotransferases), which are indicative of muscle damage [35,37].

Confirmation of the diagnosis is dependent on genetic testing. Initial genetic testing aims to detect deletions and duplications, as these mutations account for most DMD cases.

If no deletions or duplications are detected, sequencing of the whole DMD gene should be performed to look for small point mutations [35]. In exceptional cases when no mutation is detected in patients with a clear DMD phenotype, a muscle biopsy can be performed to study dystrophin protein [28]. Establishing a genetic diagnosis is important for providing optimal care in accordance with disease progression predicted by genotype-phenotype associations, guiding genetic counselling for the family, and evaluating a patient's eligibility for emerging mutation-specific therapies [28].

1.3.4 Clinical Characteristics and Prognosis

In addition to progressive muscle degeneration, orthopaedic, respiratory and cardiac complications emerge in children as DMD advances [1]. Affected children and adolescents are also at increased risk for neurodevelopmental, emotional and behavioural problems [38–40]. Muscle weakness, immobility, reduced respiratory and cardiac function, and neuropsychiatric disturbances have all been reported to be associated with fatigue in chronic health conditions, including neuromuscular disorders [5,41–48]. Prior to routine glucocorticoid therapy and non-invasive ventilation (NIV), the mean age at death was 15 years and in 90% of cases, death occurred before the age of 20 years due to respiratory or cardiac failure [49,50]. Improved medical management has prolonged survival with patients now having a possible life expectancy into their fourth or fifth decade [34,51]. In developed countries, mean age at death is now approximately 25 years [34,49,52]. Pulmonary infections and respiratory failure are the leading causes of death in DMD [53]. DMD is no longer considered purely a childhood disease, and fatigue experienced during childhood and adolescence may impact outcomes in adulthood. By limiting participation in age-related activities during childhood and adolescence, fatigue may impact

developmental milestones and consequently impact social, educational and occupational pursuits during adulthood [13,54].

Musculoskeletal Complications

Muscle weakness occurs bilaterally and symmetrically in DMD. During early stages of the disease, lower limb muscles are affected more than upper limb muscles, and proximal muscles more than distal muscles. Muscle weakness appears when skeletal muscle has degenerated and been replaced by adipose and fibrous connective tissue. In approximately 50% of affected children, walking is delayed until at least 18 months of age [34]. In most cases, children are unable to run or jump properly [33]. Affected boys report difficulty keeping up with their peers, and tenderness or stiffness after exercise, particularly in their calf muscles [34]. In addition to a waddling gait, toe-walking is a frequent complaint due to contractures of the Achilles tendon. During early stages of the disease, weakness of the pelvic girdle muscles results in an anterior pelvic tilt, and consequently progressive lumbar lordosis, an inward curvature of the lower spine, which can cause low backache [34]. Muscle weakness continues and loss of independent ambulation typically occurs by 13 years of age [55]. Initially, affected boys may only need to use a wheelchair part-time, before becoming permanently confined to a wheelchair. An earlier age at loss of ambulation is typically associated with poorer prognosis [34]. Transitioning to intermittent wheelchair use has been reported to be associated with fatigue in children and adolescents with DMD [3]. Upper extremity function declines during mid-teenage years and is followed by an inability of affected boys to independently feed or care for themselves [56]. Muscle weakness and reduced functional ability secondary to muscle weakness have been reported to be associated with fatigue in neuromuscular disorders, including

facioscapulohumeral dystrophy, myotonic dystrophy, and hereditary motor and sensory neuropathy type I [57]. In children and adolescents with DMD, objective measures of functional ability, such as timed motor function tests, were weakly associated with fatigue [58].

Around the time of loss of ambulation, most children with DMD develop some degree of kyphoscoliosis—an abnormal spinal curvature in the coronal and sagittal planes. Following its onset, kyphoscoliosis progresses rapidly and can impair unsupported sitting ability, feeding and comfort, cause pain, and further deteriorate already compromised respiratory and cardiac function of affected boys. By contributing to immobility and respiratory and cardiac function decline, kyphoscoliosis may worsen fatigue [59–61]. Additionally, DMD is associated with reduced bone mineral density (osteopenia) secondary to reduced load and immobility, and increased bone fragility (osteoporosis) secondary to chronic glucocorticoid use. Poor bone health in DMD can further contribute to immobility by increasing affected boys' risk for bone fractures [62–65].

Respiratory Complications

Onset of respiratory function decline occurs between 9–11 years of age due to progressive weakness of intercostal muscles and the diaphragm muscle [56]. Deterioration of respiratory function is exacerbated by kyphoscoliosis [66]. Forced vital capacity, a global index of respiratory function, is consistently above 70% in pre-adolescent ambulant boys and declines linearly with age during adolescent years [34,50]. Respiratory muscle weakness is associated with an ineffective cough, impaired airway clearance, pneumonia, atelectasis, sleep disordered breathing and ultimately nocturnal, followed by daytime, respiratory failure [50,64,67,68]. In neuromuscular disorders, fatigue may manifest as a

symptom of respiratory failure [69]. Onset of respiratory failure can be predicted by a forced vital capacity below 35% or an absolute forced vital capacity below 1 L. During sleep, intercostal muscles are less active and diaphragmatic breathing alone cannot sufficiently maintain normal gas exchange. Thus, early respiratory failure is characterized by nocturnal hypoventilation, resulting in oxygen desaturation (hypoxemia) and accumulation of carbon dioxide (hypercapnia), followed by restoration of normal blood gas tension upon arousal. The early respiratory failure phase can last for several months. However, when hypoxia and hypercapnia persist during the daytime, survival beyond 12 months is unlikely without the initiation of NIV [34,50,70].

Nocturnal and diurnal hypoventilation are frequently compounded with additional sleep-related breathing disorders, such as obstructive sleep apnea (OSA) secondary to oropharyngeal muscle weakness or weight gain associated with glucocorticoid therapy [71]. In young boys with DMD, OSA in the absence of clinically significant hypoventilation has also been reported. In affected boys, sleep-related breathing disorders may co-exist with additional sleep disturbance symptoms including difficulty initiating or maintaining sleep, sleep hyperhidrosis and excessive daytime sleepiness [72,73]. Bloetzer et al. reported the need to be turned by a caregiver during the night as a predictor of sleep disturbance symptoms in boys with DMD [72]. Muscle weakness and immobility may therefore contribute to sleep disturbance symptoms. Sleep disturbance symptoms, measured both subjectively by patient-report and objectively by polysomnography, have been reported to contribute to fatigue in patient populations, such as myotonic dystrophy, multiple sclerosis and cancer [7,74–82]. An association between sleep disturbance

symptoms and fatigue has also been reported in school age-children and paediatric patient populations [78,79].

Cardiac Complications

Improved respiratory management has unmasked cardiomyopathy as a major source of morbidity and mortality in DMD [83]. Premature death due to heart failure occurs in 15–20% of patients [34]. Onset of cardiomyopathy occurs at a mean age of 14–15 years and is a universal consequence by adulthood [84,85]. However, approximately 25% and 59% of affected boys present with asymptomatic cardiomyopathy at 6 and 10 years of age, respectively [86]. Fibrosis caused by the degeneration of dystrophin-deficient cardiomyocytes proceeds to progressive cardiomyopathy, characterized by left ventricular systolic dysfunction with dilation [86–88]. Canadian Cardiovascular Society paediatric heart failure guidelines define left ventricular systolic dysfunction as left ventricular ejection fraction below 50% [89]. Because of physical activity limitations associated with musculoskeletal weakness, exertional signs and symptoms of heart failure are often absent despite myocardial disease progression [90]. Fibrosis of the conduction system, in addition to the myocardium, has been demonstrated. Arrhythmias are seen in DMD; sinus tachycardia is a common finding at disease onset [91]. In advanced cardiomyopathy, patients may experience atrial fibrillation or flutter, ventricular fibrillation and ventricular tachycardia [92]. Now that survival of patients with DMD is prolonged, the cause of death in DMD is increasingly cardiac-related [34]. Cardiac dysfunction may be directly associated with fatigue [43]. Evidence also suggests that cardiac dysfunction may contribute to sleep disordered breathing. Conversely, sleep disordered breathing may contribute to heart failure [93]. Cardiac dysfunction and sleep disordered breathing may

therefore exacerbate one another and further contribute to fatigue in DMD. However, because clinical manifestations of cardiomyopathy in DMD typically occur in young adulthood [94], cardiac dysfunction may have a greater role in fatigue in adults with DMD than in children or adolescents with DMD.

Neuropsychiatric Complications

The role of dystrophin isoforms in the central nervous system remains unclear, however, it is recognized that DMD is associated with an increased risk for neuropsychiatric disturbances [38]. Approximately one third of affected boys experience learning difficulties [34]. Although there is considerable variability in intellectual ability among affected boys, overall mean intellectual quotient scores are about one standard deviation below the mean [95]. Working memory deficits have also been reported [38,40,95]. Cognitive impairment in DMD is not progressive and does not correlate with disease duration or severity [91]. Boys with DMD are reported to have a higher prevalence of neurodevelopmental disorders, including autism spectrum disorder and attention deficit hyperactivity disorder, than the general paediatric population [96,97]. Emotional and behavioural problems, including depression, anxiety, aggression and oppositional defiant disorder, are also frequently reported in affected boys [38,91]. Moreover, affected boys may experience emotional and behavior problems as adverse effects of glucocorticoid use, which is currently standard of care therapy in DMD [53]. An association between depression and fatigue has been widely reported across paediatric and adult patient populations, including neuromuscular disorders [12,44,47,98]. Depression has consistently been described as the strongest correlate of cancer-related fatigue. The association between depression and fatigue is hypothesized to be bidirectional, however, few longitudinal

studies have examined directionality [99–101]. Moreover, depressive symptoms often co-exist with sleep disturbance symptoms, and may therefore exacerbate one another to contribute to fatigue [79,102,103].

1.3.5 Management

With the characterization of the DMD gene and its protein product, novel disease-modifying therapies are under development and investigation. Disease-modifying therapeutic strategies include agents to reduce muscle damage, promote muscle regeneration following injury, or increase expression of functional dystrophin protein using gene-therapy or RNA-based approaches [53,104,105]. To date, no disease-modifying agents are licenced for use in routine clinical practice in Canada. Current therapeutic strategies focus on prolonging ambulation, managing respiratory and cardiac complications, and ultimately improving quality of life. Psychological, educational and social needs of affected boys should also be considered at all stages of the disease [53]. International consensus-based recommendations on multidisciplinary standards of care in DMD were published in 2010 [1,64].

Musculoskeletal Management

Glucocorticoids (prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day) are the only pharmacological therapy that slow the decline in muscle strength and function [1,105]. Although the exact mechanism is unclear, glucocorticoids are hypothesized to act primarily by reducing inflammation [105]. Glucocorticoid therapy is typically initiated between 5–8 years of age when the child's motor development reaches a plateau phase, and is continued indefinitely [1,26]. Long-term glucocorticoid use has been demonstrated to prolong independent ambulation by 2–5 years, reduce the risk of scoliosis and the need for spinal

fusion surgery, stabilize respiratory function and delay the need for NIV, stabilize cardiac function, and improve survival and quality of life [52]. Deflazacort is as effective as prednisone and associated with less weight gain, often making deflazacort the more desirable option in Canada [106]. In addition to weight gain secondary to increased appetite, adverse effects associated with chronic glucocorticoid use requiring proactive prevention and management include: immunosuppression, growth failure, pubertal delay, hirsutism, osteoporosis, hypertension, gastric ulceration, cataracts, and altered mood and behaviour [53,65].

In conjunction with a neurologist or neuromuscular specialist, musculoskeletal care should involve a physical therapist, physiatrist and orthopaedic surgeon. Active, active-assisted and passive stretching is recommended to prolong walking, and to prevent or minimize contractures during ambulatory and non-ambulatory phases. Orthoses, standing frames and walkers can be used to prolong ambulation and aid in standing. Lower-limb contracture surgeries, and spinal fusion surgery to correct scoliosis and prevent further deformity are considered on a case-by-case basis [53,64]. In boys with DMD, physical activity level is largely related to musculoskeletal function. Physical activity level (over-exertion or excessive rest) has been reported to be associated with fatigue, and exercise therapy has been proposed as a treatment for fatigue [44,107–109]. However, evidence supporting exercise therapy for the treatment of fatigue in neuromuscular disorders is lacking [110].

Respiratory Management

Respiratory assessment should be conducted annually during early stages of the disease, semi-annually following loss of ambulation, when forced vital capacity is below

80% and/or 12 years of age, and before any surgical procedure. To improve airway clearance and prevent pulmonary infections in patients with an ineffective cough, mechanical insufflation-exsufflation machines can be used to assist coughing [68]. NIV, particularly nocturnal nasal intermittent positive pressure ventilation, is the most effective way to attenuate the decline in respiratory function. When patients progress to daytime respiratory failure and require 24-hour ventilatory support, mouthpiece intermittent positive pressure ventilation may be introduced [53,68]. In a recent study, comparing respiratory management practices across Canada for children and adolescents with DMD, variations in the timing and choice of tests for respiratory function and sleep disordered breathing were reported. Polysomnography, overnight pulse oximetry or both were used to detect sleep disordered breathing either routinely, at a certain age, or due to abnormal pulmonary function tests [73]. However, the utility of overnight pulse oximetry alone for the detection of sleep disordered breathing in neuromuscular disorders is unclear. Moreover, the absence of abnormal pulmonary function tests and symptoms may not rule out sleep disordered breathing. Therefore, routine polysomnography may be the most effective screening practice for sleep disordered breathing and assisting in initiating NIV [71,111]. Effective detection and treatment of sleep disordered breathing may subsequently reduce fatigue.

Cardiac Management

Cardiac assessment should be conducted biannually until 10 years of age, annually after 10 years of age, and before any surgical procedure [64]. Data regarding optimal pharmacological regimens and when to initiate therapy to delay the onset of cardiomyopathy in DMD are lacking [112]. Initiation of therapy with an angiotensin-

converting enzyme inhibitor or angiotensin receptor blocker by 10 years of age is recommended, however, it is unclear if earlier therapy is warranted. With further deterioration, beta-adrenergic blocking agents are added, followed by diuretic agents at the onset of symptomatic heart failure [92].

Neuropsychiatric Management

Neuropsychiatric assessment should be conducted around the time of diagnosis, before entering school, and after a change in function. However, a brief evaluation of patients' emotional and coping status is recommended at every clinic visit. Speech language therapy is necessary for younger boys with delayed speech development and older boys with impaired speech intelligibility due to deteriorating oral muscle strength. Development of an individual education plan is recommended for all boys with DMD to address learning difficulties, physical activity limitations and accessibility issues in school. Psychological and pharmacological therapies should be considered for moderate to severe psychiatric symptoms, and prescribed according to standard practices and guidelines [64]. Antidepressants have been proposed as a possible treatment for fatigue. Studies evaluating the efficacy of antidepressants to treat fatigue have reported conflicting results across different patient populations, suggesting that the association between depression and fatigue may be modified by disease-specific mechanisms [99,113–115].

1.4 A Proposed Model of Fatigue in Duchenne Muscular Dystrophy

Figure 1.2 presents a hypothesized model of fatigue in children and adolescents with DMD. This model was developed based on the clinical characteristics and management of DMD, in conjunction with the literature relating to fatigue in other neuromuscular disorders and paediatric chronic health conditions. Sleep disturbance

symptoms may be overlooked in the management of DMD [71], and variations exist in the screening and management of sleep disordered breathing in children and adolescents with DMD across Canada, between centres and sub-specialists (neurologist and respirologists) [73]. Given the findings from the survey of respiratory management practices across Canada for DMD patients [73], and recognizing that sleep may be a modifiable factor, the need is clear for further study and consensus in this area to guide best clinical practices. In addition to musculoskeletal, respiratory and cardiac characteristics being potential predictors of fatigue in children and adolescents with DMD, we hypothesize that these clinical characteristics are also directly associated with physical activity level and functional ability related to activities of daily living. In turn, physical activity level and functional ability may be associated with fatigue in DMD, as has been reported in adult neuromuscular disorders [57,116]. Lastly, depression is the most commonly cited neuropsychiatric disturbance to be associated with fatigue across chronic health conditions [12,44,47,98], and may be associated with fatigue in boys with DMD.

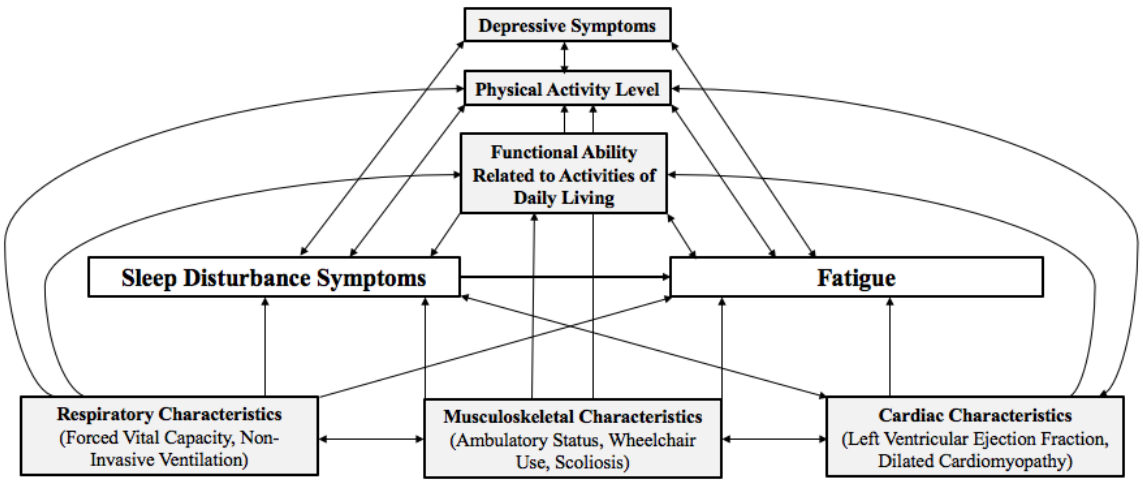

Figure 1.2. A hypothesized model of fatigue in children and adolescents with Duchenne muscular dystrophy.

1.5 Objectives

With the exception of the past finding by our group of an association between fatigue and poor health-related quality of life in children and adolescents with DMD [3], data on fatigue and factors associated with fatigue in this population are lacking. To facilitate the development of the best clinical practices to treat fatigue in children and adolescents with DMD, an understanding of fatigue from both patients' and parents' perspectives, as well as potential factors contributing to fatigue in this population is needed. The perspective of parents is important because it is typically the parents' perceptions of their child's health status that influences healthcare utilization—particularly when the child is too young, too cognitively impaired or too ill [117,118]. Therefore, the objectives of this thesis are:

1. To describe subjective fatigue in a multicentre cross-sectional sample of children and adolescents with DMD from patients' and parents' perspectives.
2. To explore associations of patient characteristics with child self-report and parent proxy-report measures of subjective fatigue in a multicentre cross-sectional sample of children and adolescents with DMD.

   Hypothesis: Sleep disturbance symptoms, depressive symptoms, physical activity level, functional ability related to activities of daily living, musculoskeletal characteristics (ambulatory status, wheelchair use and scoliosis), respiratory characteristics (forced vital capacity, NIV status) and cardiac characteristics (left ventricular ejection fraction and cardiomyopathy status) are associated with fatigue.

Chapter 2

2 Literature Review

2.1 Background

While fatigue has been established as a complaint in adult neurologic and neuromuscular disorders, the role of fatigue in paediatric neuromuscular disorders is not yet well defined or studied [4,14,17,19,119]. Moreover, data regarding the role of fatigue in Duchenne muscular dystrophy (DMD) are largely insufficient and lacking in both paediatric and adult populations [3,120]. The aim of this literature review was to summarize the current body of scientific literature relating to subjective fatigue in DMD, as well as diseases with similar clinical manifestations, particularly other muscular dystrophies and spinal muscular atrophy (SMA).

Other muscular dystrophies of interest were Becker muscular dystrophy (BMD), Emery-Dreifuss muscular dystrophy (EDMD), limb girdle muscular dystrophies (LGMDs) and facioscapulohumeral dystrophy (FSHD). BMD is a dystrophinopathy characterized by later-onset and milder progressive muscle weakness and degeneration than DMD [36]. EDMD is characterized by joint contractures and slowly progressive muscle weakness and wasting in a humeroperoneal distribution that later extends to the scapular and pelvic girdle muscles [121]. DMD, BMD and EDMD are part of a larger group of LGMDs characterized by weakness and wasting of the scapular and pelvic girdle muscles [122]. FSHD is characterized by slowly progressive weakness of the facial muscles and the stabilizers of the scapula or the dorsiflexors of the foot [123]. In contrast to the myopathies, SMA is characterized by muscle weakness and atrophy caused by degeneration of lower motor neurons in the anterior horn of the spinal cord and brain stem nuclei. SMA is amongst the

most common childhood neuromuscular disorders, following DMD, and is classified into different phenotypes per age of onset, maximum motor milestone achieved, and life expectancy. Type I SMA is the most severe phenotype with onset before 6 months of age, and characterized by sitting with support only as the maximum motor milestone attained. Types II and III SMA are intermediate phenotypes with onset between 6–18 months and after 18 months of age, respectively. Type II and III SMA are characterized by independent sitting when placed and independent ambulation, respectively, as the maximum motor milestones attained. Type IV SMA is the mildest phenotype with adult onset and normal motor milestone attainment [124].

2.2 Search Strategy and Search Results

A literature search was conducted to identify quantitative, qualitative and mixed-methods studies relating to subjective mental and/or physical fatigue, evaluated using unidimensional or multidimensional questionnaires, in paediatric and adult muscular dystrophies and spinal muscular atrophy. Studies assessing the relationship between physiological fatigue and subjective fatigue were also included. Studies that combined other disease populations with muscular dystrophies or SMA were included, so long as disease-type was controlled for in the analysis or subgroup analyses were conducted. Only studies published in English were included. Records were not excluded based on country or date of publication. Review articles, editorials, commentaries and case reports were excluded. The literature search was conducted using MEDLINE (Ovid), EMBASE, CINAHL and PsycINFO databases on October 22nd, 2016. A comprehensive search strategy was developed with guidance from a research librarian using terminology related to muscular dystrophies, SMA and fatigue. The search strategy employed database-specific

terminology and syntax, which are presented in Appendix A (Table A.1). Appropriate Boolean operators and database-specific limitations were used to optimize search results. A generic search strategy is presented below:

1. Database-specific subject headings for ‘muscular dystrophies’ OR ‘spinal muscular atrophy’
2. Keywords: muscular dystroph* OR dystrophinopath* OR Duchenne muscular dystrophy OR Becker muscular dystrophy OR Emery Dreifuss muscular dystrophy OR facioscapulohumeral muscular dystrophy OR limb girdle muscular dystrophy OR spinal muscular atrophy OR spinal muscle atrophy
3. (1) OR (2)
4. Database-specific subject headings for ‘fatigue’
5. Keywords: fatigue OR fatigability OR tired*
6. (4) OR (5)
7. (3) AND (6)

A total of 1,016 records were retrieved from databases (404 from MEDLINE (Ovid), 356 from EMBASE, 47 from CINAHL and 209 from PsycINFO), and 1 additional record was retrieved through personal communication with the author. Duplicate records were removed and records were screened in three consecutive stages by title, abstract and full-text. Of the 867 records remaining after duplicate records were removed, 50 records met eligibility criteria for full-text review and 27 records were ultimately included in this literature review [3,57,58,98,116,120,125–145]. Reference lists of included studies and excluded non-original studies were searched to ensure no records were omitted from the search strategy. A study selection flowchart is presented in Appendix B (Figure B.1).

2.3 Characteristics of Included Studies

Three themes emerged from studies included in this literature review: (1) the burden of fatigue, (2) risk factors associated with fatigue, and (3) the management of fatigue in muscular dystrophies and SMA. Although the management of fatigue in muscular dystrophies and SMA is beyond the scope of the objectives of this thesis, these studies were included as data on the effectiveness of interventions to treat fatigue can provide insight on risk factors associated with fatigue. Study characteristics and findings are summarized in Table 2.1 and Table 2.2. Studies were published between the years 2005 and 2016, underscoring the relative infancy of the study of subjective fatigue in muscular dystrophies and SMA. Studies were conducted in the Netherlands [57,116,120,128,131–133,136,139,140,142,143], United States of America [98,129,137,141], Japan [138], Denmark [135,145], Canada [3,144], Italy [58,130], France [126,127], and Turkey [125,134]. The majority of studies evaluating the burden of fatigue and/or risk factors associated with fatigue used a hypotheses-generating, cross-sectional design [3,57,98,128,129,131–133,136,138,140,145], with the exception of three studies that prospectively followed patients for 12 to 18 months [58,116,144]. Studies assessing the management of fatigue were composed of randomized controlled trials (RCTs) [126,137,142,143], non-randomized trials [125,134], single-arm trials [127,135], and a prospective cohort study [130].

Four studies focused on paediatric DMD patients [3,58,125,144] and one study focused on adult DMD patients [120], while the remaining studies primarily included adults with other muscular dystrophies or SMA. Although studies of adults with muscular dystrophies and SMA may have limited generalizability to fatigue in paediatric DMD, they

can offer preliminary guidance for this novel area of research, including the conceptual framework of this thesis. Moreover, studies of fatigue in DMD populations did not examine associations between potentially modifiable risk factors and fatigue, further justifying the need to turn to the scientific literature for other neuromuscular disorders.

2.4 Definition of Fatigue

Fatigue was most often defined as "an overwhelming sense of tiredness, lack of energy and feeling of exhaustion" [57,116,120,131–133,136,139,142,145]. Werlauff et al. added that patients experience difficulties in initiating or sustaining activities mentally, physically or both [145]. Kalkman et al. differentiated fatigue from muscle weakness and muscle fatigability [133]. Schipper et al. defined fatigue as "a subjective, unpleasant symptom which incorporates total body feeling ranging from tiredness to exhaustion, creating an unrelenting overall condition which interferes with an individual's ability to function to their normal capacity" [140]. In contrast, de Groot et al. referred to fatigue as a "physical complaint" [128], and Noto et al. defined fatigue as "activity-induced muscle weakness and fatigability" [138]. Fourteen studies did not offer a definition of fatigue [3,58,98,125–127,129,130,134,135,137,141,143,144].

The lack of a commonly accepted definition of fatigue has previously been highlighted as a challenge in studying fatigue [16]. Different definitions of fatigue may result in differences in the reported prevalence and impact of fatigue in neuromuscular disorders [9,17]. In a clinical setting, both physicians and patients often discuss fatigue without explicitly defining the term [16]. In practice, the definition of fatigue may overlap with sleepiness, depression, or muscle weakness [4,16]. Additionally, children with neuromuscular disorders may not spontaneously report fatigue as a symptom or have the

ability to clearly articulate the chief complaint [4,146]. Thus, the lack of a commonly accepted definition of fatigue in research may translate to under-diagnosis or treatment plans with unsatisfactory outcomes in clinical practice [4,9]. Furthermore, studies have defined fatigue using different terms, yet employed the same instruments to measure fatigue, calling into question the appropriateness and construct validity of these instruments [120,138].

2.5 The Burden of Fatigue in Muscular Dystrophies and Spinal Muscular Atrophy

Studies included in this literature review demonstrated that fatigue was prevalent, with far-reaching consequences on health-related quality of life (HRQOL) and patient functioning in patients with muscular dystrophies and SMA. Studies characterizing the burden of fatigue were limited to the patient populations of DMD, FSHD and SMA (Table 2.1).

2.5.1 *Duchenne Muscular Dystrophy*

In a Dutch cross-sectional study of adults with DMD (N=80), Pangalila et al. reported fatigue to be present in 40.5% (95% CI: 29.7, 51.3%) of patients, with 21.5% attributable to intermediate fatigue and 19.0% attributable to severe fatigue [120]. Fatigue was measured using the Dutch version of the Fatigue Severity Scale (FSS). The FSS is composed of nine items, each measured on a 7-point Likert scale from 1 (no signs of fatigue) to 7 (most disabling fatigue). The FSS score is the mean of all item scores. Intermediate fatigue was defined as a minimum score of 4 and severe fatigue was defined as a minimum score of 5 [120,147]. Severe fatigue was more frequent in adults with DMD (19.0%), compared to Dutch healthy controls from published data (5.0%) [120,148]. In adults with DMD, fatigue was concurrent with pain in 11.4% of patients, with affective

disorders (anxiety and depression) in 1.3% of patients, and with both pain and affective disorders in 22.8% of patients. Fatigue was more prevalent in adult DMD patients with poor quality of life (QOL) than in patients with good QOL. In multivariate logistic regression analysis, with dichotomized QOL (good/poor) outcomes, fatigue emerged as a determinant of overall QOL (OR=2.89; 95% CI: 1.71, 4.87; $P<0.001$), as well as QOL related to physical functioning (OR=6.77; 95% CI: 2.11, 21.75; $P=0.001$) and environment (OR=1.95; 95% CI: 1.16, 3.28; $P=0.01$), but not psychological functioning or social relationships [120].

In a prospective cohort study by our group of children with DMD (N=98), fatigue at baseline was significantly associated with worse overall, physical and psychosocial HRQOL at baseline, by child self-report and parent-proxy report [3]. Fatigue was measured using the Pediatric Quality of Life Inventory™ (PedsQL™) Multidimensional Fatigue Scale (MFS). The PedsQL™ MFS is an 18-item form composed of three domains: General Fatigue (six items), Sleep/Rest Fatigue (six items) and Cognitive Fatigue (six items) [117]. HRQOL was also assessed using the PedsQL™ measurement model with generic and disease-specific measures: Generic Core Scales, Neuromuscular Module and Duchenne Muscular Dystrophy Module [149,150]. Of the patient and family characteristics examined as independent variables in multivariable linear regression analysis, only fatigue was associated with all measures of HRQOL at baseline ($\beta=0.38$ to $\beta=0.88$; $P<0.001$ to $P=0.02$). Fatigue explained more of the variability in HRQOL than any other variable examined, as determined by backward elimination regression analysis. Other variables examined were age, wheelchair use, scoliosis, corticosteroid therapy, forced vital capacity, left ventricular ejection fraction, diagnosis with one or more neuropsychiatric disorder,

family stress, annual household income and parents' highest educational attainment [2,3]. Patients were then followed for 18 months and the longitudinal relationship between fatigue and HRQOL was examined in children with DMD (N=49). Change in fatigue was significantly correlated with change in HRQOL over 18 months, by child self-report and parent proxy-report (r=0.50 to r=0.81; P<0.001 to P=0.003) [144]. Because fatigue and HRQOL were both assessed using the PedsQL™ measurement model, it is possible that their association was an artifact due to common method variance—shared variance among variables attributable to the measurement model rather than the constructs the measures represent [151]. Common method variance can inflate or deflate observed relationships between predictor and criterion variables, resulting in both Type I and Type II errors, respectively [151,152].

In an Italian prospective cohort study, Messina et al. evaluated 12-month change in fatigue, also using the PedsQL™ MFS by child self-report and parent proxy-report, in ambulant children with DMD (N=98) [58]. At baseline and 12-months, children with DMD experienced greater fatigue than healthy controls from published data by child self-report and parent proxy-report [58,117,118]. No significant change in child self-reported fatigue was observed over 12 months, however parent proxy-reported fatigue significantly increased over 12 months (P=0.002) [58].

2.5.2 Other Muscular Dystrophies

Severe fatigue (Checklist Individual Strength Fatigue subscale score ≥35 [153]) was reported by 34–61% of adults with FSHD [57,142]. Adults with FSHD reported higher levels of current fatigue than healthy controls [139,142]. In a cross-sectional survey of FSHD patients, combined with myotonic dystrophy patients, fatigue was the most frequent

and severe symptom reported by patients, relative to imbalance, pain, memory loss and vision loss. Fatigue was most often reported to worsen or stay the same, rather than improve, since its onset and over the course of the past six months [141]. In adults with FSHD, fatigue has been reported to be associated with poor physical and psychological functioning, greater depressive symptoms and functional impairment [98,116,141]. Functional impairment was measured using the following subscales from the Sickness Impact Profile: body care and movement, home management, communication, work limitations, recreation and pastimes, and impairments with eating [116,154]. Despite a high prevalence of severe fatigue among FSHD patients, severe fatigue was not associated with employment status. Thus, fatigue can impair patient functioning, but is not related to participation in the workforce. However, types of occupations and number of hours worked have not been explored in this population [136]. In a qualitative study of fatigue in adults with FSHD using semi-structured interviews [140], respondents described fatigue as an overwhelming, unpredictable and capricious experience with physical and psychological components. The psychological component was described as a fear of becoming fatigued, which resulted in reluctance to participate in activities. Respondents indicated that fatigue negatively influenced activities of daily living, social participation and participation in work [140].

2.5.3 Spinal Muscular Atrophy

Data regarding the burden of fatigue in SMA are sparse, inconclusive and limited to cross-section studies. Patient populations varied across studies with respect to SMA phenotype, limiting comparability of findings [128,129,138,145]. In a study of SMA and spinal and bulbar muscular atrophy (SBMA) patients, adults with SMA (unspecified type)

or SMBA reported significantly greater fatigue than healthy controls [138]. In a study by de Groot et al., fatigue was significantly more prevalent in Type III SMA patients (61%) than in Types I and II SMA patients (34%). Moreover, fatigue was one of the most frequently reported physical complaints among Type III SMA patients, preceded only by muscle weakness and cold hands or feet [128]. In a study of adults with Type II SMA, severe fatigue was reported by only 10% of patients, corroborating the finding by de Groot et al. that fatigue may not be a common feature in Type II SMA [128,145]. Data regarding the burden of fatigue in children with SMA were limited to a published abstract [129]. Fatigue was assessed in children with Type II or III SMA using the PedsQL^{TM} MFS. Children with SMA reported greater fatigue than healthy controls from published data [117,118,129]. However, fatigue was not associated with quality of life or function in Type II or III SMA patients [129].

2.6 Factors Associated with Fatigue in Muscular Dystrophies and Spinal Muscular Atrophy

2.6.1 Duchenne Muscular Dystrophy

In the prospective cohort study conducted by our group, children with DMD using a wheelchair intermittently reported significantly greater fatigue than children not using a wheelchair, indicating that the transition into **wheelchair use** may be associated with fatigue. This association was not present by parent proxy-report [3]. Messina et al. assessed whether 12-month change in functional ability was associated with 12-month change in fatigue in ambulant children with DMD [58]. Functional ability was assessed using measures commonly used in therapeutic trials and clinical practice, including the six-minute walk test (6MWT), North Start Ambulatory Assessment (NSAA), 10-metre

walk/run test, and time to rise from the floor (Gowers' test) [155–157]. The NSAA is a 17-item scale that assesses abilities necessary to remain functionally ambulant in children with DMD [157]. Few associations between **functional ability** and fatigue were observed by Messina et al., suggesting that functional ability, a proxy for disease severity in DMD, may be weakly related to fatigue. At baseline, shorter 6MWT distance was weakly associated with greater fatigue, by child self-report (r=0.23; P=0.02) and parent proxy-report (r=0.27; P=0.006). Greater time to rise from the floor was weakly associated with greater fatigue, by child self-report (r=-0.21; P=0.04). Over 12 months, change in 10-metre walk test was weakly associated with change in fatigue, by child self-report (r=-0.22; P=0.03). Because a significant 12-month decline in functional ability was observed in children >7 years of age, a subgroup analysis was conducted for this age group. In children >7 years of age, 12-month change in 6MWT was weakly associated with change in fatigue, by child self-report (r=0.24; P=0.01) and parent proxy-report (r=0.25; P=0.03). NSAA and age were not associated with fatigue in ambulant children with DMD [58]. However, the correlation analyses using cross-sectional data by our group [3] and Messina et al. [58] do not allow for causal conclusions regarding the relationship of physical functioning with fatigue in children with DMD. No additional studies have explored factors associated with fatigue in children with DMD.

2.6.2 Other Muscular Dystrophies

Eight studies conducted in the Netherlands examined factors associated with fatigue in adults with FSHD [57,116,131–133,139,140,142]. All studies, except one [140], recruited patients from the Neuromuscular Centre at Radboud University Nijmegen Medical Centre and the Dutch Neuromuscular Diseases Association (Vereniging

Spierziekten Nederland). A common patient source across studies may limit the generalizability of findings [57,116,131–133,139,142]. Using a prospective cohort study design and structural equation modelling, Kalkman et al. aimed to identify predictors of fatigue and to develop a model of fatigue in adults with FSHD. Model testing revealed that **sleep disturbances**, **pain**, **physical activity level** and **muscle strength** were significantly associated with fatigue. Sleep disturbances, pain and physical activity level had a direct causal effect on fatigue, while muscle strength had an indirect effect on fatigue mediated by physical activity level [116]. The associations of pain and physical activity level (over-exertion or excessive rest) with fatigue reported by Kalkman et al. [116] corroborate previous findings [57,140,142]. However, van der Kooi et al. did not observe a difference in physical activity level between FSHD patients with and without severe fatigue [142]. Kalkman et al. did not observe an association between **neuropsychological functioning** (concentration, alertness, information-processing speed and motor speed) and fatigue [116]. However, it was previously reported that severely fatigued patients have more concentration problems and reduced motivation compared with less fatigued patients [57]. Data regarding the relationship between mental health and fatigue in FSHD are inconclusive. No difference in fatigue severity was observed between FSHD patients with and without current or lifetime **psychiatric disorders** evaluated using the Structured Clinical Interview for DSM-IV Axis I Disorders [131,158]. Self-reported mental health and depressive symptoms have been statistically analyzed as both determinants and outcomes of fatigue. Reports of significant associations of **mental health** and **depressive symptoms** with fatigue are inconsistent across studies [57,98,116,131,141,142]. Thus, the strength and directionality of associations of mental health and depressive symptoms with

fatigue in FSHD remain unclear. Similarly, **physical functioning** has been statistically analyzed as both a determinant and an outcome of fatigue in FSHD, and has consistently been reported to be associated with fatigue [57,98,142]. Kalkman et al. did not observe an association between **social functioning** or **social support** and fatigue [116]. However, a study assessing the influence of relatives on fatigue experienced by FSHD patients demonstrated that receiving higher levels of sympathetic or empathic support from relatives was associated with greater fatigue experienced by patients. Moreover, fatigue severity experienced by relatives was significantly associated with fatigue severity experienced by patients [132]. **Age** and **sex** were not associated with fatigue in FSHD [57,142]. In a qualitative study by Schipper et al. [140], **coping** and **stress** were identified as risk factors for fatigue in FSHD. Semi-structured interviews with adults with FSHD ultimately demonstrated that the source of fatigue may be a complex network of factors. However, patients are often unaware of the causes of fatigue, making it difficult to manage [140].

The relationship between physiological fatigue and subjective fatigue in FSHD has been examined by two studies [133,139]. Physiological fatigue—the inability to maintain the desired muscle force during sustained or repeated exercise—can originate at the level of the central nervous system (upper motor neuron) or peripheral nervous system (lower motor neuron, neuromuscular junction or muscle) [16]. Peripheral and central aspects of physiological fatigue are measured in a laboratory setting using electrophysiological protocols such as intermittent submaximal exercise protocol, sustained maximal force exercise protocol, twitch interpolation or transcranial magnetic stimulation [16,159]. Using a twitch interpolation technique [159], Schillings et al. [139] and Kalkman et al. [133]

demonstrated that total physiological fatigue, peripheral physiological fatigue, and central physiological fatigue were not correlated with subjective fatigue measures in adults with FSHD. This finding suggests that physiological and subjective fatigue are separate types of fatigue. The mechanisms and determinants of physiological and subjective fatigue may differ, requiring targeted interventions [133].

2.6.3 Spinal Muscular Atrophy

Two studies examined factors associated with fatigue in SMA and did not observe any significant associations [129,138]. Age, SMA phenotype, ambulatory status, disease duration and degree of disability were not associated with fatigue [129,138]. Physiological fatigue, determined by the decrement in distance from the first to sixth minute during the 6MWT [155], was not associated with subjective fatigue in ambulant Type II or II SMA patients [129]. Physiological fatigue, determined by activity-dependent conduction blocks during simulated-single fibre electromyography [160], was not associated with subjective fatigue in SMA (unspecified type) or SBMA patients [138].

2.7 The Management of Fatigue in Muscular Dystrophies and Spinal Muscular Atrophy

2.7.1 Duchenne muscular dystrophy

In a non-randomized trial, Alemdaroğlu et al. [125] aimed to assess the acute effects of various exercise protocols on fatigue in ambulant children with DMD (N=30). Patients were assigned to one of the following exercise protocols per session: (1) 3 minutes of 5-step stair-climbing, (2) 40 minutes of stationary cycling, or (3) a 40-minute physical therapy program of stretching the gastrocnemius, hamstring and hip flexor muscles, strengthening upper and lower extremities and aerobic activity. Fatigue was evaluated on

the same day following each exercise protocol using the Pictorial Variant of the Children's Effect Rating Scale Table scale—an illustrated visual analog scale of 0–10 with a present-state recall period [161]. Telephone-interviews were conducted the second day following exercise protocols to evaluate whether post-exercise fatigue affected patients' activities of daily living. A significant increase in fatigue was reported immediately following each exercise protocol compared to baseline, however post-exercise fatigue did not influence activities of daily living on the same day of exercise [125]. No studies have evaluated the effects of exercise therapy or other interventions on long-term fatigue in paediatric or adult DMD.

2.7.2 Other Muscular Dystrophies

The effects of exercise therapy, neuromuscular electrical stimulation therapy, pharmacological therapy with salbutamol, and cognitive behaviour therapy (CBT) on fatigue have been assessed in adults with FSHD or LGMD [126,127,134,142,143]. No significant changes in fatigue were observed following 8–26 weeks of exercise therapy consisting of strength training only in FSHD or LGMD patients [134,142]. However, a significant reduction in fatigue was observed following 16–24 weeks of aerobic exercise therapy alone or in combination with strength training [126,143]. A decrease in subjective fatigue, following combined aerobic and strength training, was associated with a decrease in physiological fatigue and an improvement in mental health [126]. Neuromuscular electrical stimulation therapy is a passive muscular training technique used to prevent muscular atrophy, which demonstrated safety and efficacy in stabilizing or improving muscular weakness in DMD patients [162–166]. Although no significant changes in fatigue were observed following neuromuscular electrical stimulation therapy in FSHD and

LGMD patients, an improvement in the impact of fatigue on activities of daily living was reported by FSHD patients [127,134]. The β_2-adrenergic receptor agonist salbutamol has previously been reported to increase muscle mass and strength in FSHD patients, however the anabolic effect diminished with prolonged use [167,168]. No significant changes in fatigue were observed following 26 weeks of therapy with salbutamol alone or in combination with strength training [142].

In contrast to therapies that target physical components of fatigue, CBT facilitates the identification of maladaptive thoughts, beliefs and attitudes. CBT challenges these cognitions through collaborative hypothesis-testing, using behavioural tasks of diary-keeping and validity-testing of beliefs between sessions, combined with the development of coping strategies within sessions [169]. Studies have demonstrated that CBT can reduce fatigue in patients with chronic fatigue syndrome and multiple sclerosis [169,170]. In an evaluator-blind RCT by Voet et al. [143], CBT significantly reduced fatigue severity in adults with FSHD compared to usual care. CBT and aerobic exercise therapy produced quantitatively similar beneficial effects on fatigue. However, CBT improved all fatigue-perpetuating factors, except pain, in the model described by Kalkman et al. [116], whereas physical activity level was the only fatigue-perpetuating factor modified by aerobic exercise therapy [143]

2.7.3 Spinal Muscular Atrophy

The effects of exercise therapy and pharmacological therapy with salbutamol on fatigue have been assessed in SMA. Following 12–24 weeks of aerobic exercise therapy (stationary cycling) alone or in combination with strength training, Type III SMA patients reported no change in fatigue or worsened fatigue [135,137]. In contrast, training-induced

fatigue was not observed in studies evaluating aerobic exercise therapy in muscular dystrophies [126,143], suggesting alternative underlying mechanisms of fatigue in muscular dystrophies and anterior horn cell disease, which may require disease-specific therapies [135].

SMA is caused by a deficit of survival motor neuron (SMN) protein encoded by the SMN1 and SMN2 genes. Patients have homozygous pathogenic variants of the SMN1 gene and retain at least one copy of the SMN2 gene. However, the SMN2 gene produces insufficient levels of functional protein due to the exclusion of exon 7 in most transcripts caused by alternative splicing [171]. Studies have demonstrated that treatment with the β_2-adrenergic receptor agonist salbutamol increase expression of full-length SMN2 transcripts, and may increase motor function in SMA patients [172–175]. Giovannetti et al. assessed the perceived effects of salbutamol on fatigue in adults with Type II, III or IV SMA. A significant reduction in fatigue was reported by patients following treatment with salbutamol [130].

2.8 Conclusions

This literature review highlights the need for additional studies to characterize the prevalence of and factors associated with fatigue in children and adolescents with DMD. Understanding the determinants of fatigue in paediatric DMD is necessary for the development of treatment strategies that produce positive clinical outcomes. This review demonstrated fatigue to be frequent and disabling in patients with DMD, FSHD and SMA, and likely caused by multiple, dynamic factors. Much of the data presented in this review focused on adults with slowly progressive forms of muscular dystrophies or mild phenotypes of SMA. The clinical presentations of FSHD, LGMD, and Type III and IV

SMA are uncharacteristic of DMD. Although findings presented in this literature review are hypothesis-generating for this thesis, they may be unrelated to phenomena in children or adults with DMD. Contrasting results across patient populations, with respect to determinants of and therapeutic interventions for fatigue, further underscore the role of disease-specific mechanisms of fatigue. Data regarding the management of fatigue in both children and adults with muscular dystrophies and SMA are largely insufficient. However, the assessment of therapeutic interventions to modify fatigue is ultimately dependent on understanding disease-specific mechanisms of fatigue in these patient populations. Prospective cohort studies with larger, representative sample sizes are needed to characterize fatigue in both paediatric and adult muscular dystrophies and SMA. However, an initial cross-sectional study of factors associated with fatigue in paediatric DMD can inform the design of future longitudinal studies.

Table 2.1. Studies on the frequency of and factors associated with fatigue in muscular dystrophies and spinal muscular atrophy

Author, Year, Country [publication]	Study Design (Follow-up)	Disease (Sample Size) Patient Source(s)	Age in Years Mean ± SD (Range)	Subjective Fatigue Assessment	Summary of Findings
Pangalila, 2015, Netherlands [120]	Cross-sectional study	DMD (80) Four Centres for Home Ventilation in the Netherlands; Dutch rehabilitation centres; Dutch patient organization for neuromuscular diseases	28.2 ± 6.3 (20–44)	FSS (recall-period not reported)	Fatigue present in 40.5% of adult DMD patients. Univariate logistic regression analysis demonstrated fatigue significantly associated with poor overall QOL and domains of physical health, psychological functioning and environment, but not social relationships. Multivariate logistic regression analysis demonstrated fatigue significantly associated with poor overall QOL and domains of physical health and environment.
Wei, 2015, Canada [144][a]	Prospective cohort study (18 months)	DMD (49) Canadian Neuromuscular Disease Registry	12.2 (5–19)	PedsQL™ MFS, patient- and parent proxy-report (4-week recall period)	Change in fatigue significantly correlated with changes in child self- and parent proxy-reported HRQOL over 18 months.
Wei, 2016, Canada [3]	Cross-sectional study	DMD (98) Canadian Neuromuscular Disease Registry	10.7 ± 3.7	PedsQL™ MFS, patient- and parent proxy-report (4-week recall period)	Multivariable linear regression analysis revealed fatigue significantly associated with child self- and parent proxy-reported overall, physical and psychosocial HRQOL. Fatigue explained more variability in HRQOL than any other patient or family characteristic.
Messina, 2016, Italy [58]	Prospective cohort study (12 months)	DMD (98) Ten tertiary neuromuscular centres in Italy	8.4 ± 2.29	PedsQL™ MFS, patient- and parent proxy-report	Included DMD patients were ambulant. Parent proxy-, but not child self-reported, fatigue significantly increased over 12 months. Baseline child self-reported fatigue significantly correlated with time to rise from floor and 6MWT. Baseline parent proxy-reported fatigue significantly correlated with 6MWT. 12-month change in patient-reported fatigue significantly correlated with change in 10-meter timed walk/run test. In children ≥7 years of age, 12-month change in child self- and parent proxy-reported fatigue significantly correlated with change in 6MWT.

Author, Year, Country [publication]	Study Design (Follow-up)	Disease (Sample Size) Patient Source(s)	Age in Years Mean ± SD (Range)	Subjective Fatigue Assessment	Summary of Findings
Kalkman, 2007, Netherlands [131]	Cross-sectional study	FSHD (65) Neuromuscular Centre, Radboud University Nijmegen Medical Centre; Dutch patient organization for neuromuscular diseases	43.1 ± 10.3	CIS-Fatigue (2-week recall period)	Current and lifetime psychiatric disorders not associated with fatigue.
Schillings, 2007, Netherlands [139]	Cross-Sectional study	FSHD (65) Neuromuscular Centre, Radboud University Nijmegen Medical Centre; Dutch patient organization for neuromuscular diseases	43.1 ± 10.3 (22.5–60.9)	SFQ (Present-state recall period)	Patients reported greater subjective fatigue than healthy controls. Total, peripheral and central physiological fatigue not correlated with subjective fatigue. FSHD patients experienced greater central activation failure than controls; central activation failure not significantly correlated with subjective fatigue.
Kalkman, 2007, Netherlands [116]	Prospective Cohort Study (18 months)	FSHD (60) Neuromuscular Centre, Radboud University Nijmegen Medical Centre; Dutch patient organization for neuromuscular diseases	44.3 ± 9.9	CIS-Fatigue (2-week recall period)	Physical activity, depressive symptoms, sleep disturbances, pain and muscle strength correlated with fatigue. Neuropsychological impairment, social functioning and social support not correlated with fatigue. Structural equation modelling demonstrated sleep disturbances at baseline had direct effect on fatigue at follow-up. Pain at baseline had direct effect on physical activity at baseline and fatigue at follow-up. Muscle strength at baseline had indirect effect on fatigue at follow-up via physical activity at baseline. Fatigue at follow-up has direct effect on functional impairment at follow-up.
Kalkman, 2008, Netherlands [133]	Cross-sectional study	FSHD (65) Neuromuscular Centre, Radboud University Nijmegen Medical Centre; Dutch patient organization for neuromuscular diseases	43.1 ± 10.3	CIS-Fatigue (2-week recall period)	Peripheral and central physiological fatigue did not correlate with subjective fatigue, suggesting that these are separate types of fatigue.
Minis, 2010, Netherlands [136]	Cross-sectional study	FSHD (138)	43.7 ± 10.1	CIS-Fatigue (2-week recall period)	Bivariate analysis demonstrated employed patients reported significantly less fatigue than unemployed patients.

Author, Year, Country [publication]	Study Design (Follow-up)	Disease (Sample Size) Patient Source(s)	Age in Years Mean ± SD (Range)	Subjective Fatigue Assessment	Summary of Findings
		Neuromuscular Centre, Radboud University Nijmegen Medical Centre; Dutch patient organization for neuromuscular diseases			However, multivariate regression analysis demonstrated fatigue not associated with employment status.
Alschuler, 2012, USA [98]	Cross-sectional study	FSHD (139) Previous study participants; Individuals responding to advertisements through Muscular Dystrophy Foundation, publications and clinics	53.6 ± 13.8 (22–89)	NRS of 0–10 with a 1-week recall period	Hierarchal linear regression analyses demonstrated greater fatigue significantly associated with poor physical functioning and greater depressive symptoms, independent of pain and age. Fatigue explained more variability in depressive symptoms than physical functioning.
Noto, 2013, Japan [138]	Cross-sectional study	SMA (5) SBMA (17) Chiba University Hospital	59 (37–75)	FSS (recall-period not reported)	SMA/SBMA patients reported significantly greater fatigue than healthy controls and other patient populations (multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy and axonal neuropathy), although differences not significant. Fatigue not correlated with age, disease duration, degree of disability or conduction blocks during stimulated-single fibre EMG.
Werlauff, 2014, Denmark [145]	Mixed methods cross-sectional study	SMA II (29) Danish National Rehabilitation Center for Neuromuscular Diseases	30.6 ± 10.5 (19–55)	FSS (2-week recall period)	Three patients (10%) patients reported severe fatigue, indicating fatigue may not be common in SMA II. Fatigue not associated with age or sex.
Dunaway, 2014, USA [129][a]	Cross-sectional study	SMA II (7); SMA III (25) -	(5–49)	PedsQL™ MFS; FSS (recall periods not reported)	All patients reported subjective fatigue. Fatigue not associated with age, SMA type, ambulatory status, function or QOL in all patients, or with physiological fatigue in ambulatory patients.
Smith, 2014, USA [141]	Cross-sectional study	FSHD (90) National Registry of DM and FSHD; University of Washington Muscular Dystrophy Association	51.9 ± 13.1 (21–90)[a]	NRS of 0–10 (severity); patients asked to indicate whether fatigue had become worse, become	Fatigue was the most common and severe symptom, relative to imbalance, pain, memory impairment and vison loss. Fatigue most often worsened or stayed the same since onset and during past 6 months. Bivariate analysis demonstrated fatigue significantly correlated with psychological

Author, Year, Country [publication]	Study Design (Follow-up)	Disease (Sample Size) Patient Source(s)	Age in Years Mean ± SD (Range)	Subjective Fatigue Assessment	Summary of Findings
		clinic roster; Previous study participants; Individuals independently contacting researchers		better or stayed the same since its onset, and during the past 6 months (symptom course)	functioning, social integration, home competency and productive activity. When controlling for other symptoms, age, sex and disease duration, multivariable linear regression analyses revealed fatigue only significantly associated with psychological functioning.[b]
Schipper, 2016, Netherlands [140]	Qualitative Cross-Sectional study	FSHD (25) Previous study participants; Computer Registry of All Myopathies and Polyneuropathies; patient support organizations	53.8 ± 12.4 (24–77)	Semi-structured interviews [Patients previously reported severe fatigue (CIS-Fatigue scores ≥35)]	Four themes identified: (1) fatigue is overwhelming and unpredictable with physical and mental component; (2) fatigue caused by combination of factors (weak muscles, physical overachieving or underachieving, stress). Causes unknown most of time, making fatigue difficult to deal with; (3) fatigue influences participation, social contacts and activities of daily of living; (4) managing fatigue requires adaption to changing situations of progressive disease, making it more difficult.

Abbreviations: DMD, Duchenne muscular dystrophy; QOL, quality of life; HRQOL, health-related quality of life; 6MWT, six-minute walk test; FSS, Fatigue Severity Scale; PedsQL™ MFS, Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale; FSHD, facioscapulohumeral dystrophy; CIS-Fatigue, Checklist Individual Strength Fatigue subscale; SFQ, Shortened Fatigue Questionnaire; NRS, numerical rating scale; SMA, spinal muscular atrophy; SBMA, spinal and bulbar muscular atrophy; VAS, visual analog scale.

[a]Meeting abstract
[b]Statistical analysis combined FSHD and myotonic dystrophy type 1 patients, however dystrophy type did not moderate associations between fatigue and criterion variables.

Table 2.2. Studies on the management of fatigue in muscular dystrophies and spinal muscular atrophy

Author, Year, Country [publication]	Study Design (Follow-up)	Intervention(s)	Disease (Sample Size) Patient Source(s)	Age in Years Mean ± SD (Range)	Subjective Fatigue Assessment	Summary of Findings
Alemdaroğlu, 2012, Turkey [125]	Open-label, non-randomized trial (1 day)	3-minute stair climbing; 40-minute cycling; 40-minute stretching-strengthening with aerobic exercises for extremities	DMD (30) Physical Therapy Department, Hacettepe University	7.87 ± 1.45 (6–11)	Pictorial Variant of the Children's Effort Rating Scale (VAS of 0–10; present state recall period)	Significant increase in fatigue observed immediately following exercise compared to baseline. Post-exercise fatigue did not affect performance of daily activities on same day of exercise.
van der Kooi, 2007, Netherlands [142]	Evaluator-blind RCT of training/non-training, followed by double-blind RCT of salbutamol/placebo (52 weeks)	Strength training of elbow flexors and ankle dorsiflexes or non-training (26 weeks), followed by salbutamol (sustained-release 8 mg BID) or placebo (26 weeks)	FSHD (65) Neuromuscular Centre, Radboud University Nijmegen Medical Centre; Dutch patient organization for neuromuscular diseases	38 ± 10	CIS-Fatigue (2-week recall period)	Twenty-two patients (34%) had severe fatigue at baseline. Patients reported greater fatigue compared to healthy controls from published data. Severely fatigued patients experienced significantly more pain, functional disability, psychological distress and depressive feelings. Age, sex and self-reported daily activity not associated with severe fatigue. Strength training and salbutamol, alone or in combination, did not affect fatigue.
Colson, 2010, France [127]	Single-arm trial (5 months)	5-month strength training with neuromuscular electrical stimulation (5 20-minute sessions weekly)	FSHD (9) Neuromuscular Disease Centre of Nice, France	55.2 (39–69)	VAS of 0–10 (present state recall period); Patients rated changes in fatigue related to daily living as worse, unchanged or improved at the end of the study period	No significant change in fatigue observed following training with electrical stimulation. Seven patients (78%) reported improved fatigue related to daily living.

Author, Year, Country [publication]	Study Design (Follow-up)	Intervention(s)	Disease (Sample Size) Patient Source(s)	Age in Years Mean ± SD (Range)	Subjective Fatigue Assessment	Summary of Findings
Voet, 2014, Netherlands [143]	Evaluator-blind RCT (28 weeks)	Aerobic exercise training (38-minute cycling 3 times weekly for 16 weeks); CBT (minimum 3 50-minute sessions over 16 weeks); usual care	FSHD I (57) Previous study participants; Dutch neuromuscular database, Computer Registry of All Myopathies and Polyneuropathies; patient support organizations	(20–79)	CIS-Fatigue (2-week recall period)	All patients severely fatigued. Fatigue significantly reduced following 16 weeks of aerobic exercise or CBT compared to usual care. Beneficial effects remained at 12-week follow-up without supervised treatment. Post-treatment, 76% in CBT group and 50% in the aerobic exercise group no longer severely fatigued. Aerobic exercise and CBT produced similar effects on fatigue, despite fewer CBT sessions.
Madsen, 2015, Denmark [135]	Single-arm trial (12 weeks)	Home-based aerobic exercise training (30-minute cycling 2–4 times weekly, totaling 42 sessions)	SMA III (6) -	32.5 ± 16.49	Patients rated changes in fatigue as worse, unchanged or improved at the end of the study period	All patients reported worsened or no change in fatigue following training. One patient dropped out due to excessive fatigue.
Montes, 2015, USA [137]	Evaluator-blind RCT (6 months)	Home-based exercise training (30-minute cycling 5 times weekly, 30-minute strength training 3 times weekly); usual care (control)	SMA III (12) SMA Clinical Research Center, Columbia University Medical Center; Pediatric Neuromuscular Clinical Research Network; ClinicalTrials.gov	27.0 ± 14.6 (10–43; exercise); 26.7 ± 17.7 (10–48; control)	PedsQL™ MFS; FSS (recall periods not reported)	No significant changes in fatigue, between or within, the exercise and control groups were observed.
Kilinç, 2015, Turkey [134]	Open-label, non-randomized trial (8 weeks)	Electrical stimulation (high voltage pulsed galvanic stimulation 3 days weekly); exercise therapy (moderate intensity progressive	LGMD (24) Physical Therapy Department, Hacettepe University	31.62 ± 16.92 (electrical stimulation); 30.14 ± 11.04 (exercise therapy)	VAS of 0–10 (present state recall period)	Fatigue did not increase after electrical stimulation applications or exercise therapy.

Author, Year, Country [publication]	Study Design (Follow-up)	Intervention(s)	Disease (Sample Size) Patient Source(s)	Age in Years Mean ± SD (Range)	Subjective Fatigue Assessment	Summary of Findings
		resistance exercises 3 days weekly)				
Bankolé, 2016, France [126]	Open-label RCT (24 weeks), followed by single-arm trial for patients initially assigned to control group (24 weeks)	Home-based exercise training (35-minute cycling 3 times weekly); usual care (control)	FSHD (16) Centre Hospitalier Universitaire de Saint-Etienne; entre Hospitalier Universitaire de Grenoble	40 ± 13 (training); 41 ± 9 (control)	FSS (recall period not reported)	Subjective Fatigue significantly decreased over 24-weeks in patients in exercise group compared to controls. Decreased subjective fatigue significantly correlated with decreased physiological fatigue (increases in VO_2 max, MAP, MVC, muscle endurance and 6MWT) and improved mental health.
Giovannetti, 2016, Italy [130]	Mixed methods; Prospective cohort study (1 year)	Salbutamol	SMA II (1) SMA III (6) SMA IV (3) -	41.3 ± 11.2	FSS (recall period not reported); Semi-structured interviews	Patients treated with salbutamol for 30 ± 20.2 months before study. At initial evaluation, patients reported significantly less fatigue after salbutamol treatment. One year after initial evaluation, patients reported stability of fatigue, not improvement.

Abbreviations: DMD, Duchenne muscular dystrophy; VAS, visual analog scale; RCT, randomized controlled trial; FSHD, facioscapulohumeral dystrophy; CIS-Fatigue, Checklist Individual Strength Fatigue subscale; CBT, cognitive behavioural therapy; SMA, spinal muscular atrophy; PedsQL™ MFS, Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale; LGMD, limb girdle muscular dystrophies; VO_2 max, maximal oxygen consumption; MAP, maximal aerobic power; MVC, isometric maximal voluntary contractions; 6MWT, six-minute walk test; FSS, Fatigue Severity Scale.

Chapter 3

3 Methods

3.1 Study Design

The study described in this thesis is a cross-sectional survey study of children and adolescents with Duchenne muscular dystrophy (DMD) identified via the Canadian Neuromuscular Disease Registry (CNDR). Eligible patients, and their parent or primary caregiver, were sent paper questionnaires by mail between July 2016 and November 2016. Approval of the study was obtained from the Health Sciences Research Ethics Board at The University of Western Ontario (Western University) and the CNDR Advisory Committee. Approval Notices from the Health Sciences Research Ethics Board at Western University are presented in Appendix C.

3.2 Study Population

3.2.1 Patient Source

Eligible patients were recruited through the CNDR. The CNDR is a multicentre clinic-based registry that was established in June 2011 to facilitate national and international research opportunities between researchers and patients, and clinical knowledge translation to allow for uniform standards of care across Canada. Paediatric and adult patients with any neuromuscular disorder who are residents in Canada are eligible for enrollment in the CNDR. The CNDR is administered and supported centrally at the National Office at the University of Calgary in Alberta, Canada. The CNDR employs a blended recruitment model in which patients are actively recruited at participating neuromuscular clinics in combination with self-registration by contacting the CNDR National Office for patients unable to attend affiliated neuromuscular clinics. Any

physician in Canada can refer a patient to the CNDR for enrollment, by completing registration forms available via the National Office or guiding patients to self-register. This recruitment model provides access to patients across Canada, including those in remote regions with limited access to specialized neuromuscular care. The CNDR includes patients recruited from nine paediatric neuromuscular clinics across Canada located in British Columbia, Alberta, Ontario, Quebec and Nova Scotia. Clinics enroll patients and collect medical and demographic information at routine clinic visits. Each neuromuscular clinic is affiliated with an academic institution and has a site principal investigator (Table D.1, Appendix D). All patients provide voluntary, informed consent for enrollment, updating of demographic and medical information at future routine clinic visits, and notification of research studies for which they may be eligible. Patients who are minors can be registered by a parent or legal guardian, and are asked to provide assent when possible. Upon reaching the age of majority in their province of residence, patients are asked for their consent to remain in the registry [176].

3.2.2 Patient Inclusion and Exclusion Criteria

Patients were identified by the CNDR National Office staff for inclusion in the study reported here according to the following inclusion and exclusion criteria:

<u>Inclusion Criteria</u>

1. Patients are enrolled in the CNDR. To be enrolled in the CNDR, subjects must:
    a. Consent to have clinical information submitted by a physician licensed and practicing in Canada.
    b. Be residents in Canada.

2. Patients have consented, or a parent or legal guardian has consented on their behalf, to be notified by the CNDR of research studies they may be eligible to participate in.
3. Patients with a diagnosis of DMD confirmed by genetic testing or a muscle biopsy demonstrating an absence of dystrophin protein, and a physician confirmed clinical presentation consistent with DMD.
4. Patients are males.
5. Patients are between 5–17 years of age.
6. Patients have a parent available to complete a parent questionnaire.

Exclusion Criteria

1. Both patient and parent are unable to adhere to the study protocol (e.g. inability to complete questionnaires, even with assistance, due to limited literacy, a communication disorder or cognitive impairment).
2. Patient has a serious health condition or comorbidity unrelated to DMD, which may influence study outcomes.

3.3 Data Collection Procedures

Data were collected using two sources: mailed paper questionnaires and registry data collected during patients' routine clinic visits. All data were de-identified. In accordance with the CNDR protocol, all contacts with eligible patients were facilitated through the CNDR National Office. No direct contacts were made with eligible patients or their parents by research personnel to avoid unintended identification of patients or their parents.

3.3.1 Mailed Questionnaires

Paper questionnaires were designed and mailed to eligible patients and their parent in accordance with the Tailored Design Method, which was formulated using social exchange theory as a rationale. Applied to questionnaire design and implementation, social exchange theory assumes that the probability of responding to a questionnaire, and doing so accurately, is greater when the respondent trusts that the perceived benefits outweigh the perceived costs of responding [177]. In accordance with the Tailored Design Method, a four-contact mailing strategy was used to maximize response rate. The four-contact mailing strategy was executed between July 2016 and November 2016. Eligible patient-parent pairs received (1) an initial questionnaire package, (2) a thank-you postcard one week after the initial invitation (Appendix G), (3) a follow-up reminder letter (Appendix H) with a replacement questionnaire package four weeks after the postcard, and (4) a final reminder letter with replacement questionnaire package four weeks after the follow-up reminder. Each questionnaire package included a letter of information (Appendix E), assent letter (Appendix F), a postage-paid return envelope to minimize the cost of responding, and two questionnaire booklets: one to be completed by the patient and one to be completed by a parent. Three sets of questionnaires were designed using age-appropriate language and instructions according to the following age groups: young children (5–7 years), older children (8–12 years) and adolescents (13–17 years). Children and parents were instructed to complete their respective questionnaires independently. If a patient was unable to independently complete his questionnaire, the parent was instructed to read the questions to the patient verbatim without providing interpretation, and to indicate the patient's answers in the questionnaire without providing guidance on how to respond. Parents of

young children were instructed to act as interviewers for their child. A Tim Hortons gift card valued at $5 CAD was included in the initial questionnaire package as a token of appreciation for patient-parent pairs. Implied consent was assumed for patients and parents who completed and returned questionnaires.

Questionnaire packages and thank-you postcards were compiled at Children's Hospital, London Health Sciences Centre in London, Ontario and forwarded to the CNDR National Office. Unique identification numbers were generated for eligible patient-parent pairs and used to label questionnaires by the CNDR National Office staff. Envelopes of questionnaire packages and thank-you postcards were labeled with patient mailing addresses and shipped to eligible patient-parent pairs by the CNDR National Office staff. Completed questionnaires were initially returned by patient-parent pairs to the CNDR National Office, and were then forwarded to Children's Hospital, London Health Sciences Centre by the CNDR National Office staff. If a questionnaire package was returned to sender, an effort was made by the CNDR National Office staff to contact the patient's clinic to verify or obtain an updated mailing address for the patient.

3.3.2 Registry Data

Patient medical histories were retrieved from the CNDR database. Patient data included in the CNDR database are collected prospectively at routine clinic visits through standardized data collection forms completed by the physician or data-entry staff reviewing patient medical records, followed by direct entry into the registry via a secure online entry system. Patients without access to a participating neuromuscular clinic are required to sign consent, assent and release of information forms to have their data submitted by their healthcare provider. All data entry personnel are trained by the CNDR National Office

staff. All data are encrypted and stored at the University of Calgary, and subject to regulations for the protection of personal health information. Data entry is reviewed weekly at the CNDR National Office to ensure data standard compliance; detected errors are logged and reported to the site data-entry personnel for correction. Local data collection forms are maintained as source documents and reviewed during annual audit visits by the CNDR National Office staff. Participating individuals may withdraw their data from the CNDR at any time [176].

Following data submission, patient-identifying information is separated from medical information for de-identification. A unique identifier code is assigned and is the only link between the two sets of information. The code is stored on a separate secure server and accessible only by the site principal investigator and CNDR National Office staff. A dataset of de-identified medical information, described below, was obtained for participating patients who completed and returned questionnaires and non-participating patients who did not complete and return questionnaires allowing for the assessment of whether clinical characteristics of non-participating patients differed from participating patients [176].

3.4 Data Management

All completed questionnaires were securely stored at Children's Hospital, London Health Sciences Centre, where data were also cleaned and coded by the author using Stata® 13.0 Data Analysis and Statistical Software. Data from patient and parent questionnaires were merged with registry data into a single Stata® 13.0 file in preparation for analysis [178].

3.5 Measures

Several measures for fatigue, physical activity level and depressive symptoms were reviewed during selection of measures to be included in the patient and parent questionnaires. Measures were selected based on validity, reliability and previous administration in children and adolescents with DMD, neuromuscular disorders or physical disabilities; appropriateness of measures for DMD patients according to clinical expertise; factors associated with ease of administration and low participation burden, such as length and use of developmentally appropriate language; and suitability for use in a mail-out questionnaire and completion in an unsupervised setting.

3.5.1 Fatigue

Fatigue was measured using the Pediatric Quality of Life Inventory (PedsQL^{TM}) Multidimensional Fatigue Scale (MFS) [179]. The PedsQL^{TM} Measurement Model was developed to integrate generic and disease-specific modules to measure paediatric health-related quality of life (HRQOL). The generic module enables comparison of HRQOL across patient and healthy populations, while disease-specific modules enhance sensitivity for detecting and quantifying minimal clinically important differences [180,181]. The PedsQL^{TM} MFS was designed as a generic module to measure patient and parent perceptions of fatigue in paediatric patients [179]. The PedsQL^{TM} MFS was developed and validated in paediatric oncology patients, and has since been validated in paediatric hematology, rheumatology and endocrinology patients [117,118,179,182,183]. In addition, the PedsQL^{TM} MFS has been administered to paediatric nephrology, psychiatry and neurology patients, including children and adolescents with DMD [3,14,58]. A recently

published systematic review of instruments to assess fatigue in paediatric chronic health conditions identified the PedsQL™ MFS as the most commonly used instrument [14].

The PedsQL™ MFS is available in child self-report formats for ages 5–17 and parent proxy-report formats for ages 2–18 years. Parent proxy-report forms are parallel to child self-report forms, and designed to assess parents' perceptions of their child's fatigue. In this study, child self-report and parent proxy-report forms for ages 5–7 years (young children), 8–12 years (older children) and 13–18 years (adolescents) were used. Items for each form are essentially identical, differing only in developmentally appropriate language for each age group, and first or third person as appropriate for child self-report and parent proxy-report forms [117,118,179].

The PedsQL™ MFS is an 18-item form composed of three domains: General Fatigue (six items), Sleep/Rest Fatigue (six items) and Cognitive Fatigue (six items). Items include statements such as "I feel too tired to do things that I like to do" (General Fatigue), "I feel tired when I wake up in the morning" (Sleep/Rest Fatigue) and "It is hard for me to keep my attention on things" (Cognitive Fatigue). The instructions ask the respondent to indicate how much of a problem each item has been in the past one month (Standard Version) or seven days (Acute Version). The PedsQL™ MFS Standard Version (one-month recall period) was used in the current study. A 5-point Likert scale is utilized across child self-report forms for ages 8–18 years and parent proxy-report forms (0=never, 1=almost never, 2=sometimes, 3=often, and 4=almost always). To increase ease for young children of ages 5–7 years, response options are simplified to a 3-point Likert scale (0=not at all, 2=sometimes, and 4=a lot) anchored to a faces scale (0=happy face, 2=neutral face, and 4=sad face). Items are reverse scored and linearly transformed to a scale of 0–100

(0=100, 1=75, 2=50, 3=25, and 4=0), such that higher scores indicate fewer problems or symptoms. Scores by domain are computed as the sum of items divided by the number of items answered within the domain. In accordance with scoring instructions, if more than 50% of items in a domain is missing, the domain score was not computed. A total score is computed as the sum of all items divided by the number of items answered on all domains. For a total score to be computed, completion of 50% or more items is required [117,118,179]. The PedsQL^{TM} MFS child self-report and parent proxy-report forms are presented in Appendices I and J, respectively.

3.5.2 Physical Activity Level

Physical activity measures may be broadly classified as objective or subjective. Objective measures aim to quantify physiological and biomechanical parameters, and estimate physical activity outcomes using methods such as accelerometry, pedometry or heart rate monitoring. Subjective measures include survey measures, interviews and activity diaries or logs [184,185]. A child self-report measure was used in the current study because of low cost, ease of administration and low participation burden.

The Physical Activity Questionnaire for Children (PAQ-C) and Physical Activity Questionnaire for Adolescents (PAQ-A) were used to measure physical activity level (Appendix K) [186]. Reliability and validity have been reported as acceptable to good in Canadian children and adolescents [187–189]. The PAQ-A has been previously administered to adolescents with physical disability secondary to a neurologic disorder—cerebral palsy [190]. The PAQ-C and PAQ-A measure physical activity level during the past seven days [186]. The PAQ-C was designed for use in children in grades 4–8 (approximately 8–14 years of age) and the PAQ-A was designed for adolescents in grades

9–12 (approximately 14–19 years of age). Questions in the PAQ-C were deemed applicable for young children (5–7 years of age) in our study based on clinical paediatric expertise. The PAQ-C was included in the patient questionnaire for young children and older children, and the PAQ-A was included in the patient questionnaire for adolescents.

The PAQ-C is composed of nine items scored on a 5-point Likert scale. The first item asks respondents to rate the frequency of participation in 22 common leisure and sport activities and two "other" fill-in choices during the past seven days. This item is scored as a mean of all activities. The remaining items ask respondents to rate their physical activity level according to time-of-day or day-of-the-week. The PAQ-C summary score is the mean of all nine items, with a score of 1 indicating low physical activity and score of 5 indicating high physical activity. In the case of missing items, a summary score was not computed in accordance with scoring instructions. The PAQ-A is composed of eight items and is identical to the PAQ-C, except that the PAQ-A does not include an item concerning physical activity during recess at school [186].

To improve applicability to DMD patients at all stages of the disease, modifications were made to the PAQ-C and PAQ-A with permission from the developers. Items 3 and 4 in the original PAQ-C, and item 3 in the original PAQ-A provide the following response options for rating physical activity during recess or lunch at school: 1=sat down (talking, reading, doing school work), 2=stood around or walked around, 3=ran or played a little bit, 4=ran around and played quite a bit, and 5=ran and played hard most of the time. To accommodate non-ambulatory children and adolescents, option 4 was modified to "ran around *or* played quite a bit" and option 5 was modified to "ran *or* played hard most of the time". The mobility and strength of DMD patients may be limited, preventing participation

in physical activity to the same extent as their healthy peers. Therefore, respondents were instructed to consider any activity that causes them to sweat, breathe hard, or causes their legs or arms to feel tired.

3.5.3 Functional Ability

Functional ability was assessed using the DMD Functional Ability Self-Assessment Tool (DMDSAT; Appendix L), a patient- or parent-reported survey measure designed and validated for assessing physical and respiratory functioning at all stages of disease progression in patients with DMD. The DMDSAT is fit for measuring functional ability from the early ambulatory to late non-ambulatory stage. The DMDSAT is composed of eight items in four domains: arm function (one item), mobility (one item), transfers (five items) and ventilatory support (one item). Each item asks respondents to rate their current level of functioning related to common activities of daily living, upper and lower extremities, or ventilation status. Item 1 is scored from 0–6, item 2 is scored from 0–5, and items 3–8 are scored from 0–2. Higher scores indicating higher functional ability. A total score is computed as the sum of all items, ranging from 0 (low functional ability) to 23 (high functional ability) [191]. In the case of missing items, a total score was computed by dividing the sum of completed items by the maximum possible score of completed items, and multiplying this fraction by the maximum possible score of all items, as advised by the developer (Landfeldt, E., Personal Communication, May 2nd 2017). The DMDSAT was included in the parent questionnaire; parents were instructed to complete the measure with their child.

3.5.4 Depressive Symptoms

Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale for Children (CES-DC; Appendix M)—a modified version of the Center for Epidemiological Studies Depression Scale [192,193]. The CES-DC is a 20-item scale comprising six symptom domains: depressive mood, feelings of guilt or worthlessness, sense of helplessness or hopelessness, psychomotor retardation, loss of appetite and sleep disturbance. Respondents are asked to indicate how strongly they experienced certain feelings during the past week, using a 4-point Likert scale. Negatively phrased items are scored as: 0=not at all, 1=a little, 2=some, and 3=a lot. Positively phrased items are reverse scored as: 3=not at all, 2=a little, 1=some, and 0=a lot. A total score is computed as the sum of all items and ranges from 0–60, with higher scores indicating greater depressive symptoms [192,193]. In the case of missing items, a total score was computed after imputing the mean of completed items as the response for missing items, as advised by the developers (Fendrich, M. and Weissman, M., Personal Communication, April 27th, 2017). The CES-DC has been validated for youth of ages 6–23 years, and is widely implemented in research and clinical settings as a screening tool for depression [194]. Questions in the CES-DC were deemed applicable for 5-year-old children with DMD included in our study based on clinical paediatric expertise. The CES-DC has been previously used in children and adolescents with physical disability secondary to a neurologic disorder—multiple sclerosis [195]. The CESD-DC was included in the patient questionnaire. A child self-report, rather than a parent proxy-report, measure of depressive symptoms was selected because previous studies have demonstrated poor to moderate agreement between child self-reported and parent proxy-reported internalizing problems, such as depressive

symptoms [196–198]. Child self-reports of depressive symptoms are often more consistent with formal psychiatric diagnoses of depression than parent proxy-reports [199,200].

3.5.5 Sleep Disturbance Symptoms

Sleep disturbance symptoms were assessed using the Sleep Disturbance Scale for Children (SDSC; Appendix N). The SDSC is a 26-item parent proxy-report measure encompassing six domains: disorders of initiating and maintaining sleep (seven items), sleep-related breathing disorders (three items), disorders of arousal (three items), sleep-wake transition disorders (six items), disorders of excessive somnolence (five items), and sleep hyperhidrosis (two items). In answering questions, respondents are asked to consider their child's sleep behaviour during the past six months. Using a 5-point Likert scale, respondents indicate how frequently certain behaviours are exhibited by their child: 1=never, 2=occasionally (once or twice per month or less), 3=sometimes (once or twice per week), 4=often (3 or 5 times per week), and 5=always (daily). Respondents are also asked to provide estimates of sleep quantity and sleep onset latency. Domain scores are computed as the sum of items within each domain. A total score is computed as the sum of domain scores, and ranges from 26–130. Higher scores indicate greater sleep disturbance symptoms. In the case of missing items, the domain score and total score were not computed as advised by the developer (Bruni, O., Personal Communication, April 27th, 2017). The SDSC was designed for use in research and clinical settings, and has been validated in healthy and patient populations of ages 6–15 years [201]. The SDSC has previously been used in children and adolescents with DMD of ages 4–18 years [72]. The SDSC was included in the parent questionnaire.

3.5.6 Patient Medical Information

Patient medical histories were retrieved from the CNDR for both participating and non-participating patients. The patient's age (years) as of June 13th, 2016 was obtained from the CNDR. Musculoskeletal characteristics retrieved from the CNDR included: unsupported ambulatory status (ambulant, non-ambulant), unsupported sitting ability status (yes, no), wheelchair use (never, intermittent or permanent), scoliosis status (none, surgically corrected, or uncorrected), corticosteroid therapy status (never, past, or current), and corticosteroid type (deflazacort or prednisone). Respiratory characteristics retrieved from the CNDR included: forced vital capacity (%), non-invasive ventilatory status (never, part-time, or full-time) and invasive ventilatory status (never, part-time, or full-time). Cardiac characteristics retrieved from the CNDR included: left ventricular ejection fraction (%), cardiomyopathy status (yes, no) and use of cardiac medications (yes, no).

In addition to patient medical histories retrieved from the CNDR, a patient medical information section was included in the parent questionnaire (Appendix O). The patient medical information questionnaire was adapted from the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES), with permission from the principal investigator [202]. Parents reported the presence of serious health conditions or co-morbidities unrelated to DMD, such as cystic fibrosis, diabetes, cerebral palsy, epilepsy and cancer. Parents reported whether their child had been formally diagnosed with any of the following neuropsychiatric disorders: developmental delay, learning disability, attention deficit disorder, attention hyperactivity deficit disorder, autism spectrum disorder, oppositional defiant disorder, conduct disorder, depression and anxiety. To evaluate the relationship between neuropsychiatric disorders and fatigue, a single binary variable was

used: diagnosis with one or more neuropsychiatric disorder. Parents reported whether their child has ever needed and ever received: pharmacological or psychotherapy for behavioural or emotional problems, speech language therapy, occupational therapy, and special education. Lastly, parents reported their child's ambulatory status (ambulant, non-ambulant) and if applicable, time since loss of ambulation (less than one year ago, or one year ago or more). Parent-reported non-invasive ventilatory status was also extracted from DMDSAT. Where possible medical information of participating patients retrieved from the CNDR was cross-referenced with parent-report medical information (ambulatory status and non-invasive ventilatory status). In the case of discrepancies between registry and parent-reported medical information, the most recently dated information available was used, which was parent-reported information in all cases. Discrepant information was reviewed by a paediatric neurologist to ensure the most recently dated information was reflective of the progressive functional decline of the disease and interpreted in the context of other clinical characteristics.

3.5.7 Sociodemographic Information

A sociodemographic information section was included in the parent questionnaire (Appendix P). Parents reported their age, sex, relationship to the patient, highest educational attainment, employment status and marital status. If applicable, parents reported the highest educational attainment and employment status of their spouse or partner. Lastly, household size and annual household income before taxes (CAD) were collected by parent-report.

3.6 Statistical Analyses

All statistical analysis was performed using Stata® 13.0 [178]. A two-sided level of significance at α=0.05 was assumed.

3.6.1 Sample Characteristics

Descriptive statistics were computed for patient medical information and sociodemographic information. Mean ± standard deviation or median (interquartile range), minimum and maximum were computed for continuous variables. Frequencies and percentages were computed for categorical variables. To assess differences between participating and non-participating patients, unpaired two-sample *t*-tests were used for continuous variables, and χ^2 tests of independence or Fisher's exact tests were used for categorical variables. Fisher's exact tests were used in place of χ^2 tests of independence when an expected frequency in a response category was less than 5.

3.6.2 Objective 1: To describe subjective fatigue in children and adolescents with DMD from patients' and parents' perspectives.

Distributions of child self-report and parent proxy-report PedsQL^{TM} MFS scores were assessed using graphical methods (normal quantile-quantile plots, box-and-whisker plots and histograms) and statistical methods (Shapiro-Wilk test of normality). Descriptive statistics were computed for child self-report and parent proxy-report PedsQL^{TM} MFS scores for the total sample and for subgroups according to age (young children, 5–7 years; older children, 8–12 years; and adolescents, 13–17 years) and ambulatory status (ambulant and non-ambulant). Mean ± standard deviation, median (interquartile range), minimum and maximum were computed for total fatigue, general fatigue, sleep/rest fatigue and cognitive fatigue scores. PedsQL^{TM} MFS scores of DMD patients in the current study were compared

with PedsQL^{TM} MFS scores of healthy children and adolescents from published data [117,118]. Agreement between child self-reports and parent proxy-reports of PedsQL^{TM} MFS scores were examined using pairwise correlation analyses with Pearson's correlation coefficient (r), or Spearman's rank correlation coefficient (ρ) if non-normality of data was observed.

3.6.3 Objective 2: To explore associations of patient characteristics with child self-report and parent proxy-report measures of subjective fatigue in children and adolescents with DMD.

Bivariate analyses were conducted to explore associations of patient characteristics with child self-reported and parent proxy-reported fatigue. For dichotomous variables (ambulatory status, time since loss of ambulation, current glucocorticoid use, cardiomyopathy, diagnoses with one or more neuropsychiatric disorder), unpaired two-sample *t*-tests or non-parametric Wilcoxin Rank Sum tests were used to assess differences in PedsQL^{TM} MFS scores between categories. Wilcoxin Rank Sum tests were used in place of unpaired two-sample *t*-tests when $n<30$ in one or more category or normality of the PedsQL^{TM} MFS score was violated. For categorical variables of more than two categories (age group, wheelchair use, scoliosis and non-invasive ventilatory status), one-way analysis of variance (ANOVA) or non-parametric Kruskal-Wallis tests were used to assess differences in PedsQL^{TM} MFS scores between categories. Kruskal-Wallis tests were used in place of one-way ANOVA when $n<30$ in one or more category or normality of the PedsQL^{TM} MFS score was violated.

Distributions of continuous variables were assessed using graphical methods (normal quantile-quantile plots, box-and-whisker plots and histograms) and statistical

methods (Shapiro-Wilk test of normality). Relationships of continuous variables (age, physical activity level, functional ability, depressive symptoms, sleep disturbance symptoms, forced vital capacity and left ventricular ejection fraction) with PedsQL^{TM} MFS scores were visually inspected using scatter plots. Associations of continuous variables with PedsQL^{TM} MFS scores were examined using pairwise correlation analyses with Pearson's correlation coefficient (r), or Spearman's rank correlation coefficient (ρ) if non-normality of the data was observed.

Multivariable linear regression analyses were used to further explore the association between total sleep disturbance symptoms with child self-reported and parent proxy-reported fatigue, while adjusting for additional patient characteristics. Given the exploratory nature of this thesis, bivariate analyses and clinical expertise were used to guide selection of patient characteristics to be adjusted for in the linear regression analyses, as described in Chapter 4 (Results). Linear regression analyses were initially performed with complete case analysis (listwise deletion), followed by linear regression analyses with multiple imputation using chained equations as a sensitivity analysis for examining the impact of missing data. Normally distributed continuous variables were imputed using linear regression. Non-normally distributed continuous variables were imputed using predictive mean matching [203,204].

Chapter 4

4 Results

4.1 Sample Characteristics

A total of 193 eligible participants, composed of 26 young children (13.5%; ages 5–7 years), 75 older children (38.9%; ages 8–12 years) and 92 adolescents (47.7%; ages 13–17 years), were identified through the Canadian Neuromuscular Disease Registry (CNDR) and received mailed paper questionnaires. An overall response rate of 36.8% was achieved, with N=71 eligible patient-parent pairs returning completed questionnaires. Questionnaire packages were returned to sender for seven patients for whom mailing addresses could not be corrected by contacting their clinic. Participating patients included 12 young children (16.9%), 25 older children (35.2%) and 34 adolescents (47.9%). Both patient and parent questionnaires were completed by 64 patient-parent pairs, while for five participants only the parent questionnaire was completed and for two participants only the patient questionnaire was completed. No patients were excluded due to a parent-reported comorbidity unrelated to Duchenne muscular dystrophy (DMD). One parent answered "Yes" to their child having all comorbidities: asthma, cystic fibrosis, diabetes, cerebral palsy, epilepsy and cancer. Based on clinical judgement, however, this was assumed to be a response error and the patient was included. Three additional patients were reported to have asthma. These patients were included under the assumption that their asthma was well-managed due to routine clinical respiratory care typically received by DMD patients. Additionally, asthma may be an adverse effect of medications used in the cardiac management of DMD, such as angiotensin-converting enzyme inhibitors or beta-adrenergic blocking agents [205].

4.1.1 Comparison of Participating and Non-Participating Patients

Patient medical histories were retrieved from the CNDR for both participating and non-participating patients, and are summarized in Table 4.1. No statistically significant differences were observed between participating and non-participating patients with respect to any clinical characteristic examined: age, genetic mutation, musculoskeletal characteristics (unsupported ambulation, unsupported sitting ability, wheelchair use, scoliosis and corticosteroid use), respiratory characteristics (forced vital capacity and non-invasive and invasive ventilatory support) and cardiac characteristics (left ventricular ejection fraction, cardiomyopathy status and cardiac medications), and clinical trial participation. Additionally, no statistically significant difference was observed between participating and non-participating patients with respect to geographic region in Canada (Table 4.1).

4.1.2 Patient Medical Information

In addition to patient medical histories from the CNDR, parents of participating patients completed a patient medical information questionnaire as summarized in Table 4.2. On average, participating patients were 11.6 ± 3.6 years of age (mean ± standard deviation), and ranged from 5–17 years of age. Most patients had a deletion (60.6%) in the *DMD* gene, followed by a duplication (16.9%) or point mutation (16.9%). More than half of patients were ambulant (59.2%). Among non-ambulant patients, the majority lost ambulation more than one year ago (74.1%). Most patients did not have scoliosis (64.8%). Most patients were currently receiving corticosteroid therapy (73.2%). Of patients currently receiving corticosteroid therapy, most were receiving deflazacort (90.2%). On average, forced vital capacity of patients was 85.2 ± 18.3% (mean ± standard deviation),

and ranged from 50–127%. Four patients (5.6%) were receiving non-invasive ventilatory support either part-time (N=2) or full-time (N=2). No patients were receiving invasive ventilatory support. On average, left ventricular ejection fraction of patients was 63.3 ± 7.0% (mean ± standard deviation), and ranged from 48–76%. Five patients (7%) were diagnosed with cardiomyopathy. More than half of children have been diagnosed with at least one neuropsychiatric disorder (53.5%). A learning disability was the most commonly reported neuropsychiatric disorder (33.8%), followed by developmental delay (22.5%), attention deficit disorder or attention deficit hyperactivity disorder (15.5%) and anxiety (12.7%).

4.1.3 Sociodemographic Information

A sociodemographic information questionnaire was completed by parents as summarized in Table 4.3. On average, parents of participating patients were 44.6 ± 6.3 years of age (mean ± standard deviation), and ranged from 29–56 years of age. Of the primary caregivers who completed the parent questionnaire, 84.5% were female and 94.4% were the child's biological parent. Most parents completed post-secondary education (70.4%), and more than half were employed either part-time or full-time (60.6%). Most parents were married or living common law (71.8%). Median annual household income before taxes was $75,000 to $99,999 CAD, which is consistent with the national median household income [206].

4.2 Objective 1: To describe subjective fatigue in children and adolescents with DMD from patients' and parents' perspectives.

Descriptive statistics for child-self report and parent proxy-report Pediatric Quality of Life Inventory Inventory™ (PedsQL™) Multidimensional Fatigue Scale (MFS) scores

are summarized in Tables 4.4–4.6 for all respondents, by age group, and by ambulatory status, respectively. Possible PedsQL™ MFS scores range from 0–100 for total fatigue, general fatigue, sleep/rest fatigue and cognitive fatigue, with higher scores indicating less fatigue [118]. For reference, data from the current study were compared to PedsQL™ MFS scores of healthy children and adolescents from published data (Table 4.4). On average, healthy children and adolescents were 13.7 ± 2.2 years of age (mean ± standard deviation), and ranged from 10–17 years of age. The healthy sample included 74 males (47.1%) and 83 females (52.9%) [118]. PedsQL™ MFS scores were also compared to published data from a second healthy sample, which included younger children of ages 8.9 ± 11.0 years (mean ± standard deviation) ranging from 2–18 years. The healthy sample was composed of 69 males (67.6%) and 33 females (32.4%) who were administered the PedsQL™ MFS Acute Version (seven-day recall period) [117].

4.2.1 PedsQL™ Multidimensional Fatigue Scale by Child Self-Report

Children and adolescents with DMD reported greater fatigue (lower scores) compared with healthy children and adolescents from published data across all domains, irrespective of age group or ambulatory status [117,118]. The average fatigue score by child self-report was 71.6 ± 15.2 (mean ± standard deviation). Median general fatigue score by child self-report was 70.8, with an interquartile range of 58.3–83.3. Median sleep/rest fatigue score by child self-report was 75 with an interquartile range of 64.6–87.5. Median cognitive fatigue score by child self-report was 70.8, with an interquartile range of 54.2–91.7. The trajectory of child self-reported fatigue across disease stages was examined through PedsQL™ MFS scores stratified by age group (Table 4.5) and ambulatory status (Table 4.6). Older children tended to report greater total fatigue compared with young

children and adolescents. Older children and adolescents tended to report greater general fatigue and sleep/rest fatigue compared with young children. Young children and older children tended to report greater cognitive fatigue compared with adolescents. Ambulant and non-ambulant patients reported similar total fatigue and sleep/rest fatigue. Non-ambulant patients tended to report greater general fatigue compared with ambulant patients. Ambulant patients tended to report greater cognitive fatigue compared with non-ambulant patients.

4.2.2 PedsQL™ Multidimensional Fatigue Scale by Parent Proxy-Report

PedsQL™ MFS scores by child self-report were significantly correlated with PedsQL™ MFS scores by parent proxy-report across domains (Table 4.7): total fatigue (ρ=0.69; P<0.001), general fatigue (ρ=0.63; P<0.001), sleep/rest fatigue (ρ=0.50; P<0.001) and cognitive fatigue (ρ=0.68; P<0.001). However, parents perceived their child's level of general fatigue to be worse than that perceived by the patient. Children and adolescents with DMD experienced greater fatigue (lower scores) by parent proxy-report compared with healthy children and adolescents from published data across all domains, irrespective of age group or ambulatory status [117,118]. The average total fatigue score by parent proxy-report was 70.8 ± 16.0 (mean ± standard deviation). General fatigue scores by parent proxy-report were 64.2 ± 20.1 (mean ± standard deviation). Median sleep/rest fatigue score by parent proxy-report was 79.2 with an interquartile range of 66.7–91.7. Median cognitive fatigue score by parent proxy-report was 75, with an interquartile range of 54.2–91.7. The trajectory of parent proxy-reported fatigue across disease stages was examined through PedsQL™ MFS scores stratified by age group (Table 4.5) and ambulatory status (Table 4.6). Parents reported that older children tended to experience greater total fatigue

compared with young children and adolescents. According to parents, older children and adolescents tended to experience greater general fatigue and sleep/rest fatigue compared with young children. Young children and older children tended to experience greater cognitive fatigue with adolescents. Ambulant and non-ambulant patients experienced similar total fatigue. Non-ambulant patients tended to experience greater general fatigue and sleep/rest fatigue compared with ambulant patients. Ambulant patients tended to experience greater cognitive fatigue compared with non-ambulant patients.

4.3 Objective 2: To explore associations of patient characteristics with child self-report and parent parent-proxy report measures of subjective fatigue in children and adolescents with DMD.

4.3.1 Age

Age was assessed as a categorical variable (young children, older children, adolescents) and a continuous variable. Age group was not significantly associated with any child self-report or parent proxy-report measure of fatigue (Table 4.5). Similarly, age (years) was not significantly correlated with any measure of fatigue by child self-report (Table 4.8) or parent proxy-report (Table 4.9).

4.3.2 Musculoskeletal Characteristics

No significant differences were observed between ambulant and non-ambulant patients for total fatigue, general fatigue, sleep/rest fatigue or cognitive fatigue by child self-report or parent proxy-report (Table 4.6).

Among non-ambulant patients, no significant differences were observed between patients who lost ambulation less than one year ago compared with patients who lost ambulation one year ago or more for total fatigue by child self-report (Z=-0.85; P=0.40) or

parent proxy-report (Z=-0.22; P=0.82); general fatigue by child self-report (Z=-1.18; P=0.24) or parent proxy-report (Z=-0.69; P=0.49); sleep/rest fatigue by child self-report (Z=0.34; P=0.73) or parent proxy-report (Z=0.39; P=0.70); and cognitive fatigue by child self-report (Z=-0.58; P=0.56) or parent proxy-report (Z=-0.31; P=0.76).

No significant differences were observed among patients who never, intermittently or permanently use a wheelchair for total fatigue by child self-report (χ^2=0.37; P=0.83) or parent proxy-report (χ^2=3.15; P=0.21); general fatigue by child self-report (χ^2=2.73; P=0.26) or parent proxy-report (χ^2=4.24; P=0.12); sleep/rest fatigue by child self-report (χ^2=0.54; P=0.76) or parent proxy-report (χ^2=4.48; P=0.11); and cognitive fatigue by child self-report (χ^2=1.89; P=0.39) or parent proxy-report (χ^2=2.06; P=0.36).

No significant differences were observed among patients without scoliosis, with surgically corrected scoliosis, or with uncorrected scoliosis for total fatigue by child self-report (χ^2=0.75; P=0.69) or parent proxy-report (χ^2=4.11; P=0.13); general fatigue by child self-report (χ^2=0.86; P=0.65) or parent proxy-report (χ^2=1.94; P=0.38); sleep/rest fatigue by child self-report (χ^2=0.03; P=0.98) or parent proxy-report (χ^2=1.33; P=0.51); and cognitive fatigue by child self-report (χ^2=1.87; P=0.39) or parent proxy-report (χ^2=4.25; P=0.12).

Ten patients (14.1%) in our sample were not currently receiving glucocorticoid therapy. However, current glucocorticoid use was not associated with total fatigue by child self-report (Z=-0.04; P=0.97) or parent proxy-report (Z=-0.02; P=0.98); general fatigue by child self-report (Z=1.77; P=0.08) or parent proxy-report (Z=0.74; P=0.46); sleep/rest fatigue by child self-report (Z=-0.84; P=0.40) or parent proxy-report (Z=0.98; P=0.33); and

cognitive fatigue by child self-report (Z=-0.95; P=0.34) or parent proxy-report (Z=-0.65; P=0.53).

4.3.3 Respiratory Characteristics

Greater forced vital capacity was significantly associated with less general fatigue by child self-report (ρ=0.34; P=0.03). Forced vital capacity was not associated with other domains of fatigue by child self-report (Table 4.8) or parent-proxy report (Table 4.9). Kruskal-Wallis test demonstrated a significant difference in parent proxy-reported sleep/rest fatigue between patients not treated with non-invasive ventilation (NIV; N=66), patients treated with part-time NIV (N=2) and patients treated with full-time NIV (N=2; χ^2=7.02; P=0.03). Post-hoc analysis using Dunn's test with Bonferroni adjustment demonstrated that parent proxy-reported sleep/rest fatigue was stochasticity greater for patients treated with part-time NIV compared with children not treated with NIV (P=0.03). Sleep/rest fatigue scores of the two patients receiving part-time NIV were 8.3 and 54.2 by parent proxy-report, and 8.3 and 66.7 by child self-report. In comparison, the median sleep/rest fatigue score of the entire sample was 79.2 by parent proxy-report and 75 by child self-report. Total fatigue scores of the two patients receiving part-time NIV were 63.9 and 58.3 by parent proxy-report, and 44.4 and 63.9 by child self-report. In comparison, the mean total fatigue score of the entire sample was 70.8 by parent proxy-report and 71.6 by child self-report.

NIV status was not associated with total fatigue by child self-report (χ^2=0.4.25; P=0.12) or parent proxy-report (χ^2=0.98; P=0.61); general fatigue by child self-report (χ^2=2.38; P=0.30) or parent proxy-report (χ^2=2.58; P=0.27); sleep/rest fatigue by child

self-report (χ^2=2.95; *P*=0.23); and cognitive fatigue by child self-report (χ^2=1.80; *P*=0.41) or parent proxy-report (χ^2=0.40; *P*=0.82).

4.3.4 Cardiac Characteristics

Left ventricular ejection fraction was not associated with any measure of fatigue by child self-report (Table 4.8) or parent-proxy report (Table 4.9). Patients with cardiomyopathy (N=5) had stochastically less cognitive fatigue compared with patients without cardiomyopathy (N=59) by child self-report (*Z*=-2.39; *P*=0.02) and parent proxy-report (*Z*=-2.11; *P*=0.04). Cardiomyopathy status was not associated with total fatigue by child self-report (*Z*=-0.22; *P*=0.83) or parent proxy-report (*Z*=-1.13; *P*=0.26); general fatigue by child self-report (*Z*=1.01; *P*=0.31) or parent proxy-report (*Z*=0.71; *P*=0.48); and sleep/rest fatigue by child self-report (*Z*=0.33; *P*=0.74) or parent proxy-report (*Z*=0.31; *P*=0.76).

4.3.5 Neuropsychiatric Characteristics

Diagnosis with one or more neuropsychiatric disorder was not associated with total fatigue by child self-report (*t*=0.85; *P*=0.40) or parent proxy-report (*t*=1.93; *P*=0.06); general fatigue by child self-report (*t*=1.50; *P*=0.14) or parent proxy-report (*t*=0.92; *P*=0.36); sleep/rest fatigue by child self-report (*t*=0.47; *P*=0.64) or parent proxy-report (*t*=1.87; *P*=0.07); and cognitive fatigue by child self-report (*t*=-0.05; *P*=0.96) or parent proxy-report (*t*=1.82; *P*=0.07).

4.3.6 Physical Activity Level

Physical activity level was measured using the Physical Activity Questionnaire for Children and Adolescents (PAQ-C/A). Possible PAQ-C/A scores range from 1 (low physical activity) to 5 (high physical activity) [187]. Median PAQ-C/A score was 1.7, with

an interquartile range of 1.3–2.3 and range of 1–3.7. Greater physical activity was significantly associated with less general fatigue (ρ=0.27; P=0.04) by child self-report. Physical activity level was not associated with other domains of fatigue by child self-report (Table 4.8) or parent-proxy report (Table 4.9).

4.3.7 Functional Ability

Overall functional ability was measured using the Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool (DMDSAT). Possible DMDSAT scores range from 0 (low functional ability) to 23 (high functional ability) [191]. Median DMDSAT score was 18, with an interquartile range of 9–21 and range of 3–23. Lower functional ability was significantly associated with greater total fatigue by parent proxy-report only (ρ=0.26; P=0.03); with greater general fatigue by child self-report (ρ=0.30; P=0.02) and parent proxy-report (ρ=0.30; P=0.01); and with greater sleep/rest fatigue by parent proxy-report only (ρ=0.35; P=0.003). Functional ability was not associated with cognitive fatigue by child self-report (Table 4.8) or parent proxy-report (Table 4.9).

4.3.8 Depressive Symptoms

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale for Children (CES-DC). Possible CES-DC scores range from 0–60 with higher scores indicating greater depressive symptoms [193,207]. Median CES-DC score was 7.5, with an interquartile range of 4–15 and range of 0–45. More depressive symptoms were significantly associated with greater total fatigue by child self-report (ρ=-0.46; P<0.001) and parent proxy-report (ρ=-0.45; P<0.001); with greater general fatigue by child self-report (ρ=-0.30; P=0.02) and parent proxy-report (ρ=-0.37; P=0.002); with greater sleep/rest fatigue by child self-report (ρ=-0.30; P=0.02) and parent proxy-report (ρ=-0.35;

P=0.005); and with greater cognitive fatigue by child self-report (ρ=-0.46; *P*<0.001) and parent proxy-report (ρ=-0.32; *P*=0.009).

4.3.9 Sleep Disturbances Symptoms

Sleep disturbance symptoms were measured using the Sleep Disturbance Scale for Children (SDSC), composed of six sleep disturbance factors: disorders of initiating and maintaining sleep, sleep-related breathing disorders, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence, and sleep hyperhidrosis. Factor scores and total scores were computed. Possible SDSC total scores range from 26–130, with higher scores indicating greater sleep disturbance symptoms [201]. Median SDSC total score was 38, with an interquartile range of 33–41 and range of 28–81. More sleep disturbance symptoms were significantly associated with greater total fatigue by child self-report (ρ=-0.42; *P*=0.003) and parent proxy-report (ρ=-0.51; *P*<0.001); with greater general fatigue by child self-report (ρ=-0.32; *P*=0.03) and parent proxy-report (ρ=-0.45; *P*=0.001); with greater sleep/rest fatigue by child self-report (ρ=-0.30; *P*=0.04) and parent proxy-report (ρ=-0.48; *P*<0.001); and with greater cognitive fatigue by child self-report (ρ=-0.33; *P*=0.03) and parent proxy-report (ρ=-0.34; *P*=0.01). Spearman's rank correlation coefficients for each SDSC factor score and PedsQL^{TM} MFS scores by child self-report and parent proxy-report are presented in Table 4.8 and Table 4.9, respectively. Significant correlations with fatigue were most frequently observed for disorders of initiating and maintaining sleep, disorders of arousal, sleep/wake transition disorders, and disorders of excessive somnolence.

Exploratory multivariable linear regression analyses were performed to test the association between total sleep disturbance symptoms with child self-reported fatigue and

parent proxy-reported fatigue, while adjusting for physical activity level, functional ability and depressive symptoms (Figure 4.1). Because bivariate analyses did not consistently demonstrate significant associations between objective measures of musculoskeletal, respiratory and cardiac function and fatigue, overall functional ability may be more related to fatigue than any single musculoskeletal, respiratory or cardiac characteristic. Thus, functional ability measured using the DMDSAT was included as a covariate in the multivariable linear regression analyses, rather than single measures of musculoskeletal, respiratory and cardiac function. Although cardiac function is not reflected in the DMDSAT score, it was not included as a covariate because clinical manifestation of cardiac dysfunction that may impact fatigue are more likely to present in adulthood than in childhood or adolescence [94].

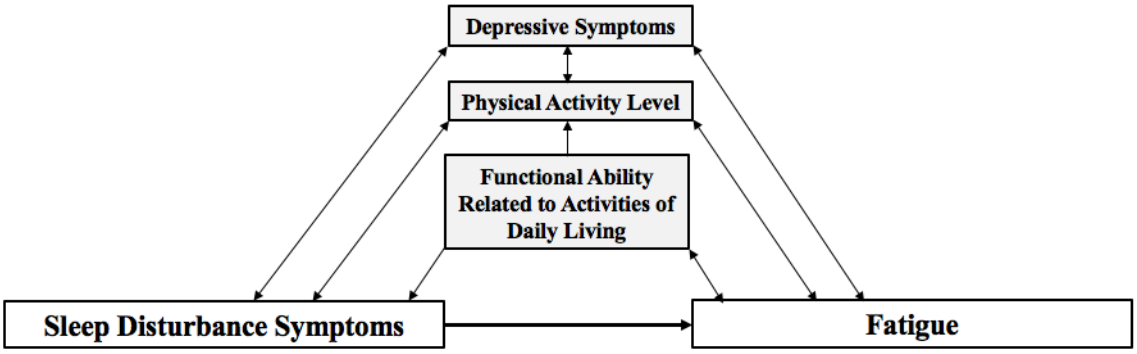

Figure 4.1. A model of fatigue in children and adolescents with Duchenne muscular dystrophy tested using multivariable linear regression analyses.

Linear regression analyses with listwise deletion are presented in Tables 4.10 and 4.11 for child self-reported and parent proxy-reported fatigue, respectively (N=41). More sleep disturbance symptoms were significantly associated with greater child self-reported total fatigue (β=-0.84; P=0.001), general fatigue (β=-0.97; P=0.003) and cognitive fatigue (β=-1.24; P=0.006), but not with child self-reported sleep/rest fatigue (β=-0.28; P=0.31),

while adjusting for physical activity level, functional ability and depressive symptoms (Table 4.10). Sleep disturbance symptoms, physical activity level, functional ability and depressive symptoms explained 38% of the variability in child self-reported total fatigue, 39% of the variability in child self-reported general fatigue, and 22% of the variability in child self-reported cognitive fatigue. More sleep disturbance symptoms were significantly associated with parent proxy-reported total fatigue (β=-0.91; P<0.001), general fatigue (β=-1.08; P=0.002), sleep/rest fatigue (β=-0.62; P=0.01) and cognitive fatigue (β=-1.03; P=0.02), while adjusting for physical activity level, functional ability and depressive symptoms (Table 4.11). Sleep disturbance symptoms, physical activity level, functional ability and depressive symptoms explained 44% of the variability in parent proxy-reported total fatigue, 32% of the variability in parent proxy-reported general fatigue, 32% of the variability in parent proxy-reported sleep/rest fatigue, and 18% of the variability in parent proxy-reported cognitive fatigue.

Linear regression analyses with multiple imputation using chained equations performed to examine the impact of missing data are presented in Tables 4.12 and 4.13 for child self-reported and parent proxy-reported fatigue, respectively (N=71). This sensitivity analysis yielded similar results for child self-reported and parent proxy-reported fatigue compared with the analysis using listwise deletion. More sleep disturbance symptoms were significantly associated with greater child self-reported total fatigue (β=-0.62; P=0.008), general fatigue (β=-0.73; P=0.03) and cognitive fatigue (β=-0.94; P=0.005), but not with child self-reported sleep/rest fatigue (β=-0.17; P=0.60), while adjusting for physical activity level, functional ability and depressive symptoms (Table 4.12). More sleep disturbance symptoms were significantly associated with parent proxy-reported total

fatigue (β=-0.66; P=0.03), general fatigue (β=-0.74; P=0.04), but not with sleep/rest fatigue (β=-0.39; P=0.27) or cognitive fatigue (β=-0.73; P=0.10), while adjusting for physical activity level, functional ability and depressive symptoms (Table 4.13). Although the associations between sleep disturbance symptoms and parent proxy-reported sleep/rest fatigue and cognitive fatigue were no longer significant, the direction of the regression coefficients remained the same with more sleep disturbance symptoms being associated with greater fatigue.

Table 4.1. Comparison of clinical characteristics retrieved from the Canadian Neuromuscular Disease Registry between participating and non-participating patients

	Participating Patients (N=71)	Non-Participating Patients (N=122)	*P*-Value[a]
Region			0.18
British Columbia	13 (18.3%)	36 (29.5%)	
Alberta	10 (14.1%)	15 (12.3%)	
Ontario	40 (56.4%)	65 (53.3%)	
Quebec	8 (11.3%)	6 (4.9%)	
Age	11.6 ± 3.6 (5, 17)	12.0 ± 3.3 (5, 17)	0.56
Genetic Mutation			0.32
Deletion	43 (60.6%)	82 (67.2%)	
Duplication	12 (16.9%)	10 (8.2%)	
Point Mutation	12 (16.9%)	19 (15.6%)	
None Detected	1 (1.4%)	3 (2.5%)	
Unreported	3 (4.2%)	8 (6.6%)	
Musculoskeletal Characteristics			
Unsupported ambulation			0.45
Ambulant	42 (59.2%)	84 (68.9%)	
Non-ambulant	28 (39.4%)	31 (25.4%)	
Unreported	1 (1.4%)	7 (5.7%)	
Unsupported sitting ability			0.75
No	4 (5.6%)	6 (4.9%)	
Yes	57 (80.3%)	104 (83.3%)	
Unreported	10 (14.1%)	12 (9.8%)	
Wheelchair use			0.50
Never	30 (42.3%)	47 (38.5%)	
Intermitted	16 (22.5%)	38 (31.1%)	
Permanent	17 (23.9%)	27 (22.1%)	
Unreported	8 (11.3%)	10 (8.2%)	
Scoliosis			0.92
No	46 (64.8%)	82 (67.2%)	
Surgically corrected	1 (1.4%)	1 (0.8%)	
Uncorrected	9 (12.7%)	19 (15.6%)	
Unreported	15 (21.1%)	20 (16.4%)	
Corticosteroid therapy			0.25
Never	9 (12.7%)	8 (6.6%)	
Past	1 (1.4%)	2 (1.6%)	
Current	52 (73.2%)	101 (82.8%)	
Unreported	9 (12.7%)	11 (9.0%)	
Corticosteroid type			0.60
Deflazacort	47 (90.4%)	95 (96.0%)	
Prednisone	2 (3.9%)	2 (2.0%)	
Unreported	3 (5.8%)	2 (2.0%)	

	Participating Patients (N=71)	Non-Participating Patients (N=122)	*P*-Value[a]
Respiratory Characteristics			
Forced vital capacity	85.2 ± 18.3 (50, 127)	80.6 ± 23.0 (16, 135)	0.28
Non-invasive ventilatory support			0.15
No	66 (93.0%)	105 (86.1%)	
Part-time	2 (2.8%)	6 (4.9%)	
Full-time	2 (2.8%)	-	
Unreported	1 (1.4%)	11 (9.0%)	
Invasive ventilatory support			-
No	62 (87.3%)	109 (89.3%)	
Part-time	-	-	
Full-time	-	-	
Unreported	9 (12.7%)	13 (10.7%)	
Cardiac Characteristics			
Left ventricular ejection fraction	63.3 ± 7.0 (48, 76)	62.9 ± 9.9 (17.4, 80)	0.85
Cardiomyopathy			0.50
No	59 (83.1%)	106 (86.9%)	
Yes	5 (7.0%)	5 (4.1%)	
Unreported	7 (9.9%)	11 (9.0%)	
Cardiac medications			0.78
No	46 (64.8%)	91 (74.6%)	
Yes	13 (18.3%)	23 (18.9%)	
Unreported	12 (16.9%)	8 (6.6%)	
Research			
Clinical trial participation			0.31
Never	35 (49.3%)	70 (57.4%)	
Past	1 (1.4%)	7 (5.7%)	
Current	15 (21.1%)	21 (17.2%)	
Unreported	20 (28.2%)	24 (19.7%)	

Data are mean ± standard deviation (range) or frequency (percentage)

[a]Unpaired *t*-tests were used for continuous variables, and χ^2 tests or Fisher's exact tests were used for categorical variables to assess differences between respondents and non-respondents. Unreported values were not included in analyses.

Table 4.2. Patient medical information by parent-report (respondents only, N=71)

	Frequency	Percentage
Motor Function		
Ambulant	42	59.2%
Non-ambulant	28	39.4%
Lost ambulation less than one year ago	7	25.0%
Lost ambulation one year ago or more	20	71.4%
Neuropsychiatric Disorders		
Developmental delay	16	22.5%
Learning disability	24	33.8%
Attention Deficit Disorder or Attention Deficit Hyperactivity Disorder	11	15.5%
Autism spectrum disorder	1	1.4%
Oppositional defiant disorder	4	5.6%
Conduct disorder	2	2.8%
Depression	5	7.0%
Anxiety	9	12.7%
One or more neuropsychiatric disorder	38	53.5%
Therapies		
Pharmacotherapy or psychotherapy for behavioural problems		
Ever needed	14	19.7%
Ever received	12	16.9%
Pharmacotherapy or psychotherapy for emotional problems		
Ever needed	12	16.9%
Ever received	11	15.5%
Occupational therapy		
Ever needed	44	62.0%
Ever received	42	59.2%
Speech language therapy		
Ever needed	26	36.6%
Ever received	26	36.6%
School Information		
Special education (individualized education plan, special needs classroom, tutoring, etc.)		
Ever needed	50	70.4%
Ever received	47	66.2%
Research		
Current clinical trial or other research participation	31	44.9%

Table 4.3. Sociodemographic information by parent-report (respondents only, N=71)

	Frequency	Percentage
Primary Caregiver[a]		
Age	44.6 ± 6.3[b]	(29, 56)[b]
Sex		
Male	9	12.8%
Female	60	84.5%
Relationship to Child		
Biological parent	67	94.4%
Adoptive parent	-	-
Step parent	-	-
Foster parent	2	2.8%
Guardian	-	-
Highest educational attainment		
Less than secondary school graduation	5	7.1%
Secondary school diploma or equivalent	13	18.3%
Vocational training	7	9.9%
College or university diploma or degree	38	53.5%
Graduate degree	5	7.0%
Employment status		
Unemployed	17	24.0%
Employed (part-time or full-time)	43	60.6%
Stay-at-home parent	8	11.3%
Student	-	-
Marital status		
Married or living common law	51	71.8%
Widowed	1	1.4%
Separated	6	8.5%
Divorced	5	7.0%
Single	6	8.5%
Spouse or Partner of Primary Caregiver		
Highest educational attainment		
Less than secondary school graduation	7	9.9%
Secondary school diploma or equivalent	9	12.7%
Vocational training	7	9.9%
College or university diploma or degree	27	38.0%
Graduate degree	7	9.9%
Employment status		
Unemployed	5	7.0%
Employed (part-time or full-time)	49	69.0%
Stay-at-home parent	3	4.2%
Student	-	-

	Frequency	Percentage
Household		
Household size	4 (3, 5)[c]	(2, 9)[c]
Annual household income before taxes (CAD)		
$14,999 and under	1	1.4%
$15,000 to $34,999	7	9.9%
$35,000 to $49,999	7	9.9%
$50,000 to $74,999	9	12.7%
$75,000 to $99,999	14	19.7%
$100,000 and over	24	33.8%

[a]Primary caregiver describes the parent who completed the questionnaire
[b]Data are mean ± standard deviation; (range)
[c]Data are median (interquartile range); (range)

Table 4.4. Descriptive statistics for the Pediatric Quality of Life Inventory™ (PedsQL™) Multidimensional Fatigue Scale by child self-report and parent proxy-report

	Duchenne Muscular Dystrophy Sample				Healthy Sample[a]	
	N	Mean ± SD	Median (IQR)	Range	N	Mean ± SD
Child Self-Report						
Total fatigue	66	71.6 ± 15.2	69.4 (62.5, 81.9)	(25, 100)	157	82.2 ± 12.3
General fatigue	66	70.2 ± 19.7	70.8 (58.3, 83.3)	(0, 100)		86.4 ± 13.1
Sleep/rest fatigue	66	74.0 ± 17.5	75 (64.6, 87.5)	(8.3, 100)		77.4 ± 15.4
Cognitive fatigue	65	70.9 ± 23.0	70.8 (54.2, 91.7)	(0, 100)		82.8 ± 16.3
Parent Proxy-Report						
Total fatigue	69	70.8 ± 16.0	69.4 (58.3, 84.7)	(37.5, 100)	157	87.2 ± 10.9
General fatigue	69	64.2 ± 20.1	62.5 (45.8, 79.2)	(25, 100)		88.4 ± 11.7
Sleep/rest fatigue	69	76.9 ± 18.0	79.2 (66.7, 91.7)	(8.3, 100)		86.7 ± 12.6
Cognitive fatigue	69	69.7 ± 24.6	75 (54.2, 91.7)	(0, 100)		86.6 ± 16.4

Abbreviations: N, sample size; SD, standard deviation; IQR, interquartile range.
[a]From published data: Varni JW et al. Int J Ped Obes 2010;5:34–42.

Table 4.5. Descriptive statistics for the Pediatric Quality of Life Inventory™ (PedsQL™) Multidimensional Fatigue Scale by age group

	Age Group[a]	N	Mean ± SD	Median (IQR)	Range	*P*-Value[b]
Child Self-Report						
Total fatigue	Young children	10	72.5 ± 21.4	72.2 (63.9, 88.9)	(25, 100)	0.66
	Older children	23	69.9 ± 14.9	69.4 (56.9, 81.9)	(45.8, 98.6)	
	Adolescents	33	72.5 ± 13.6	69.4 (65.3, 81.9)	(44.4, 97.2)	
General fatigue	Young children	10	75.0 ± 28.9	83.3 (75, 91.7)	(0, 100)	0.23
	Older Children	23	70.3 ± 19.0	66.7 (54.2, 87.5)	(25, 100)	
	Adolescents	32	68.6 ± 17.1	70.8 (56.3, 81.3)	(25, 100)	
Sleep/rest fatigue	Young children	10	80.0 ± 16.3	79.2 (66.7, 91.7)	(50, 100)	0.45
	Older children	23	72.9 ± 15.3	70.8 (62.5, 83.3)	(41.7, 100)	
	Adolescents	33	72.9 ± 19.4	75 (62.5, 87.5)	(8.3, 100)	
Cognitive fatigue	Young children	10	62.5 ± 31.2	62.5 (41.7, 91.7)	(0, 100)	0.12
	Older children	23	66.9 ± 20.8	62.5 (50, 87.5)	(29.2, 100)	
	Adolescents	33	76.1 ± 21.1	75 (62.5, 95.8)	(8.3, 100)	
Parent Proxy-Report						
Total fatigue	Young children	12	74.8 ± 23.8	84.0 (51.4, 95.8)	(37.5, 100)	0.32
	Older children	25	67.3 ± 16.3	62.5 (56.9, 79.2)	(40.3, 100)	
	Adolescents	32	71.9 ±11.8	71.5 (64.6, 81.3)	(51.4, 93.1)	
General fatigue	Young children	12	75.0 ± 25.6	77.1 (54.2, 100)	(25, 100)	0.13
	Older children	25	60.7 ± 19.8	58.3 (45.8, 75)	(25, 100)	
	Adolescents	32	62.9 ± 17.1	62.5 (47.9, 75)	(25, 91.7)	
Sleep/rest fatigue	Young children	12	84.7 ± 16.3	89.6 (68.8, 100)	(58.3, 100)	0.21
	Older children	25	77.0 ± 16.6	75 (62.5, 87.5)	(45.8, 100)	
	Adolescents	32	73.9 ± 19.2	77.1 (64.6, 89.6)	(8.3, 100)	
Cognitive fatigue	Young children	12	64.6 ± 34.2	70.8 (37.5, 100)	(0, 100)	0.28
	Older children	25	64.3 ± 26.8	58.3 (45.8, 91.7)	(0, 100)	
	Adolescents	32	75.8 ± 16.8	75 (62.5, 89.6)	(33.3, 100)	

Abbreviations: N, sample size; SD, standard deviation; IQR, interquartile range.

[a]Young children, ages 4–7 years; older children, ages 8–12 years; adolescents, age 13–17 years.

[b]Kruskal-Wallis tests were used to assess differences between age groups.

Table 4.6. Descriptive statistics for the Pediatric Quality of Life Inventory™ (PedsQL™) Multidimensional Fatigue Scale by ambulatory status

	Ambulatory Status	N	Mean ± SD	Median (IQR)	Range	*P*-Value[a]
Child Self-Report						
Total fatigue	Ambulant	39	71.6 ± 16.3	72.2 (59.7, 83.3)	(25, 100)	0.92
	Non-ambulant	26	71.9 ± 13.9	69.4 (65.3, 81.9)	(44.4, 97.2)	
General fatigue	Ambulant	39	72.8 ± 21.0	75 (62.5, 87.5)	(0, 100)	0.12
	Non-ambulant	25	66.7 ± 17.5	70.8 (54.2, 75)	(25, 100)	
Sleep/rest fatigue	Ambulant	39	73.7 ± 17.2	75 (62.5, 87.5)	(33.3, 100)	0.75
	Non-ambulant	26	73.9 ± 18.5	75 (66.7, 83.3)	(8.3, 100)	
Cognitive fatigue	Ambulant	39	68.6 ± 23.3	70.8 (50, 91.7)	(0, 100)	0.21
	Non-ambulant	26	75.3 ± 22.2	70.8 (58.3, 91.7)	(8.3, 100)	
Parent Proxy-Report						
Total fatigue	Ambulant	42	71.0 ± 18.0	70.8 (58.3, 84.9)	(37.5, 100)	0.84
	Non-ambulant	27	70.3 ± 12.7	68.1 (58.3, 81.9)	(51.4, 93.1)	
General fatigue	Ambulant	42	65.8 ± 22.1	62.5 (45.8, 87.5)	(25, 100)	0.55
	Non-ambulant	27	61.7 ± 16.7	62.5 (45.8, 75)	(25, 87.5)	
Sleep/rest fatigue	Ambulant	42	79.4 ± 15.1	81.3 (66.7, 91.7)	(45.8, 100)	0.27
	Non-ambulant	27	72.9 ± 21.4	75 (62.5, 91.7)	(8.3, 100)	
Cognitive fatigue	Ambulant	42	67.9 ± 27.9	72.9 (50, 91.7)	(0, 100)	0.72
	Non-ambulant	27	72.5 ± 18.3	75 (58.3, 87.5)	(33.3, 100)	

Abbreviations: N, sample size; SD, standard deviation; IQR, interquartile range.
[a]Wilcoxin Rank Sum tests were used to assess differences between ambulant and non-ambulant individuals.

Table 4.7. Correlation analyses between child self-report and parent proxy-report Pediatric Quality of Life Inventory™ (PedsQL™) Multidimensional Fatigue Scale scores

		Spearman's Rank Correlation Coefficient (ρ) N *P*-Value			
		Child Self-Report			
		Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Parent Proxy-Report	Total fatigue	0.69 64 <0.001			
	General fatigue		0.63 63 <0.001		
	Sleep/rest fatigue			0.50 64 <0.001	
	Cognitive fatigue				0.68 64 <0.001

Table 4.8. Correlation analyses between child characteristics and Pediatric Quality of Life Inventory™ (PedsQL™) Multidimensional Fatigue Scale scores by child self-report

	Spearman's Rank Correlation Coefficient (ρ) N *P*-Value			
	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Clinical Characteristics				
Age (years)	0.01 66 0.92	-0.19 65 0.14	-0.06 66 0.62	0.23 66 0.07
Forced vital capacity (%)	0.29 40 0.07	0.34 39 **0.03**	0.15 40 0.35	0.03 40 0.87
Left ventricular ejection fraction (%)	0.00 42 0.99	0.10 41 0.52	-0.22 42 0.16	0.08 42 0.60
Child Self-Report or Parent Proxy-Report Measures				
Physical Activity Questionnaire for Children and Adolescents	0.13 58 0.32	0.27 57 **0.04**	0.12 58 0.35	-0.06 58 0.67
Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool	0.05 64 0.67	0.30 63 **0.02**	-0.01 64 0.94	-0.13 64 0.31
Center for Epidemiological Studies Depression Scale for Children	-0.46 66 **<0.001**	-0.30 65 **0.02**	-0.30 66 **0.02**	-0.46 66 **<0.001**

Sleep Disturbance Scale for Children				
Disorders of initiating and maintaining sleep	-0.54 51 **<0.001**	-0.37 50 **0.008**	-0.26 51 0.07	-0.49 51 **<0.001**
Sleep-related breathing disorders	-0.14 62 0.27	-0.33 61 **0.009**	-0.06 62 0.62	0.06 62 0.64
Disorders of Arousal	-0.35 62 **0.005**	-0.27 61 **0.03**	-0.13 62 0.32	-0.41 62 **0.001**
Sleep-wake transition disorders	-0.26 60 **0.04**	-0.26 59 **0.05**	-0.15 60 0.25	-0.14 60 0.28
Disorders of excessive somnolence	-0.34 58 **0.009**	-0.15 57 0.26	-0.33 58 **0.01**	-0.24 58 0.07
Sleep hyperhidrosis	-0.03 62 0.82	-0.12 61 0.37	0.15 62 0.26	-0.06 62 0.66
Total sleep disturbance symptoms	-0.42 46 **0.003**	-0.32 45 **0.03**	-0.30 46 **0.04**	-0.33 46 **0.03**

P-Values in bold are statistically significant at α=0.05 two-sided level of significance.

Table 4.9. Correlation analyses between child characteristics and Pediatric Quality of Life Inventory™ (PedsQL™) Multidimensional Fatigue Scale scores by parent proxy-report

	Spearman's Rank Correlation Coefficient (ρ) N *P*-Value			
	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Clinical Characteristics				
Age (years)	0.06 69 0.62	-0.10 69 0.42	-0.18 69 0.15	0.20 69 0.10
Forced vital capacity (%)	0.12 40 0.48	0.22 40 0.17	0.07 40 0.68	-0.01 40 0.93
Left ventricular ejection fraction (%)	0.06 41 0.71	0.22 41 0.17	-0.07 41 0.68	0.02 41 0.89
Child Self-Report or Parent Proxy-Report Measures				
Physical Activity Questionnaire for Children and Adolescents	0.09 57 0.49	0.16 57 0.24	0.18 57 0.17	-0.11 57 0.43
Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool	0.26 69 **0.03**	0.30 69 **0.01**	0.35 69 **0.003**	0.08 69 0.52
Center for Epidemiological Studies Depression Scale for Children	-0.45 64 **<0.001**	-0.37 64 **0.002**	-0.35 64 **0.005**	-0.32 64 **0.009**

Sleep Disturbance Scale for Children				
Disorders of initiating and maintaining sleep	-0.53 55 **<0.001**	-0.36 55 **0.008**	-0.40 55 **0.003**	-0.46 55 **<0.001**
Sleep-related breathing disorders	-0.20 67 0.10	-0.14 67 0.24	-0.19 67 0.12	-0.17 67 0.18
Disorders of Arousal	-0.43 67 **<0.001**	-0.34 67 **0.005**	-0.27 67 **0.03**	-0.37 67 **0.002**
Sleep-wake transition disorders	-0.35 65 **0.004**	-0.29 65 **0.02**	-0.33 65 **0.007**	-0.28 65 **0.02**
Disorders of excessive somnolence	-0.42 63 **<0.001**	-0.41 63 **<0.001**	-0.58 63 **<0.001**	-0.12 63 0.35
Sleep hyperhidrosis	-0.16 67 0.20	-0.07 67 0.56	-0.11 67 0.39	-0.19 67 0.12
Total sleep disturbance symptoms	-0.51 50 **<0.001**	-0.45 50 **0.001**	-0.48 50 **<0.001**	-0.34 50 **0.01**

P-Values in bold are statistically significant at α=0.05 two-sided level of significance.

Table 4.10. Multivariable linear regression analyses with listwise deletion to predict child self-reported fatigue (N=41)

$\hat{\beta}$
(95% Confidence Interval)
P-Value

	Dependent Variable			
Independent Variables	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Sleep Disturbance Scale for Children	-0.84 (-1.31, -0.38) **0.001**	-0.97 (-1.59, -0.35) **0.003**	-0.28 (-0.84, 0.27) 0.31	-1.24 (-2.10, -0.39) **0.006**
Physical Activity Questionnaire for Children and Adolescents	2.50 (-3.08, 8.08) 0.37	3.08 (-4.44, 10.61) 0.41	4.39 (-2.28, 11.05) 0.19	0.35 (-9.95, 10.64) 0.95
Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool	-0.18 (-0.81, 0.45) 0.57	0.22 (-0.62, 1.07) 0.59	-0.54 (-1.29, 0.21) 0.15	-0.22 (-1.39, 0.94) 0.70
Center for Epidemiological Studies Depression Scale for Children	-0.32 (-0.94, 0.30) 0.31	-0.70 (-1.55, 0.14) 0.10	-0.01 (-0.75, 0.73) 0.97	-0.33 (-1.47, 0.82) 0.56
R^2 (Adjusted)	0.38	0.39	0.02	0.22

P-Values in bold are statistically significant at α=0.05 two-sided level of significance.

Table 4.11. Multivariable linear regression analyses with listwise deletion to predict parent proxy-reported fatigue (N=41)

$\hat{\beta}$
(95% Confidence Interval)
P-Value

	Dependent Variable			
Independent Variable	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Sleep Disturbance Scale for Children	-0.91 (-1.36, -0.46) **<0.001**	-1.08 (-1.74, -0.42) **0.002**	-0.62 (-1.11, -0.13) **0.01**	-1.03 (-1.85, -0.21) **0.02**
Physical Activity Questionnaire for Children and Adolescents	-1.37 (-6.78, 4.04) 0.61	1.00 (-6.93, 8.93) 0.80	1.52 (-4.34, 7.38) 0.60	-6.64 (-16.53, 3.24) 0.18
Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool	0.68 (0.07, 1.29) **0.03**	0.43 (-0.46, 1.33) 0.34	0.83 (0.17, 1.49) **0.02**	0.78 (-0.34, 1.90) 0.17
Center for Epidemiological Studies Depression Scale for Children	-0.28 (0.88, 0.32) 0.36	-0.38 (-1.26, 0.50) 0.39	-0.15 (-0.80, 0.50) 0.64	-0.30 (-1.40, 0.79) 0.58
R^2 (Adjusted)	0.44	0.32	0.32	0.18

P-Values in bold are statistically significant at α=0.05 two-sided level of significance.

Table 4.12. Multivariable linear regression analyses with multiple imputation using chained equations to predict child self-reported fatigue (N=71)

	$\hat{\beta}$ (95% Confidence Interval) *P*-Value			
	Dependent Variable			
Independent Variable	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Sleep Disturbance Scale for Children	-0.62 (-1.06, -0.18) **0.008**	-0.73 (-1.38, -0.09) **0.03**	-0.17 (-0.83, 0.49) 0.60	-0.94 (-1.58, -0.30) **0.005**
Physical Activity Questionnaire for Children and Adolescents	1.94 (-2.95, 6.83) 0.43	2.82 (-3.40, 9.04) 0.37	3.22 (-3.53, 9.96) 0.34	0.07 (-8.22, 8.35) 0.99
Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool	0.29 (-0.26, 0.83) 0.29	0.84 (0.10, 1.58) **0.03**	0.17 (-0.60, 0.94) 0.66	-0.13 (-0.99, 0.73) 0.76
Center for Epidemiological Studies Depression Scale for Children	-0.77 (-1.17, -0.38) **<0.001**	-0.80 (-1.32, -0.28) **0.003**	-0.60 (-1.17, -0.03) **0.04**	-0.93 (-1.54, -0.32) **0.004**

P-Values in bold are statistically significant at α=0.05 two-sided level of significance.

Table 4.13. Multivariable linear regression analyses with multiple imputation using chained equations to predict parent proxy-reported fatigue (N=71)

	$\hat{\beta}$ (95% Confidence Interval) *P*-Value			
	Dependent Variable			
Independent Variables	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Sleep Disturbance Scale for Children	-0.66 (-1.26, -0.06) **0.03**	-0.74 (-1.45, -0.03) **0.04**	-0.39 (-1.13, 0.34) 0.27	-0.73 (-1.61, 0.15) 0.10
Physical Activity Questionnaire for Children and Adolescents	-1.55 (-7.23, 4.12) 0.58	0.08 (-6.45, 6.62) 0.989	-0.47 (-6.90, 5.95) 0.88	-4.17 (-14.24, 5.91) 0.41
Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool	0.79 (0.21, 1.38) **0.001**	1.11 (0.35, 1.86) **0.005**	1.19 (0.49, 1.90) **0.001**	0.47 (-0.54, 1.48) 0.36
Center for Epidemiological Studies Depression Scale for Children	-0.82 (-1.27, -0.37) **0.001**	-0.91 (-1.44, -0.38) **0.001**	-0.71 (-1.26, -0.16) **0.01**	-0.98 (-1.79, -0.18) **0.02**

P-Values in bold are statistically significant at α=0.05 two-sided level of significance.

Chapter 5

5 Discussion

To our knowledge, this is the first study to describe fatigue in children and adolescents with Duchenne muscular dystrophy (DMD), from the perspective of patients and their parents. Additionally, we have proposed a novel conceptual model of factors associated with fatigue in children and adolescents with DMD, and tested associations of patient characteristics with fatigue in this population. Our results demonstrated fatigue to be a significant issue in children and adolescents with DMD, across age groups from early childhood to adolescence, and across disease stages from the early ambulatory to late non-ambulatory stages, highlighting the need for fatigue to be addressed in the routine clinical care of affected boys. We have identified several factors associated with fatigue, which have contributed to our understanding of the subjective experience of fatigue as a complex, multi-causal and multidimensional phenomenon in paediatric DMD. Our findings demonstrated greater sleep disturbance symptoms, greater depressive symptoms and lower functional ability related to activities of daily living to be associated with greater fatigue in children and adolescents with DMD. These findings warrant further investigation in the development of evidence-based therapeutic strategies aimed at reducing fatigue and improving health-related quality of life. This chapter discusses our results in the context of existing literature and interprets key findings pertaining to each objective, while highlighting their clinical and research implications.

5.1 Sample Characteristics

Our sample was composed of 71 children and adolescents with DMD between the ages of 5–17 years, and included patients with DMD across all disease stages: early

ambulatory, late ambulatory, early non-ambulatory and late non-ambulatory. Over half of the patients in our sample were ambulatory and most were without known severe respiratory or cardiac complications, which may cause concern about non-response bias and whether participating patients were at a less severe disease stage than non-participating patients. However, comparison of registry data of participating and non-participating patients demonstrated that there were no significant differences between participating and non-participating patients. Our sample was representative of DMD patients registered in the Canadian Neuromuscular Disease Registry (CNDR) with respect to both clinical characteristics (age, genetic mutation, musculoskeletal, respiratory and cardiac characteristics, and clinical trial participation) and geographic region in Canada.

5.2 Objective 1: To describe subjective fatigue in children and adolescents with DMD from patients' and parents' perspectives

Children and adolescents with DMD in our study experienced greater fatigue than healthy children and adolescents from published data, from both patients' and parents' perspectives [117,118,179]. Child self-reported and parent proxy-reported total and general fatigue scores of boys with DMD in our study were comparable to previously published scores of a multicentre cohort of ambulant boys with DMD of ages 5–13 years in Italy [58]. Moreover, child self-reported and parent proxy-reported fatigue for children and adolescents with DMD in our study were comparable to those for children and adolescents with cancer from published data—for whom fatigue is recognized as a frequent and debilitating symptom, warranting the development of the term cancer-related fatigue and its diagnostic criteria [13,179,208–211].

In our study, child self-reports and parent proxy-reports of fatigue were similar, except for general fatigue, in which parents perceived their child's level of general fatigue to be worse than that perceived by the patient. The general fatigue domain of the PedsQL™ Multidimensional Fatigue Scale (MFS) has been reported to be more related to patient functional ability [58]. Parents may therefore attribute their child's fatigue to functional ability more so than patients themselves do. This is supported by our finding that patient functional ability was more strongly associated with parent proxy-reported fatigue than with child self-reported fatigue. Our results comparing patients' and parents' perceptions of fatigue are in contrast with the literature, which demonstrate poor agreement between child self-reported and parent proxy-reported fatigue. In previous studies of children and adolescents with chronic health conditions, parents typically underestimated their child's level of fatigue [118,212–215]. Imperfect agreement between child self-reported and parent proxy-reported internalizing symptoms, such as fatigue, has consistently been documented across paediatric patient populations [216]. Discrepancies between patients' and parents' perceptions of fatigue may impact treatment decisions and ultimately, clinical outcomes. Gaultney et al. reported greater discrepancy between child self-reported and parent proxy-reported fatigue to be associated with more depressed mood in patients with juvenile idiopathic arthritis [212].

Although our results demonstrated similar perceptions of fatigue by patients and their parents, it is unclear whether this finding would translate to a clinical setting, where parallel child self-report and parent proxy-report fatigue rating scales may not be used. Hinds et al. demonstrated that paediatric oncology patients and their parents often use different language to define and describe fatigue in a clinical setting [213], reaffirming the

need for clinicians to assess both patients' and parents' perspectives of fatigue when making treatment decisions [118,212]. It may be that in the case of a condition involving progressive motor impairment with onset as young as infancy, like DMD, parents have a greater appreciation of their child's fatigue as they are more vigilant about their child's mobility and conscious of potential difficulties their son may encounter keeping up with peers [217]. Parents' expectations and observations of muscle weakness interfering with their child's daily activities may therefore foster a shared understanding of fatigue severity between patients with DMD and their parents. Additional studies are required to draw firm conclusions regarding agreement between child self-reported and parent proxy-reported fatigue in the paediatric DMD population. Studies involving qualitative interviews and focus groups with children and adolescents with DMD, and their parents, can enhance our understanding of similarities and discrepancies between patients' and parents' perceptions of fatigue [213].

We used age and ambulatory status to describe fatigue in children and adolescents with DMD across different disease stages. No statistically significant differences in fatigue were observed between young children (5–7 years of age), older children (8–12 years of age) and adolescents (13–17 years of age), or between ambulant and non-ambulant patients, by child self-report or parent proxy-report. Patients with DMD in our study consistently experienced greater fatigue than their healthy peers when compared to published data, by child self-report and parent proxy-report, across age groups and ambulatory status [117,118,179]. Therefore, fatigue may be a prominent issue in paediatric patients with DMD at all disease stages.

Although not statistically significant, child self-reported and parent proxy-reported total fatigue was greater for older children, compared with young children and adolescents. Older children are typically in an ambulatory decline phase and may therefore experience greater fatigue due to continued participation in physical activities that are becoming progressively more challenging and exhausting over time. In a previous study, patients with DMD using a wheelchair intermittently were more fatigued than patients not using a wheelchair, suggesting that the time around transitioning to wheelchair use during the ambulatory decline phase may be associated with greater fatigue [3]. In our study, intermittent wheelchair users were also more fatigued than non-wheelchair users, although differences were not statistically significant.

General fatigue and sleep/rest fatigue, which are reflective of the physical component of fatigue [16], were more severe among older children and adolescents compared with young children, whereas cognitive fatigue, which is reflective of the mental component of fatigue [16], was more severe among young children and older children compared with adolescents. Hinds et al. reported that children with cancer of ages 7–12 years emphasized physical fatigue, whereas adolescents with cancer of ages 13–18 years emphasized a dynamic combination of physical and mental fatigue when describing their fatigue during focus groups [213]. Greater general and sleep/rest fatigue in older children and adolescents with DMD may be attributable to greater disease severity—particularly muscle weakness and reduced functional ability, which are known risk factors for fatigue in adult neuromuscular disorders [47,57]. Items in the cognitive fatigue domain of the PedsQL^{TM} MFS focus on problems with working memory, information retrieval and attention—all of which improve with age [179,218]. Adolescents have better working and

long term memory, shorter information processing speeds and longer attention spans compared with young children and older children [218]. Greater cognitive fatigue in young children and older children with DMD compared with adolescents may therefore be attributable to normal age-related cognitive development. Similar trends were observed for non-ambulant patients who are at a more severe disease stage and typically older than ambulant patients, such that non-ambulant patients experienced greater general and sleep/rest fatigue, and less cognitive fatigue than ambulant patients with DMD.

These findings have implications for potential therapeutic strategies for fatigue in DMD, such that younger patients at early disease stages may benefit from therapies targeting mental fatigue and older patients at late disease stages may benefit from therapies targeting physical fatigue. However, to our knowledge, the minimal clinically important differences for child self-reported and parent proxy-reported PedsQL^{TM} MFS scores have not yet been defined. Therefore, the clinical significance of trends described from our findings are speculative and require further investigation.

5.3 To explore associations of patient characteristics with child self-report and parent proxy-report measures of subjective fatigue in children and adolescents with DMD.

Of the patient characteristics explored in our study, sleep disturbance symptoms and depressive symptoms emerged as the strongest correlates of child self-reported and parent proxy-reported fatigue. Functional ability emerged as a correlate of parent proxy-reported fatigue more so than child self-reported fatigue. Physical activity level and clinical characteristics including age, and musculoskeletal, respiratory and cardiac function were not consistently associated with child self-reported or parent proxy-reported fatigue.

Because sleep disturbances are frequent in children and adolescents with DMD [72,219], and variations exist in the diagnostic assessment and management of sleep disturbances in DMD across Canada [73], we hypothesized sleep disturbance symptoms to be a potentially modifiable factor associated with fatigue. Our findings demonstrate that greater sleep disturbance symptoms were significantly associated with greater fatigue from both patients' and parents' perspectives. To our knowledge, the relationship between sleep disturbances and fatigue has not been studied in paediatric neuromuscular disorders. However, a link between sleep disturbances and fatigue has been established in adults with myotonic dystrophy or multiple sclerosis, and other childhood chronic health conditions, such as cancer [7,74–82].

Sleep-related breathing disorders, of both non-obstructive and obstructive origin, are the most commonly documented sleep disturbances in DMD [71,72,111,219]. In our study, symptoms of sleep-related breathing disorders did not emerge as a correlate of fatigue. However, the accuracy of parent-reported symptoms of sleep-related breathing disorders compared with objective sleep measurements is unclear [72]. Moreover, symptoms such as restless sleep, nightmares, morning confusion and excessive daytime sleepiness may be related to sleep-related breathing disorders, but were scored as items of other domains in the Sleep Disturbance Scale for Children [201]. Therefore, the lack of association between sleep disordered breathing and fatigue should be interpreted cautiously.

Further examination of the relationship between sleep disordered breathing and fatigue is warranted. The relationship between sleep disordered breathing and fatigue may additionally be explored by examining the level of fatigue experienced by patients

receiving non-invasive ventilation (NIV) for the management of respiratory failure, which initially presents as nocturnal hypoventilation [53]. In our study, the two patients receiving part-time (nocturnal) NIV experienced greater total fatigue, general fatigue and sleep/rest fatigue compared with non-ventilated patients. However, this finding was only statistically significant for parent proxy-reported sleep/rest fatigue. No clear relationship between full-time (nocturnal and diurnal) NIV and fatigue was observed. Because the optimal time to initiate NIV is still under debate [50], the absence of NIV may not accurately identify patients without sleep disordered breathing. Therefore, no firm conclusions can be drawn regarding the relationship between sleep-related breathing disorders or NIV and fatigue. Moreover, our study was underpowered to detect differences in fatigue between ventilated and non-ventilated patients. Symptoms related to disorders of initiating and maintaining sleep, disorders of arousal, sleep-wake transition disorders and disorders of excessive somnolence demonstrated the strongest associations with fatigue. Bloetzer et al. previously reported disorders of initiating and maintaining sleep and disorders of excessive somnolence to be prevalent in 29.7% and 10.9% of children and adolescents with DMD, respectively [72]. Thus, clinical sleep evaluations in children and adolescents with DMD should not be limited to detecting sleep-related breathing disorders, as other sleep disturbances may be present and impact fatigue.

Consensus-based recommendations for sleep evaluations in DMD are included in respiratory care recommendations by the American Thoracic Society and the international DMD Care Considerations Working Group convened by the Centers for Disease Control and Prevention [1,68,220]. The optimal time to screen for sleep disordered breathing in DMD has not been determined, however annual polysomnography, or overnight pulse

oximetry with continuous carbon dioxide monitoring (capnography) if polysomnography is not available, is recommended starting from loss of ambulation and/or when clinically indicated (i.e. at the onset of daytime symptoms of sleep disordered breathing or abnormal pulmonary function tests) [68]. Polysomnography is a multi-parametric test used as a diagnostic tool in sleep medicine to record physiological changes during sleep. The polysomnogram monitors cerebral cortical activity (electroencephalogram), cardiac activity (electrocardiogram), muscle activity (electromyogram), eye movements (electrooculogram), respiratory airflow, thoracoabdominal movements, oximetry and capnography [50].

Because oximetry with capnography has limited utility for detecting sleep disturbances not associated with hypoxemia or hypercapnia, and because there is poor correlation between daytime symptoms, abnormal pulmonary function and sleep disturbances, a "polysomnography for all policy" has been proposed in the management of children and adolescents with DMD [71,111]. However, polysomnography is costly and not universally available across clinics [221]. In addition, because polysomnography requires admission to a sleep laboratory and may result in the disruption of normal sleep architecture and respiratory patterns, portable home monitoring has been proposed as an alternative diagnostic tool for sleep disturbances in DMD. However, the validity of portable home monitoring in paediatric neuromuscular disorders remains unclear [41,71,221,222]. In Canada, routine polysomnography to assess for sleep disordered breathing is ordered by approximately half of neurologists and respirologists caring for children and adolescents with DMD [73]. Polysomnography is important for indicating the need for timely intervention with NIV, which can reduce symptoms of sleep disordered

breathing and potentially confer a beneficial effect on fatigue [223]. In addition to determining the optimal time to screen for sleep disturbances using polysomnography, further research is warranted to validate more affordable screening technologies in the paediatric DMD population, such as portable home monitoring, and to determine sensitive and specific daytime predictors of sleep disordered breathing [221,224,225].

In boys with DMD, sleep can be further complicated by disease-related, psychological and social factors. Muscle weakness and the subsequent need to be turned by a caregiver during the night has been reported to be associated with sleep disturbance symptoms in boys with DMD [72]. Overnight use of ankle-foot orthotics or knee-ankle-foot orthotics may cause further discomfort during sleep for some patients [55]. Although the role of dystrophin in the central nervous system remains unclear, the absence of dystrophin has been hypothesized to alter neuronal function, which may subsequently impact sleep patterns [55]. Moreover, boys with DMD are at increased risk for emotional and behavioural problems, including anxiety, depression and attention deficit hyperactivity disorder (ADHD), which have been reported to contribute to sleep disturbances during childhood and adolescence [91,226]. Parental exhaustion, sleep deprivation and poor mental health, associated with caring for a child with DMD [227,228], can further contribute to the vulnerability of these families and interfere with the development of effective sleep hygiene practices in affected boys. Parents of children with DMD are at higher risk for experiencing depression and lower self-esteem compared with parents of healthy children [229]. Both maternal and paternal depression have been reported to be associated with sleep disturbances in children [230]. Compromised parental mental health may contribute to parenting inconsistency, which has been reported to be associated with

sleep disturbances in children with ADHD [231]. It is therefore imperative that recommendations for the assessment and management of sleep disturbances in children and adolescents with DMD are interdisciplinary and extend beyond sleep disordered breathing to include other sleep disorders, as well as disease-related, psychological and social factors.

Cognitive behavioural therapy (CBT) has been proposed as a treatment for disorders of initiating and maintaining sleep. Concomitant treatment of sleep disturbances and fatigue using CBT has been evaluated in adults with facioscapulohumeral dystrophy, multiple sclerosis, chronic fatigue syndrome and traumatic brain injury, demonstrating beneficial effects on sleep disturbances and fatigue, as well as comorbid depression [103,143,232,233]. CBT has also been reported to reduce fatigue in adolescents with chronic fatigue syndrome [234–236].

Our study demonstrated an association between greater depressive symptoms and greater fatigue in children and adolescents with DMD from both patients' and parents' perspectives. This finding is consistent with studies that have examined the relationship between depression and fatigue in other paediatric patient populations, such multiple sclerosis, chronic fatigue syndrome and cancer [45,237–240]. Studies examining emotional disturbances in children and adolescents with DMD are limited. However, there is evidence to suggest boys with DMD are at increased risk for depression compared with their healthy peers or other paediatric patient populations with physical disabilities, with older boys at greater risk than young boys [55,91,241]. In a cross-sectional study of adults with DMD, Pangalila et al. reported fatigue and affective disorders (depression and/or anxiety) to co-exist in 24.1% of patients [120]. However, this finding is equivocal, as diagnoses of fatigue

and affective disorders were made by dichotomizing self-reported scores of the Fatigue Severity Scale and Hospital Anxiety and Depression Scale, respectively, as either indicative or not indicative of clinical significance [120,242,243]. In addition to concerns regarding sensitivity and specificity of these measures and the potential of misclassification bias, dichotomization of continuous variables results in loss of information, produces associations of lower magnitude and reduces statistical power [244–248].

Despite a strong association between depression and fatigue in chronic health conditions, the causal relationships between depression and fatigue remain to be elucidated [99,249]. Three causal hypotheses have been proposed in the literature relating to cancer-related fatigue: (1) fatigue is caused by the illness, and treatment of the illness causes depression, (2) fatigue develops in patients because of depression, or (3) no causal relationship exists, and a third factor is the cause of both depression and fatigue. However, demonstrating these relationships has proven to be a methodological challenge [249]. Understanding the causal relationship between fatigue and depression has clinical implications for developing effective therapeutic strategies for fatigue. If depression and fatigue are causally associated, a predominant effect in one direction may support a strategy that targets either depression or fatigue first. Alternatively, a bidirectional causal relationship may support a strategy that treats depression and fatigue as a symptom cluster. For example, physical exercise has been proposed as a symptomatic therapy for both depression and fatigue in patient populations, including children and adolescents with physical disabilities [250,251]. Physical exercise has been evaluated as a treatment for fatigue in children and adolescents with cancer with inconclusive results [252]. The

feasibility of physical exercise as a treatment for fatigue may be limited in non-ambulant boys with DMD due to functional limitations.

In our study, physical activity level was not associated with fatigue in children and adolescents with DMD from patients' or parents' perspectives. This contrasts with findings by Maher et al. in children and adolescents with physical disabilities, which included neuromuscular disorders such as Charcot-Marie-Tooth disease, myotonia congenita and myotubular myopathy [251]. Using an accelerometer to objectively measure physical activity level, Maher et al. reported physical inactivity to be associated with fatigue in children and adolescents with physical disabilities. Similarly, lower physical activity has been reported to be associated with greater fatigue in children and adolescents with multiple sclerosis [195]. It is possible that the Physical Activity Questionnaire for Children and Adolescents used in our study did not adequately capture variability in the physical activity level of children and adolescents with DMD [187]. Limited variability in the data may have reduced the magnitude of correlation coefficients between physical activity level and fatigue in our study [253].

Because most measures of physical activity level are intended for use in typically developing children, there is a need for the development of feasible, valid and reliable measures to assess physical activity level in children and adolescents with neuromuscular disorders, which quantify both lower limb and upper limb activity [184]. The combined use of subjective and objective measures has been recommended to achieve a better understanding of physical activity level in children and adolescents with neuromuscular disorders, as no single instrument can quantify all dimensions of physical activity [185]. Physical activity level is, at least in part, determined by functional ability in children and

adolescents with DMD [184]. In our study, objective measures of musculoskeletal, respiratory and cardiac function did not emerge as correlates of fatigue. Although cardiomyopathy was associated with less cognitive fatigue from both patients' and parents' perspectives, this association may have been confounded by age. Onset of cardiomyopathy in DMD typically occurs during adolescence and in our study, adolescents experienced less cognitive fatigue compared with young children and older children. Lower functional ability related to activities of daily living, however, was associated with greater fatigue from parents' perspective. Thus, parents may be more likely to perceive their child's fatigue as an outcome of or contributor to the progressive functional decline associated with DMD more so than the patients themselves.

5.4 Strengths and Limitations

A strength of our study was that our sample was composed of children and adolescents with DMD across disease stages. Moreover, the use of a national registry to recruit patients facilitated the inclusion of patients from multiple clinics and regions within Canada, thereby further enhancing the generalizability of our results. To our knowledge, descriptive data of fatigue in paediatric DMD have only previously been published for ambulant boys of ages 5–13 years in Italy, and only for total and general fatigue scores measured using the PedsQL^{TM} MFS [58].

The use of the PedsQL^{TM} MFS was an additional strength of our study. A recently published systematic review of instruments to assess fatigue in paediatric chronic health conditions identified the PedsQL^{TM} MFS to have the best evidence for strong psychometric properties (reliability, content validity and hypothesis testing) in a range of paediatric chronic health conditions across childhood, and as the only subjective fatigue measure with

robust evidence for use in young children [14]. Additionally, the use of a generic instrument, the PedsQL^{TM} MFS, enabled comparison of fatigue in children and adolescents with DMD with healthy children and other patient populations to better comprehend the severity of fatigue in paediatric DMD.

The assessment of fatigue from both patients' and parents' perspectives is also considered to be strength of our study. A lack of agreement between child self-reported and parent proxy-reported fatigue previously observed in other paediatric chronic health conditions underscores the need to consider both patients' and parents' perspectives to characterize fatigue during childhood and adolescence [14]. Understanding how parents' perspectives compare with patients' perspectives of fatigue is particularly important in a clinical setting when a child is too young, too cognitively impaired or too ill to express health concerns to their practitioner.

Our results should be interpreted considering several limitations. The cross-sectional design of our study does not allow for temporality or causality to be established regarding the associations explored between patient characteristics and fatigue in children and adolescents with DMD. Additionally, a response rate of 36.8% and sample size of 71 may have resulted in a lack of statistical power to detect associations between some clinical characteristics and fatigue. Although the Tailored Design Method was employed to maximize our response rate to questionnaires, we were unable to implement a key component of the Tailored Design Method due to privacy and confidentiality protocols of the CNDR: personalization of contacts with eligible patients [177]. Personalization of questionnaires and letters with a person's name has been demonstrated to increase the response rate of mailed paper questionnaires [177,254]. Personalization can reduce the

social distance between the researcher and eligible patient, reduce the likelihood of a survey request being ignored using the rationale that others will respond, establish authenticity of the researcher and the study being conducted, and ultimately, establish trust between the researcher and eligible patient—all of which should increase the response rate [177]. However, the CNDR does not allow for identification of eligible patients or for investigators to contact eligible patients directly.

No differences in registry data were observed between participating and non-participating patients, demonstrating that our sample was representative of children and adolescents with DMD registered in the CNDR with respect to clinical characteristics and geographical region. However, the CNDR only included patients from British Columbia, Albert, Ontario and Quebec, with Ontario contributing most patients to the registry. Therefore, it is unclear whether children and adolescents with DMD registered in the CNDR are representative of all children and adolescents with DMD across Canada, particularly in remote regions. This has important implications in the study of fatigue given the variations in clinical practices that exist across Canada for the screening and management of sleep disordered breathing in children and adolescents with DMD [73]. Moreover, it is unclear whether patients enrolled in the CNDR systematically differ from patients with DMD not enrolled in the CNDR with respect to clinical characteristics. Epidemiological data on DMD in Canada is limited. To our knowledge, no Canadian population-based descriptive studies on DMD have been published to allow for comparison. Selection bias may have been introduced if patients at a more severe disease stage were more likely to decline invitations to enroll in the CNDR. Nevertheless, the use

of the CNDR allowed for a more representative sample than would have been achieved through patient recruitment from our neuromuscular clinic only.

In addition to discrepancies in care practices or clinical characteristics between patients enrolled in the CNDR and patients with DMD not enrolled in the CNDR, selection bias and non-response bias may have been introduced from behavioural, socioeconomic or cultural factors. For example, patients and parents who are more knowledgeable and vigilant about their health may be more motivated to enroll in the registry and participate in research studies. Similarly, higher educational attainment and income are associated with greater health literacy [255], which may ultimately result in greater motivation to enroll in the registry and participate in research studies. Factors that may prevent patients and parents from responding to questionnaires include difficulties reading and writing or cognitive impairment. Patients' and parents' past experiences in research studies, whether positive or negative, may have also influenced both enrollment in the registry and participation in the current study.

An additional limitation associated with the CNDR is the possibility of outdated patient medical histories in the registry database. Most clinical data included in the registry were obtained from clinic visits between 2013 and 2016. However, the inclusion of a patient medical information section in the parent questionnaire allowed us to cross-reference registry data and parent-reported data related to major disease milestones, such as loss of ambulation and initiation of NIV. Discrepancies between registry and parent-reported ambulatory status and ventilatory status were observed for five and four participating patients, respectively.

It is also possible that child self-report and parent proxy-report measures were subject to a degree of response bias, such as recall bias or social-desirability bias. In our study, fatigue was assessed over a one-month recall period, as previous research evaluating the accuracy of fatigue ratings across recall periods demonstrated that momentary assessments of fatigue were often more highly correlated with ratings from a one-month recall period compared with a seven-day recall period [256]. Given the difficulty of recalling many days, as in the case of a one-month recall period, patients with a chronic illness refer to beliefs based on their extensive experience with symptoms, which provide a reasonably accurate estimate of average symptom levels. When asked to construct a rating to represent the past seven days, patients may attempt to retrieve memories from the past week, which are subject to cognitive heuristics that give disproportionate weight to peak and most recent symptoms experienced, thereby decreasing accuracy [256]. Lastly, because questionnaires were not completed in a supervised setting, we cannot be certain that patients and parents independently completed their respective questionnaires, or that parents did not interpret questions or answers for their child if assistance was provided.

Due to similarities between the constructs of sleep disturbance symptoms and depressive symptoms, it is possible that the multivariable regression analyses conducted were affected by multicollinearity. Multicollinearity occurs when two or more independent variables in a multivariable regression model are moderately to highly correlated. Multicollinearity can reduce the precision of regression coefficient estimates, as demonstrated by large standard errors and wide confidence intervals, and consequently increase the risk of a type II error (failure to reject a false null hypothesis) [257].

5.5 Implications of Findings and Future Directions

Our results have implications in both clinical and research settings. Our findings contribute to the limited literature on fatigue in a broader paediatric patient population of children and adolescents with neuromuscular disorders. We have identified fatigue to be a prominent issue in children and adolescents with DMD across disease stages, from both patients' and parents' perspectives. This finding emphasizes the need for healthcare providers to become more familiar with fatigue in children and adolescents with DMD and to engage in dialogue about fatigue with DMD patients and their caregivers. Regular assessment of fatigue at routine clinic visits may provide clinicians with insight about the onset and patterns of fatigue in relation to other clinical manifestations or changes in function, and aid in the identification of individualized therapeutic targets for fatigue. For example, an increase in fatigue may be observed around the time of transition into wheelchair use, as affected boys struggle to maintain independent ambulation. To reduce fatigue, clinicians may encourage more flexible wheelchair use by focusing on the potential benefit of improved fatigue, and aim to shift patient and parent attitudes about the negative milestone of wheelchair use by emphasizing wheelchair use as a rehabilitative practice for improving mobility, rather than a loss of independence [258].

We developed a conceptual model of factors associated with fatigue in paediatric DMD, and tested the associations between factors included in the model and fatigue. In doing so, we have identified several factors that may be associated with fatigue in paediatric DMD, which warrant further investigation. Although causal conclusions cannot be made regarding the associations of sleep disturbance symptoms, depressive symptoms, physical activity level, functional ability and clinical characteristics with fatigue, our study

serves as a hypothesis-generating starting point in this novel area of research in paediatric DMD. Our results identified sleep disturbance symptoms, depressive symptoms and functional ability as potentially modifiable risk factors associated with fatigue, warranting further attention in clinical settings and in future research aimed at developing evidence-based interventions for the management of fatigue in paediatric DMD. Studies evaluating interventions for the treatment of fatigue in paediatric patient populations are limited and have primarily been conducted in paediatric chronic fatigue syndrome or cancer populations. CBT may be worth exploring as a therapy for fatigue in children and adolescents with DMD as it can simultaneously target fatigue, sleep disturbance symptoms and depressive symptoms. Moreover, it has demonstrated promising effects on fatigue in adult neuromuscular disorders and paediatric chronic fatigue syndrome [143,233–236].

In designing and conducting our study, we have identified several methodological challenges of studying fatigue and factors associated with fatigue in children and adolescents with DMD. Here, we provide insights on how these obstacles can be addressed or ameliorated in future studies. Although registries are intended to be representative of certain patient populations and reflective of the clinical practices of healthcare providers in certain geographical regions, registries are often associated with challenges, such as difficulties with patient recruitment and retention, that can have profound consequences on the validity of registry data [259]. The representativeness of our sample to our target population of children and adolescents across Canada may have been improved with the recruitment of additional neuromuscular clinics to the CNDR. At the registry level, providing innovative nonfinancial incentives that meet the needs of decision-makers at potential recruitment sites has been demonstrated to increase patient enrollment and

subsequently improve the validity and generalizability of research facilitated through registries [259].

Additional large-scale prospective cohort studies are required to characterize the trajectory of fatigue in paediatric DMD and to determine causal relationships of sleep disturbance symptoms, depressive symptoms, physical activity level, functional ability and clinical characteristics with fatigue. In our study, sleep disturbance symptoms and depressive symptoms were identified as potentially modifiable factors associated with fatigue in children and adolescents with DMD, as these symptoms may be overlooked in the routine management of DMD. Child self-report and parent proxy-report symptom-based measures are easy to administer, and are associated with low participation burden. However, measures of sleep disturbance symptoms and depressive symptoms provide limited information on the associations of formal diagnoses of sleep disturbances and depression with fatigue. To further understand these relationships, polysomnographic data and psychiatric evaluations conducted by clinicians are required in future studies.

In the early research of cancer-related fatigue, many qualitative studies were conducted to better comprehend the complex, multi-causal and multidimensional subjective experience of fatigue [260–263]. A qualitative study of fatigue in children and adolescents with DMD can provide unprecedented insight on the origin, severity, patterns and impact of fatigue. Moreover, qualitative interviews with DMD patients and their parents may facilitate our understanding of similarities and differences of how patients and their parents define and perceive fatigue. A qualitative study of fatigue in children and adolescents with DMD may also facilitate the identification of additional factors, and

potential therapeutic targets, associated with fatigue that were not included in our proposed model.

5.6 Conclusions

This is the first study to comprehensively describe fatigue in children and adolescents with DMD from patients' and parents' perspectives, and to explore associations of patient characteristics with fatigue in this population. Children and adolescents with DMD experienced greater fatigue compared with their healthy peers, and experience comparable levels of fatigue as children and adolescents with cancer, across all disease stages from both patients' and parents' perspectives. Our findings underscore fatigue as a prominent issue in paediatric DMD, which may be overlooked in the current management of children and adolescents with DMD because of the lack of literature describing the presentation and implications of fatigue in this population. Greater sleep disturbance symptoms were associated with greater fatigue from patients' and parents' perspectives. Sleep disturbance symptoms may be overlooked in the management of children and adolescents with DMD [71], and therefore warrant further investigation as a potentially modifiable risk factor for fatigue in this population. Moreover, greater depressive symptoms were associated with greater fatigue from patients' and parents' perspectives, and lower functional ability was associated with greater fatigue from parents' perspective. Additional large-scale prospective cohort studies are required to establish causality between these patient characteristics and fatigue in children and adolescents with DMD, to facilitate the development of targeted therapeutic strategies to effectively reduce fatigue and subsequently improve health-related quality of life.

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Appendices

Appendix A: Literature Review Search Strategy Terminology and Syntax

Table A.1. Database-specific terminology and syntax used in literature search strategy

Concept	MEDLINE	EMBASE	CINAHL	PsychINFO	Keywords
Muscular Dystrophies/Spinal Muscular Atrophy	exp Muscular dystrophies/ or exp Muscular atrophy, spinal/	muscular dystrophy/ or becker muscular dystrophy/ or duchenne muscular dystrophy/ or dystrophinopathy/ or emery dreifuss muscular dystrophy/ or facioscapulohumeral muscular dystrophy/ or limb girdle muscular dystrophy/ or progressive muscular dystrophy/ or exp spinal muscular atrophy/	(MH "Muscular Dystrophy") or or (MH "Muscular Dystrophy, Duchenne+") or (MH "Muscular Atrophy, Spinal+")	SU.EXACT("Muscular Dystrophy") or SU.EXACT("Muscular Disorders")	Muscular dystroph* or dystrophinopath* or duchenne muscular dystrophy or becker muscular dystrophy or emery dreifuss muscular dystrophy or facioscapulohumeral muscular dystrophy or limb girdle muscular dystrophy or spinal muscular atrophy or spinal muscle atrophy
Fatigue	exp fatigue/	fatigue/	(MH "Mental Fatigue") OR (MH "Fatigue")	SU.EXACT("Fatigue")	Fatigue or fatigability or tired*
Search Limits	-	Full text Human English Language	-	-	-
Total Citations	**404**	**356**	**47**	**209**	**1,016**

Appendix B: Literature Review Study Selection

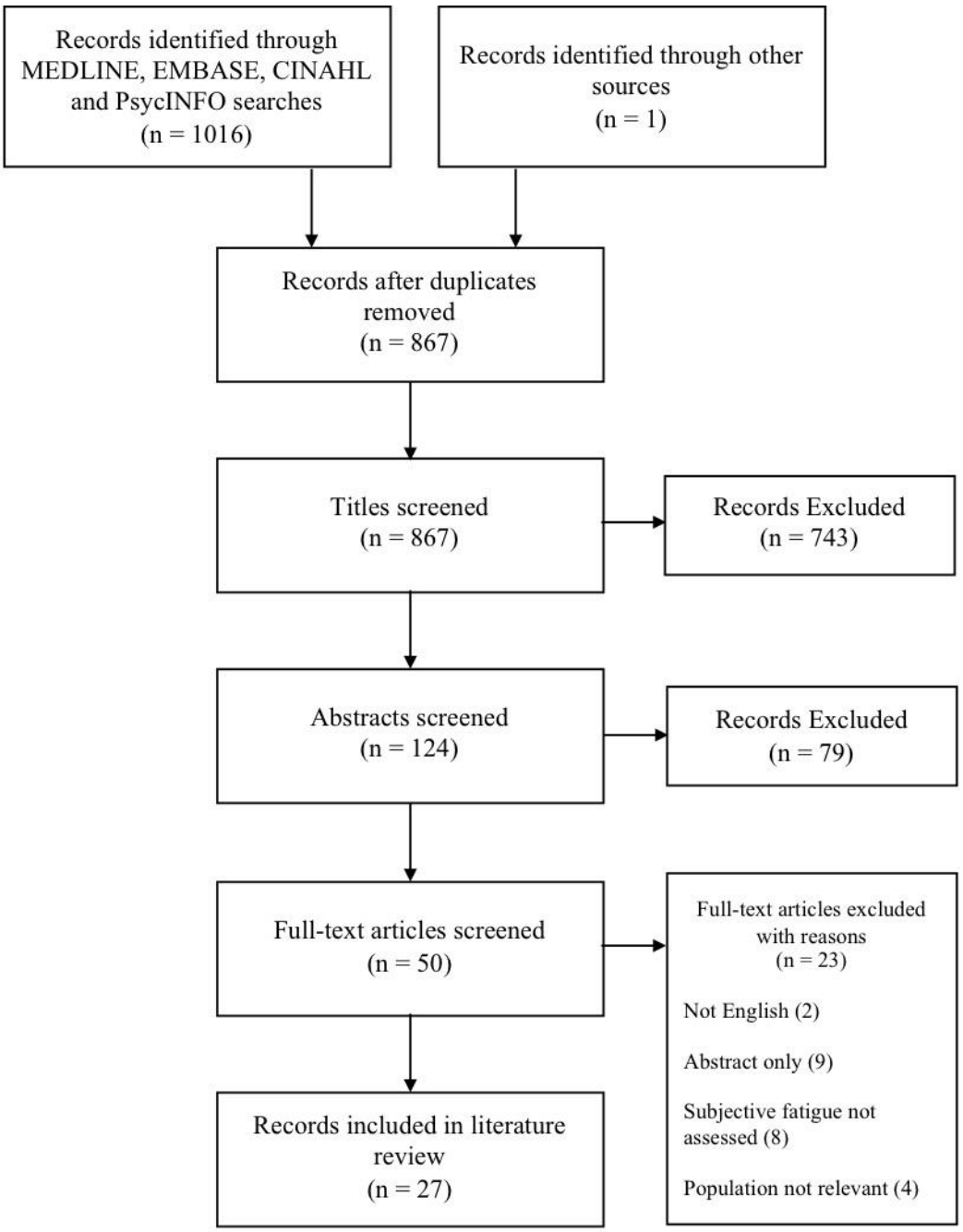

Figure B.1. Flowchart of study selection for literature review

Appendix C: Research Ethics Board Approval Notice

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Craig Campbell
Department & Institution: Schulich School of Medicine and Dentistry\Epidemiology & Biostatistics,London Health Sciences Centre

Review Type: Expedited
HSREB File Number: 103358
Study Title: Understanding Quality of Life and Health Related Quality of Life in Children Affected by Duchenne Muscular Dystrophy
Sponsor:

HSREB Amendment Approval Date: June 09, 2016
HSREB Expiry Date: February 06, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	Revised child (ages 8–12 years) parent proxy-report questionnaire for data collection time-point 3. Includes all new measures	2016/05/17
Instruments	Revised child (ages 8–12 years) self-report questionnaire for data collection time-point 3. Includes all new measures (clean version).	2016/05/10
Revised Assent	Revised assent letter for data collection time-point 3 (clean version)	2016/05/09
Revised Letter of Information & Consent	Revised letter of information for data collection time-point 3 (clean version)	2016/05/09
Revised Western University Protocol	Revised ROMEO protocol (clean version)	2016/05/10

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Appendix D: Canadian Neuromuscular Disease Registry Affiliate Clinics

Table D.1. Current and former paediatric neuromuscular clinics participating in the Canadian Neuromuscular Disease Registry

City	Clinical Sites	Academic Affiliation
	Current	
Vancouver, BC	British Columbia Children's Hospital	University of British Columbia
Calgary, AB	Alberta Children's Hospital	University of Calgary
Toronto, ON	Holland Bloorview Kids Rehabilitation Hospital	University of Toronto
London, ON	Thames Valley Children's Centre	Western University
Ottawa, ON	Children's Hospital of Eastern Ontario	University of Ottawa
Kingston, ON	Child Development Centre, Hotel Dieu Hospital	Queen's University
Montreal, QC	Montreal Children's Hospital	McGill University
Halifax, NS	IWK Health Centre	Dalhousie University
	Former	
Mississauga, ON	ErinoakKids Centre for Treatment and Development	McMaster University

Appendix E: Letter of Information

Project Title: Understanding Quality of Life and Health Related Quality of Life in Children Affected by Duchenne Muscular Dystrophy

Investigators: Dr. Craig Campbell, Dr. Kathy Speechley and Sally Wei, Department of Paediatrics, Children's Hospital, London Health Sciences Centre, and Basmah El-Aloul, Department of Epidemiology and Biostatistics, Western University

Research Coordinator: Rhiannon Hicks

Letter of information

You are being invited to participate in a research study looking at the quality of life in children with Duchenne Muscular Dystrophy (DMD) because you have indicated that you are interested in research opportunities through the Canadian Neuromuscular Disease Registry.

Some of you may remember participating in this study in the past—if that's the case, thank you for your contribution. With your help, we have gained a better understanding of the factors that influence quality of life in the DMD population. We would like to ask for your participation one more time. You may notice some additional questionnaires have been added; this was done to deepen our understanding of quality of life in DMD.

If you have not completed our questionnaires in the past, we ask you to consider participating at this time. Having more responses will give a more complete picture of quality of life in the DMD community. If you agree to participate, you and a parent will be asked to complete the set of questionnaires included with this letter. These questionnaires should take about 30 minutes to complete. There are two booklets—one for you to complete on your own and one to be completed by your parent. If you do require help with the questionnaires that you are to complete on your own (e.g. you have trouble writing or do not understand how to fill out the forms), you may certainly ask your parents to help you. If you do get help, please do your best to answer the questions based on how you feel about your life and your health. There are no right or wrong answers for these questionnaires. For the parent questionnaires, we ask that the same parent complete all the forms, and it does not matter if this is your mother or father. Please note that some questions are similar or even identical to each other, we ask that you complete all of the questions on each page. Because we are trying to assess which questionnaires work best for the DMD population, it is important that each questionnaire is completed. Once the questionnaires are complete, we would ask that you send them back to us using the postage-paid return envelope included with this package.

Consent: Consent for this study is implied consent, meaning that if you complete and return the questionnaires, you are agreeing to participate in the study.

Schulich MEDICINE & DENTISTRY | Children's Hospital London Health Sciences Centre | Western

Risks: There are no known risks or discomforts associated with participating in this study. However, if you or your parent experiences any problems or discomfort while completing the questionnaires, you may discontinue the task at any time.

Benefits: While you or your parent may not directly benefit from participating in this research, information from this study may provide benefits to the DMD population as a whole by allowing healthcare workers to better understand factors impacting quality of life in children with DMD.

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care. As a token of appreciation for considering participating, we have included a Tim Hortons gift card with this letter.

All data collected will remain anonymous, confidential and accessible only by the investigators of this study. If the results are published, your name or any identifying information will not be used. If you choose to withdraw from this study, your data will be removed and destroyed from our database. Your questionnaires will be stored in a secure research office at London Health Sciences Centre until the study results are published.

If you require further information regarding this research project or your participation in the study you may contact [redacted]

If you have any questions about your rights as a research participant, please contact Dr. David Hill, Scientific Director, Lawson Health Research Institute at 519-667-6649. If you would like to receive a copy of any potential study results, please contact 519-685-8441.

Please keep a copy of this Letter of Information for you records.

Appendix F: Assent Letter

Project Title: Understanding Quality of Life and Health Related Quality of Life in Children Affected by Duchenne Muscular Dystrophy

Principal Investigator: Dr. Craig Campbell, MD, Department of Paediatrics, Children's Hospital, London Health Sciences Centre

Assent Letter

1. **What is this study about?**
   Dr. Campbell and some researchers would like to find out about how you feel and what you think about your health. They want to see if you would like to be in this study. Some of you may remember that you have answered some similar questions last year; this is a follow-up study to see if there have been any changes in how you feel. If you have not answered these questions before, we would also love to hear from you!

2. **What will happen to you?**
   If you want to be in the study, you will answer some questions about your life. The questions are not part of a test, and there are no right or wrong answers. If you have answered our questionnaires before, you may recognize some of the questions from before, but we have also added some new questions. If you do not feel comfortable answering any of the questions, you don't have to answer them.

3. **Will the study help you?**
   No, this study will not help you directly. In the future, it might help other children with Duchenne Muscular Dystrophy.

4. **What if you have any questions?**
   You can ask questions at any time, now or later. You can talk to your family or someone else. You or your parents can also call the researchers to ask questions.

5. **Do you have to be in the study?**
   You do not have to be in the study. No one will be mad at you if you do not want to do this. If you do not want to be in the study, just say so. Even if you say yes, you can change your mind later. It is up to you. If you want to be in the study, please fill out the questionnaire and return it. If not, you do not have to do anything.

Appendix G: Thank-You Postcard

July 4th, 2016

Last week a questionnaire was mailed to you from the Duchenne Muscular Dystrophy Quality of Life study.

If you have already completed and returned the questionnaire to us, please accept our sincere thanks. If not, please consider participating in our study today. We are especially grateful for your help because it is only by asking patients and parents like you to share your experiences that we can achieve our ultimate goal of optimizing health-related quality of life for children and families such as yours.

If you did not receive a questionnaire, or it was misplaced, please call us at [redacted] and we will get another one in the mail to you today.

Appendix H: Follow-up Reminder Letter

October 12th, 2016

Dear Resident,

A few weeks ago, a set of questionnaires was sent to you from the Canadian Neuromuscular Disease Registry entitled, **"Quality of Life and Health Related Quality of Life in Children with Duchenne Muscular Dystrophy"**. To the best of our knowledge, it has not yet been returned.

Many people have already returned their questionnaires and they include a wide variety of experiences with Duchenne Muscular Dystrophy (DMD). We can see that the results are going to help us better understand the experiences of children living with DMD and their families to learn how we can best support children with DMD.

We are writing again because of the importance that your questionnaires have for helping us to get accurate results. Although we are sending questionnaires to people living all across Canada, it is only by hearing from nearly everyone in the sample that we can be sure the results are truly representative.

We would like to remind you that all information will be kept strictly confidential. Only a questionnaire number will be associated with the information you give us. No personal information that could identify you will be left on the questionnaires once they are returned to the research office.

We hope that you will fill out and return the questionnaire soon using the stamped envelope provided. If, for any reason, you prefer not to answer it, please let us know by returning a note or blank questionnaire in the enclosed stamped envelope.

Appendix I: PedsQL™ Multidimensional Fatigue Scale (Child Self-Report)

*In the past **ONE month,** how much of a **problem** has this been for you…*

GENERAL FATIGUE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel tired	0	1	2	3	4
2. I feel physically weak (not strong)	0	1	2	3	4
3. I feel too tired to do things that I like to do	0	1	2	3	4
4. I feel too tired to spend time with my friends	0	1	2	3	4
5. I have trouble finishing things	0	1	2	3	4
6. I have trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I sleep a lot	0	1	2	3	4
2. It is hard for me to sleep through the night	0	1	2	3	4
3. I feel tired when I wake up in the morning	0	1	2	3	4
4. I rest a lot	0	1	2	3	4
5. I take a lot of naps	0	1	2	3	4
6. I spend a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4
6. I have trouble remembering more than one thing at a time	0	1	2	3	4

Appendix J: PedsQL™ Multidimensional Fatigue Scale (Parent Proxy-Report)

*In the past **ONE month**, how much of a **problem** has this been for **your child**…*

GENERAL FATIGUE (*problems with…*)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
7. Feeling tired	0	1	2	3	4
8. Feeling physically weak (not strong)	0	1	2	3	4
9. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
10. Feeling too tired to spend time with his/her	0	1	2	3	4
11. Trouble finishing things	0	1	2	3	4
12. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE (*problems with…*)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
7. Sleeping a lot	0	1	2	3	4
8. Difficulty sleeping through the night	0	1	2	3	4
9. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
10. Resting a lot	0	1	2	3	4
11. Taking a lot of naps	0	1	2	3	4
12. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE (*problems with…*)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
7. Difficulty keeping his/her attention on things	0	1	2	3	4
8. Difficulty remembering what people tell him/her	0	1	2	3	4
9. Difficulty remembering what he/she just heard	0	1	2	3	4
10. Difficulty thinking quickly	0	1	2	3	4
11. Trouble remembering what he/she was just thinking	0	1	2	3	4
12. Trouble remembering more than one thing at a time	0	1	2	3	4

Appendix K: Physical Activity Questionnaire for Children

We are trying to find out about your level of physical activity from ***THE LAST 7 DAYS*** **(IN THE LAST WEEK).** This includes sports or dance that make you sweat or make your legs or arms feel tired, or games that make you breathe hard, like tag, skipping, running, climbing, and others.

We understand that the mobility and strength of children with Duchenne muscular dystrophy may be limited and may prevent you from participating in physical activities to the same extent as your peers. However, we are interested in any and all activities that ***you*** consider to be physically active.

Remember:

1. There are no right and wrong answers—this is not a test
2. Please answer all the questions as honestly and accurately as you can—this is very important.

---

1. Physical activity in your spare time: Have you done any of the following activities in the past 7 days (last week)? If yes, how many times? (Check only one box per row.)

	No	**1–2**	**3–4**	**5–6**	**7 times or more**
Skipping	☐	☐	☐	☐	☐
Rowing/canoeing	☐	☐	☐	☐	☐
In-line skating	☐	☐	☐	☐	☐
Tag	☐	☐	☐	☐	☐
Walking for exercise	☐	☐	☐	☐	☐
Bicycling	☐	☐	☐	☐	☐
Jogging or running	☐	☐	☐	☐	☐
Aerobics	☐	☐	☐	☐	☐
Swimming	☐	☐	☐	☐	☐
Baseball, softball	☐	☐	☐	☐	☐
Dance	☐	☐	☐	☐	☐
Football	☐	☐	☐	☐	☐
Badminton	☐	☐	☐	☐	☐
Skateboarding	☐	☐	☐	☐	☐
Soccer	☐	☐	☐	☐	☐
Street hockey	☐	☐	☐	☐	☐
Basketball	☐	☐	☐	☐	☐
Ice skating	☐	☐	☐	☐	☐
Cross-country skiing	☐	☐	☐	☐	☐
Ice hockey/ringette	☐	☐	☐	☐	☐
Other:					
_____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐

2. In the last 7 days, during your physical education (PE) classes, how often were you very active (playing hard, running, jumping, throwing)? (Check one only.)

☐ I don't do PE
☐ Hardly ever
☐ Sometimes
☐ Quite often
☐ Always

3. In the last 7 days, what did you do most of the time *at recess*? (Check one only.)

- ☐ Sat down (talking, reading, doing schoolwork)
- ☐ Stood around or walked around
- ☐ Ran or played a little bit
- ☐ Ran around or played quite a bit
- ☐ Ran or played hard most of the time

4. In the last 7 days, what did you normally do *at lunch* (besides eating lunch)? (Check one only.)

- ☐ Sat down (talking, reading, doing schoolwork)
- ☐ Stood around or walked around
- ☐ Ran or played a little bit
- ☐ Ran around or played quite a bit
- ☐ Ran or played hard most of the time

5. In the last 7 days, on how many days *right after school*, did you do sports, dance, or play games in which you were very active? (Check one only.)

- ☐ None
- ☐ 1 time last week
- ☐ 2 or 3 times last week
- ☐ 4 times last week
- ☐ 5 times last week

6. In the last 7 days, on how many *evenings* did you do sports, dance, or play games in which you were very active? (Check one only.)

- ☐ None
- ☐ 1 time last week
- ☐ 2 or 3 times last week
- ☐ 4 or 5 times last week
- ☐ 6 or 7 times last week

7. *On the last weekend*, how many times did you do sports, dance, or play games in which you were very active? (Check one only.)

- ☐ None
- ☐ 1 time
- ☐ 2 or 3 times
- ☐ 4 or 5 times
- ☐ 6 or more times

8. Which *one* of the following describes you best for the last 7 days? Read *all five* statements before deciding on the *one* answer that describes you.

- ☐ All or most of free time was spent doing things that involve little physical effort
- ☐ I sometimes (1–2 times last week) did physical things in my free time (e.g. played sports, went running, swimming, bike riding, did aerobics)
- ☐ I often (3–4 times last week) did physical things in my free time
- ☐ I quite often (5–6 times last week) did physical things in my free time
- ☐ I very often (7 or more times last week) did physical things in my free time

9. Mark how often you did physical activity (like playing sports, games, doing dance, or any other physical activity) for each day last week.

	None	Little bit	Medium	Often	Very often
Monday	☐	☐	☐	☐	☐
Tuesday	☐	☐	☐	☐	☐
Wednesday	☐	☐	☐	☐	☐
Thursday	☐	☐	☐	☐	☐
Friday	☐	☐	☐	☐	☐
Saturday	☐	☐	☐	☐	☐
Sunday	☐	☐	☐	☐	☐

10. Were you sick last week, or did anything prevent you from doing your normal physical activities? (Check one.)

☐ No
☐ Yes

→ If **yes**, please specify in the box below:

11. Think about the past 7 days (last week) in comparison to other usual weeks. Were you ***more*** physically activity last week than you normally would be in a typical week?

☐ No
☐ Yes

Appendix L: Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool

Please complete this section with your child. The questions below describe levels of activity for arm function, mobility, transfers, and need for ventilatory support. The activities are intended to be in order of difficulty and we would like you to check the box that best applies to **your child's** current level of function.

Question 1: Arm function	*Select one*
Can put an item, such as a book, onto a shelf above shoulder height	☐
Can eat a meal without any help	☐
Needs help to cut up food, but can feed and drink independently	☐
Needs help to drink or feed self	☐
Can pick objects up e.g. pen/money	☐
Can move fingers e.g. press on mobile or other electronic device	☐
Cannot move fingers	☐

Question 2: Mobility	*Select one*
Walks independently long distances outdoors (more than 1 km)	☐
Walks independently medium distances outdoors (less than 1 km)	☐
Walks outdoors for short distances e.g. to car with or without help from a person	☐
Walks indoors with or without help from a person, but requires wheelchair for outdoors	☐
Uses wheelchair indoors and outdoors	☐
Uses wheelchair indoors and outdoors, but unable in some situations e.g. cold weather or unable to control wheelchair without help	☐

Question 3 to 7: Transfers	*Can do independently*	*Can do with help*	*Needs to be lifted or hoisted or cannot*
Get on and off the floor	☐	☐	☐
Get in and out of a chair	☐	☐	☐
Get in and out of bed	☐	☐	☐
Get on and off the toilet	☐	☐	☐
Go up and down stairs	☐	☐	☐

Question 8: Ventilatory support	*Not ventilated*	*Ventilated at night*	*Ventilated during day and night*
Ventilatory status	☐	☐	☐

Appendix M: Center for Epidemiological Studies Depressive Scale for Children

INSTRUCTIONS: Below is a list of the ways you might have felt or acted. Please check how *much* you have felt this way during the **past week.**

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating, I wasn't very hungry.	☐	☐	☐	☐
3. I wasn't able to feel happy, even when my family or friends tried to help me feel better.	☐	☐	☐	☐
4. I felt like I was just as good as other kids.	☐	☐	☐	☐
5. I felt like I couldn't pay attention to what I was doing.	☐	☐	☐	☐

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
6. I felt down and unhappy.	☐	☐	☐	☐
7. I felt like I was too tired to do things.	☐	☐	☐	☐
8. I felt like something good was going to happen.	☐	☐	☐	☐
9. I felt like things I did before didn't work out right.	☐	☐	☐	☐
10. I felt scared.	☐	☐	☐	☐

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
11. I didn't sleep as well as I usually sleep.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I was more quiet than usual.	☐	☐	☐	☐
14. I felt lonely, like I didn't have any friends.	☐	☐	☐	☐
15. I felt like kids I know were not friendly or that they didn't want to be with me.	☐	☐	☐	☐

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
16. I had a good time.	☐	☐	☐	☐
17. I felt like crying.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt people didn't like me.	☐	☐	☐	☐
20. It was hard to get started doing things.	☐	☐	☐	☐

Appendix N: Sleep Disturbance Scale for Children

INSTRUCTIONS: This questionnaire will allow to your doctor to have a better understanding of the sleep-wake rhythm of **<u>your child</u>** and of any problems in his/her sleep behavior. Try to answer every question; in answering, consider each question as pertaining to the **past 6 months** of the child's life. Please answer the questions by circling the number 1 to 5. Thank you very much for your help.

1. How many hours of sleep does your child get on most nights?	1 ***9-11 hrs***	2 ***8-9 hrs***	3 ***7-8 hrs***	4 ***5-7 hrs***	5 ***Less than 5 hrs***
2. How long after going to bed does your child usually fall asleep?	1 ***Less than 15 min***	2 ***15-30 min***	3 ***30-45 min***	4 ***45-60 min***	5 ***More than 60 min***

					5 **Always (daily)**
				4 **Often (3 or 5 times per week)**	
			3 **Sometimes (once or twice per week)**		
		2 **Occasionally (once or twice per month or less)**			
	1 **Never**				
3. The child goes to bed reluctantly	1	2	3	4	5
4. The child has difficulty getting to sleep at night	1	2	3	4	5
5. The child feels anxious or afraid when falling asleep	1	2	3	4	5
6. The child startles or jerks parts of the body while falling asleep	1	2	3	4	5
7. The child shows repetitive actions such as rocking or head banging while falling asleep	1	2	3	4	5
8. The child experiences vivid dream-like scenes while falling asleep	1	2	3	4	5
9. The child sweats excessively while falling asleep	1	2	3	4	5
10. The child wakes up more than twice per night	1	2	3	4	5
11. After waking up in the night, the child has difficulty to fall asleep again	1	2	3	4	5
12. The child has frequent twitching or jerking of legs while asleep or often changes position during the night or kicks the covers off the bed.	1	2	3	4	5
13. The child has difficulty in breathing during the night	1	2	3	4	5
14. The child gasps for breath or is unable to breathe during sleep	1	2	3	4	5
15. The child snores	1	2	3	4	5
16. The child sweats excessively during the night	1	2	3	4	5
17. You have observed the child sleepwalking	1	2	3	4	5
18. You have observed the child talking in his/her sleep	1	2	3	4	5
19. The child grinds teeth during sleep	1	2	3	4	5
20. The child wakes from sleep screaming or confused so that you cannot seem to get through to him/her, but has no memory of these events the next morning	1	2	3	4	5
21. The child has nightmares which he/she doesn't remember the next day	1	2	3	4	5
22. The child is unusually difficult to wake up in the morning	1	2	3	4	5
23. The child awakes in the morning feeling tired	1	2	3	4	5
24. The child feels unable to move when waking up in the morning	1	2	3	4	5
25. The child experiences daytime somnolence	1	2	3	4	5
26. The child falls asleep suddenly in inappropriate situations	1	2	3	4	5

Appendix O: Patient Medical Information Section

We would like to ask you a few questions ask about some other health experiences **your child** may have had.

1. Has your child ever been formally diagnosed with any of the following developmental disorders?

	No	**Yes**
Developmental Delay		
A Learning Disability		
Attention Deficit Disorder (ADD) or Attention Deficient Hyperactivity Disorder (ADHD)		
Autism, Pervasive Developmental Disorder (PDD) or Asperger's Syndrome		
Oppositional Defiant Disorder		
Conduct Disorder		
Depression		
Anxiety		

2. Does your child have any of the following health conditions?

	No	**Yes**
Asthma		
Cystic Fibrosis		
Diabetes		
Cerebral Palsy		
Epilepsy		
Cancer		
Any other long-term health conditions. Please specify:		

3. For each of the following, please provide 2 answers. Whether your child has a) ever needed and b) ever received:

	a) Ever Needed		b) Ever Received	
	No	**Yes**	**No**	**Yes**
Extra help with schoolwork (e.g. tutoring, working with a special education resource teacher, having an Individualized Educational Program). Please specify:				
Placement in a special class for children with learning difficulties.				
Speech-language therapy				
Occupational therapy				
Medication or therapy for behaviour problems. Please specify:				
Medication or therapy for emotional problems (e.g. depression). Please specify:				

4. Is your child currently involved in any clinical trials or other research studies for his Duchenne muscular dystrophy?
   - ☐ No
   - ☐ Yes

5. Is your child able to walk?
   - ☐ No
   - ☐ Yes

   → If **no**, when did your child stop walking?
   - ☐ Less than 1 year ago
   - ☐ More than 1 year ago

6. Have there been any major changes in your child's health within the last year (e.g. major illness, hospitalization, etc.)?
   - ☐ No
   - ☐ Yes

   → If **yes**, please specify in the box below:

Appendix P: Sociodemographic Information Section

1. Are you:

☐ Male
☐ Female

2. Who currently lives with your child? Please do not use any people's names when completing the table below:

Person	Their relationship to your child (e.g. Mom, Dad, brother, sister, grandparent, aunt, uncle, friend, roommate, partner/spouse)	Their Age	Their Sex
1			☐ Male ☐ Female
2			☐ Male ☐ Female
3			☐ Male ☐ Female
4			☐ Male ☐ Female
5			☐ Male ☐ Female
6			☐ Male ☐ Female
7			☐ Male ☐ Female
8			☐ Male ☐ Female

3. Which of the following best describes your current work status? Check one box only.

☐ Not working due to my child's health
☐ Not working for "other" reasons
☐ Looking for work outside the home
☐ Working full- or part-time (either outside the home or at a home-based business)
☐ Full time homemaker
☐ Student

4. What is your relationship to this child? Check one box only.

☐ Biological parent
☐ Step parent
☐ Foster parent
☐ Adoptive parent
☐ Guardian
☐ Other (please explain on the line below)

_____

5. What is the highest grade of school you have completed?
   - ☐ Less than 8 years
   - ☐ 8 to 12 years
   - ☐ Completed high school
   - ☐ Completed vocational/technical training
   - ☐ Completed college/university
   - ☐ Completed graduate school
   - ☐ Prefer not to disclose

6. What is your age? ☐☐

7. What is your current marital status? Check one box only.

☐ Married	☐ Widowed	☐ Divorced	☐ Separated	☐ Remarried	☐ Never married

8. Are you currently living with a spouse or partner?
   - ☐ No → If **no**, skip to question **11**.
   - ☐ Yes → If **yes**, proceed to question **9**.

9. Which of the following best describes your spouse's/partner's current work status? Check one box only.

☐ Not working due to my child's health	☐ Not working for "other" reasons	☐ Looking for work outside the home	☐ Working full- or part-time (either outside the home or at a home-based business)	☐ Full time homemaker	☐ Student

10. What is the highest grade of school your spouse/partner has completed?
    - ☐ Less than 8 years
    - ☐ 8 to 12 years
    - ☐ Completed high school
    - ☐ Completed vocational/technical training
    - ☐ Completed college/university
    - ☐ Completed graduate school
    - ☐ Prefer not to disclose

11. In which category is your total yearly household income before taxes? Check one box only.

- ☐ Less than $5,000
- ☐ $5,000 to $9,999
- ☐ $10,000 to $14,999
- ☐ $15,000 to $19,999
- ☐ $20,000 to $24,999
- ☐ $25,000 to $ 34,999
- ☐ $35,000 to $49,999
- ☐ $50,000 to $74,999
- ☐ $75,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 to $200,000
- ☐ Over $200,000
- ☐ I don't know

12. Thinking about your total family income, from which sources did your family receive income during the past year? Check all that apply.

- ☐ Wages and salaries
- ☐ Income from self-employment
- ☐ Family allowance (baby bonus)
- ☐ Unemployment insurance or strike pay
- ☐ Worker's compensation
- ☐ Old Age Security, Guaranteed Income Supplement, Canada or Quebec Pension Plan, Retirement Pension Plan, Superannuation
- ☐ Dividends and interest on bonds, deposits and saving certificates
- ☐ Other government sources such as welfare, mother's allowance, etc.
- ☐ Other source(s). Please specify: _____
- ☐ Prefer not to disclose

Curriculum Vitae

Name Basmah El-Aloul

Education

The University of Western Ontario (Western University)
London, Ontario, Canada
2011–2015 BMSc
Honors Specialization in Medical Sciences with distinction
Minor in Pharmacology

Western University
London, Ontario, Canada
2015–2017 MSc in Epidemiology & Biostatistics

Honours & Awards

Children's Health Research Institute Quality of Life Initiative Graduate Research Fellowship
2015–2016; 2016–2017

Related Work Experience

Graduate Teaching Assistant
Western University
2015–2017

Publications

El-Aloul, B., Altamirano-Diaz, L., Zapata-Aldana, E., Rodrigues, R., Malvankar, M., Nguyen, C., Campbell, C. Pharmacological therapy for the prevention and management of cardiomyopathy in Duchenne muscular dystrophy: a systematic review. *Neuromuscular Disorders*. 2017;27:4–14

Conference Presentations
italics = presenter(s)

1. ***El-Aloul, B.***, Wei Y., Speechley, K., *Campbell, C*. Factors associated with fatigue in children and adolescents with Duchenne muscular dystrophy: A Canada-wide cross-sectional survey.
    a. Poster Presentation at the Canadian Neurological Sciences Federation, 52nd Annual Congress, Victoria, British Columbia, Canada. (2017, June).
    b. Poster Presentation at the Child Health Symposium, Thames Valley Children's Centre, Western University, London, Ontario, Canada. (2017, May).
    c. Poster Presentation at the Department of Paediatrics 30th Annual Research Day, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada. (2017, May).

2. *Wei, Y.*, **El-Aloul, B.**, Nguyen, C., Zapata-Aldana, E., Campbell, C. The relationship between fatigue and health-related quality of life in a clinical trial population of

Duchenne muscular dystrophy patients. Oral Presentation at the Canadian Neurological Sciences Federation, 52nd Annual Congress, Victoria, British Columbia, Canada. (2017, June).

3. *Rogers, S.*, **El-Aloul, B.**, *Ceballos-Saenez, D.*, Hicks, R., Bax, K., Zapata-Aldana, E, Pucillo, E., Dibella, D., Johnson, N., Campbell, C. Factors associated with health-related quality of life in children with congenital myotonic dystrophy.
    a. Poster Presentation at the Canadian Paediatric Society 94th Annual Conference, Vancouver, British Columbia, Canada. (2017, June).
    b. Poster Presentation at the Child Health Symposium, Thames Valley Children's Centre, Western University, London, Ontario, Canada. (2017, May)
    c. Poster Presentation at the Department of Paediatrics 30th Annual Research Day, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada. (2017, May).
    d. Poster Presentation at London Health Research Day, London, Ontario, Canada. (2017, May).

4. *Nowicki, M.*, Hicks, R., Pearlman, L., Hutchison, J., **El-Aloul, B.**, Campbell C. Validity of the Agitated Behavior Scale in Paediatric Traumatic Brain Injury. Poster Presentation at London Health Research Day, London, Ontario, Canada. (2017, May).

5. *Rodrigues, R.*, **El-Aloul, B.**, Anderson, K. The traumatic experience of first episode psychosis: a systematic review and meta-analysis.
    a. Poster presentation at Canadian Academy of Psychiatric Epidemiology Annual Scientific Symposium, Toronto, Ontario, Canada. (2016, September).
    b. Oral presentation at Department of Psychiatry Academic Research Day, Schulich School of Medicine & Dentistry, London, Ontario, Canada. (2016, June).
    c. Poster presentation at London Health Research Day, London, Ontario, Canada. (2016, March).

6. ***El-Aloul, B.***, Rodrigues, R., Altamirano-Diaz, L., Malvankar, M., Nguyen, C., Campbell, C. Pharmacological therapy for the prevention and management of cardiomyopathy in Duchenne muscular dystrophy: a systematic review. Oral presentation at Canadian Neurological Sciences Federation, 51st Annual Congress, Quebec City, Quebec, Canada. (2016, June)

7. *Wei, Y.*, **El-Aloul B.**, Campbell, C. Duchenne muscular dystrophy: the impact on parental health-related quality of life and family functioning. Oral presentation at Child Health Symposium, Thames Valley Children's Centre, Western University, London, Ontario, Canada. (2016, May).