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Quality of Life and Health-Related Quality of Life in Children with Duchenne Muscular Dystrophy

Yi Wei, *The University of Western Ontario*

Supervisor: Dr. Craig Campbell, *The University of Western Ontario*
Joint Supervisor: Dr. Kathy Speechley, *The University of Western Ontario*
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QUALITY OF LIFE AND HEALTH-RELATED QUALITY OF LIFE IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY

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by

Yi Sally Wei

Graduate Program in Epidemiology and Biostatistics

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The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

Abstract

Quality of life studies in Duchenne Muscular Dystrophy are scarce. This study explores the relationship between the broad concept of quality of life and the more focused concept of health-related quality of life and examines the relationships between patient and family characteristics and health-related quality of life. Participants were recruited from the Canadian Neuromuscular Disease Registry, 98 parents and 85 children completed the Quality of My Life and Pediatric Quality of Life Inventory questionnaires. Simple regression was used to examine the relationship between quality of life and health-related quality of life. Multivariable linear regressions were used to determine child and family characteristics associated with health-related quality of life outcomes. Higher levels of subjective fatigue and use of wheelchair emerged as factors most consistently associated with lower levels health-related quality of life. Interventions to reduce fatigue could lead to improvement of health-related quality of life for children with Duchenne Muscular Dystrophy.

Keywords

Duchenne muscular dystrophy, health-related quality of life, quality of life, cross-sectional study, registry, parent proxy, child self, multivariable regression, fatigue

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List of Abbreviations

CHQ – Child Health Questionnaire

CNDR – Canadian Neuromuscular Disease Registry

DMD - Duchenne Muscular Dystrophy

HRQOL – Health-related Quality of life

FILE – Family Inventory of Life Events

FVC- Forced vital capacity

LVEF- Left ventricular ejection volume

MCID- Minimally clinically important difference

PedsQL- Pediatric Quality of Life Inventory

PODCI – Pediatric Outcomes Data Collection Instrument

QOL- Quality of life

QoML- Quality of My Life questionnaire

SMA- Spinal muscular atrophy

VAS- Visual analogue scale

Chapter 1

Introduction and Research Objectives

1.1 Overview of thesis

Duchenne Muscular Dystrophy (DMD) is a progressive, chronic neuromuscular disorder, affecting 1 in 5,000 boys. It is characterized by gradual loss of muscle strength resulting in profound physical disability and premature death. Due to the life-limiting and chronic nature of this disease, maximizing quality of life in these children is of the utmost importance. This thesis aims to provide a comprehensive description of quality of life and health-related quality of life in children with DMD from the children's and parents' perspectives. Furthermore, the relationship between the broader concept of quality of life and the narrower concept of health-related quality of life is investigated. Finally, this thesis explores the clinical and demographic factors associated with quality of life and health-related quality of life in children with DMD.

1.2 Background

1.2.1 Quality of life and health-related quality of life in children with chronic illnesses

Advances in medicine have expanded the focus of healthcare from extending life to also include improving quality of life. The World Health Organization Quality of Life group has defined quality of life as an 'individual's perception of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns' ("The World Health Organization quality of life assessment (WHOQOL)," 1995). Health-related quality of life (HRQOL) narrows the scope of quality of life (QOL) and focuses specifically on the impact of illness and treatments on a person's life (De Civita et al., 2005; Guyatt et al., 1993; Spieth & Harris, 1996). HRQOL does not pertain to aspects of life such as environmental quality and political stability (Guyatt et al., 1993; Taylor et al., 2008), which are important, but

cannot be influenced by healthcare intervention. The primary focus of this thesis is on HRQOL, with one component aimed at distinguishing and exploring the relationship between QOL and HRQOL. Although there has not been a complete consensus on the operational definition of HRQOL, two recurrent characteristics that underlie most measurements of HRQOL have emerged: they are subjective and multidimensional (Matza et al., 2004). Subjectivity refers to the fact that HRQOL measures patient's own perception of their health or life, in contrast with objective clinical measures such as blood pressure; multidimensionality refers to measurement of HRQOL from multiple aspects of a person's life, for example, the physical, psychological and social aspects.

Rationale for studying HRQOL in children with chronic illnesses

As survival rates and life expectancy for many childhood illnesses increase, improvement in quality of life for these children becomes increasingly important. The rationale for studying HRQOL in children with chronic illnesses is manifold. First, HRQOL is an important component of outcome assessment and provides information not captured by traditional clinical measures. More often, patient-reported outcomes such as HRQOL are being recognized as important end-points of clinical trials in conjunction with traditional clinical measures (Drotar, 2004; Eiser & Morse, 2001a). Apart from clinical trials, HRQOL measures may also be used to evaluate the success of interventions and services in clinical settings (Eiser & Morse, 2001a). Second, while traditional medical care tends to rely on physiological measurements such as blood pressure, there are evidence that these measures are not always of the most importance to patients (Guyatt et al., 1993; Ronen et al., 2011). Furthermore, physiological measures do not necessarily correlate well with subjective well-being. Two patients who exhibit the same physical symptoms may have very different subjective experiences (Eiser & Morse, 2001a; Guyatt et al., 1993).Thus, management of physical symptoms is no longer sufficient in the treatment of a chronic illness. HRQOL studies allow researchers and clinicians to elucidate the determinants of HRQOL, identify risk factors for poor HRQOL, and ultimately improve HRQOL, which some have argued is the ultimate goal of managing chronic illnesses (Eiser & Morse, 2001b; Payot & Barrington, 2011).

Considerations in assessing QOL and HRQOL in children

There are a number of conceptual and methodological considerations when studying childhood QOL and HRQOL. Three of these considerations: the distinction between quality of life and health-related quality of life; the existence of generic and disease-specific measures, and the existence of child and parent reports, are discussed below.

Quality of life and health-related quality of life

Quality of life and health-related quality of life are terms that are often used interchangeably, but in fact represent different concepts. A systematic review of paediatric QOL and HRQOL measures (Davis et al., 2006) identified eleven different definitions of QOL and HRQOL across fourteen generic and 25 disease specific measures. Although it is recognized that there should be distinction between QOL and HRQOL, few studies have empirically differentiated these two concepts (Davis et al., 2006; De Civita et al., 2005; Eiser & Morse, 2001a; Gill & Feinstein, 1994; Guyatt et al., 1993; Ronen et al., 2011). It has been suggested that two global ratings, one for overall QOL, and one for HRQOL be used (Gill & Feinstein, 1994). Despite these recommendations, to our knowledge, there is only one example in paediatric patients where the distinction between QOL and HRQOL has been examined. Feldman *et al.* (2000) designed the Quality of My Life (QoML) questionnaire to ask children and their parents to rate the child's 'overall' quality of life (QOL) and their quality of life 'considering my health' (HRQOL) and found that both children and their parents differentiated between these two constructs, and that HRQOL only explained 30% of the variability in QOL. This was done in a sample of children being treated for rheumatoid arthritis. Thus, there exist empirical support for the distinction between QOL and HRQOL.

Another reason for examining the relationship between QOL and HRQOL is the notion of 'disability paradox', which is the phenomenon whereby people with disabilities report good or excellent QOL, when external observers might assume they have quite poor QOL (Albrecht & Devlieger, 1999). As part of the development of the QoML measure, Feldman *et al*. (2000) conducted qualitative debriefing with children and parents, many

of whom reported that health contributed only in small part to overall QOL. People may attach different weights to the various aspects they deem to contribute to their QOL. Therefore it is possible for someone to have good or excellent QOL despite poorer HRQOL and it is reasonable to assume that the relationship between the two may change at different stages of disease progression. Determining the factors that contribute to QOL beyond HRQOL is especially important to patients with DMD, where physical deterioration is inevitable but a good QOL may be achievable.

Generic and disease-specific measures

HRQOL measures can be divided into generic and disease-specific. Generic measures are applicable across different disease populations and thus are often used to compare of HRQOL in groups with various diseases and to those in the general population. Disease-specific questionnaires include items that are pertinent to a particular condition. Compared to generic measures, disease-specific measures have greater sensitivity and specificity, and are better at detecting treatment effects and changes across time (Eiser & Morse, 2001a; Quittner et al., 2003; Spieth & Harris, 1996), however, they do not allow for comparison to other disease groups or to a general population. Therefore, it has been recommended that both disease–specific and generic measures be used in a complementary fashion (Spieth & Harris, 1996).

Child self-reports and parent proxy-reports

Assessing QOL and HRQOL in children has its unique challenges. Children were once considered incapable of reliably reporting their own QOL or HRQOL out of concerns they were not cognitively able to understand measures of QOL or HRQOL, and parent-proxy measures were used instead (Eiser & Morse, 2001c; Quittner et al., 2003). However, it has since been recognized that children, like adults, are the best informants on their own subjective experiences and should report their own QOL and HRQOL whenever possible. There are evidence supporting the reliability and validity of children's report of their health state (Drotar, 2004). Children as young as five have been found able to reliably report their HRQOL (Varni et al., 2007a). Furthermore, parents may not always be able to accurately interpret their children's emotional state or be able to

directly observe their social interactions (Quittner et al., 2003). On the other hand, in situations where the child is too young, sick or cognitively impaired to report their QOL and HRQOL, parent-proxy measures need to be used. In addition, parent reports are still important because of parents' influence on healthcare decisions for their children (Palermo et al., 2008). Both child and parent perspectives offer unique information and thus it has been recommended that QOL and HRQOL be collected from multiple informants (Drotar, 2004; Eiser & Morse, 2001d; Palermo et al., 2008).

1.2.2 Duchenne Muscular Dystrophy

Genetics and pathology

Duchenne Muscular Dystrophy (DMD) is the most common and severe form of childhood muscular dystrophy. It is the result of mutations in the dystrophin gene, located on the X-chromosome (Hoffman et al., 1988). Due to the X-linked mode of inheritance, almost all affected individuals are male. The incidence for DMD is estimated to be in the range of 1 in 3600-6000 live-born male infants (Emery, 1991). A retrospective study carried out in Nova Scotia found that the incidence of DMD has remained stable between the years of 1969 and 2008 (Dooley et al., 2010).

Dystrophin proteins are thought to play a structural role in muscle cell membrane, maintaining its integrity. Absence of dystrophin results in muscle cells being more prone to damage from mechanical stress (Deconinck & Dan, 2007; McDonald et al., 1995). In DMD patients, skeletal muscles are affected at birth, but most boys do not show symptoms of the disease until they are between 3 to 5 years of age. With increasing availability and efficiency of molecular technology, genetic testing has become the gold standard diagnostic tool (Bushby et al., 2010a).

Clinical features

Progressive muscle weakness

Proximal, lower extremity muscles are the first to show signs of degeneration. As muscle deterioration progresses, the boys lose ambulation. Age of loss ambulation has historically been between the ages of 7 to 12 (Biggar, 2006; Brooke et al., 1989). Loss of

ambulation happens rapidly, over the span of a few weeks to a few months. By mid-teens, almost all boys are in wheelchairs. As the disease progresses, the affected individual becomes gradually weaker in the upper limbs, eventually losing the ability to perform daily activities. It has been thought that there are two 'plateaus' in the progression of DMD: the period between diagnosis and loss of ambulation and the period from loss of ambulation to significant cardio and respiratory compromises. During these plateau phases, the health of the child with DMD can remain relatively stable.

Throughout the progression of DMD, initial diagnosis and loss of ambulation are perhaps the two most life-altering events faced by the affected child and his family. Parents report that they are overwhelmed and devastated by the diagnosis of DMD in their child (Green & Murton, 1996), often more so than the children themselves. Parents have also reported experiencing increased stress and emotional upheaval around the time their son loses ambulation (Bothwell et al., 2002; Bray et al., 2011; Erby et al., 2006). However, as with any other major stress, families adjust to it (McCubbin & McCubbin, 1993). The periods immediately after diagnosis and after loss of ambulation may be particularly vulnerable times for the child and his family and warrant closer scrutiny.

Orthopedic complications

One of the most concerning complications related to DMD is the development of scoliosis. Various studies have reported that between 74% and 100% of DMD subjects develop scoliosis (Muntoni et al., 2006). In addition to causing discomfort, scoliosis further impedes respiratory function, which is already compromised in DMD patients. Bone fractures are common, occurring in 21% to 44% of boys (Kornberg & Yiu, 2008). Some patients have lost mobility permanently due to bone fractures (McDonald et al., 2002). Taken together, these complications indicate bone health of boys with DMD is compromised, and may have serious impact on their quality of life.

Pulmonary function decline

Boys with DMD begin to experience respiratory problems between the ages of 9 and 11 years due to loss of respiratory muscle strength. Respiratory insufficiency first manifests during sleep, boys with DMD may experience sleep apnea, decreased quality of sleep or

frequent wakening throughout the night (Polat et al., 2012). Along with muscular deterioration, vital capacity further decreases. Eventually, all boys require assisted ventilation, usually in the form of nocturnal bilevel positive airway pressure (BiPAP) to support their breathing (Biggar, 2006).

Cardiomyopathy

Cardiac muscles are affected in DMD patients. Cardiomyopathies may often be subclinical in younger boys due to the boys' lack of strenuous activities and thus low demand placed on the heart. However, as cardiac muscles weakens further, the likelihood of symptomatic cardiomyopathies increases. One study reports that clinically apparent cardiac problems are present in one-third of DMD patients by 14 years of age, and present in all patients over 18 years of age (Nigro et al., 1990).

Cognitive delay and psychological functioning

The prevalence of intellectual disability in the Duchenne population is higher in the general population. Dystrophin is expressed in the central nervous system in a number of different isoforms, regulated by different promoters (Mehler, 2000). There is evidence that mutations in specific regulatory regions in these brain isoforms are linked with mental retardation (Bardoni et al., 2000). There is also evidence of increased likelihood of being diagnosed with a developmental disorder such as attention deficit hyperactivity disorder or autism (Hendriksen & Vles, 2008). While boys with DMD are more likely to exhibit cognitive and psychosocial deficits, there is still great variability within this population. The extent of heterogeneity in intellectual and psychological deficits is greater than in motor deficits in boys with DMD.

Survival

The most common cause of death for Duchenne patients is respiratory failure, followed by heart failure (Finsterer, 2006). As with many other diseases, improvement in medical technology and quality of care has increased survival in DMD patients. The mean life expectancy has increased from 14 years of age in the 1960s to 25 years of age in the 1990s (Eagle et al., 2002; Passamano et al., 2012).

Treatment and Care

Glucocorticoids

There is no cure for Duchenne muscular dystrophy. The most commonly prescribed medications are glucocorticoids, which have become the standard of practice in treating DMD. Long term cohort studies have shown that glucocorticoids can prolong ambulation for up to five years (Moxley et al., 2010). While glucocorticoids have obvious benefits, they also have serious side-effects. one of the most common side-effects is weight gain, and it can lead adverse health consequences such as increased incidence of sleep apnea and increased burden on the respiratory system (McMillan et al., 2010). Other adverse effects include increase risk of fracture, growth retardation, delayed puberty, behavioral changes, and immune suppression (Ay et al., 2009; Bushby et al., 2010a; Moxley et al., 2010).

Multidisciplinary care

Due to the multi-systemic nature of the disease, it has been recommended that children with DMD be followed up in multidisciplinary clinics where comprehensive care can be provided by a variety of specialists (Bushby et al., 2010b). In Canada, paediatric neuromuscular clinics exist across the country and care teams are composed of neurologists, respirologists, physical therapists and other health care professionals (McMillan et al., 2010). Patients visit clinics every 6 to 12 months, and in addition to receiving management of muscle deterioration, are monitored routinely for orthopedic, respiratory and cardiac abnormalities so that complications can be managed as they arise.

DMD patients experience gradual loss of respiratory muscle, resulting in hypoventilation, particularly during sleep. Non-invasive positive pressure assisted ventilation is normally the first step in providing respiratory support to DMD patients (McMillan et al., 2010). Cardiac function is monitored regularly via electrocardiogram and echocardiogram. Dilated cardiomyopathies are treated with angiotensin converting enzyme inhibitors and beta-blockers (Bushby et al., 2010b; Finsterer, 2006).

While pharmaceutical and technological interventions have improved quantity and quality of life for Duchenne patients over the past few decades, the disease remains a

relentlessly progressive one that is devastating for the affected child and his family. In the past decade, with the advancement of molecular techniques, many therapies that show promise in the treatment of DMD have emerged. As more of these therapies undergo clinical trials, proper assessment of trial outcomes is crucial.

1.3 Objectives

The literature assessing QOL and HRQOL in children with DMD is scarce. The available studies have several limitations that will be discussed in more detail in the next chapter. Briefly, many of these studies have small sample sizes, uses only parent-reported HRQOL and draw samples from a single clinic. Furthermore, almost all studies are descriptive, and do not examine potential determinants of HRQOL.

There is a need for a more comprehensive examination of QOL and HRQOL in children with DMD from both children's and parents' perspectives, using general and disease-specific measures. Examining the relationship between QOL and HRQOL will allow us to gain a better understanding of the role health plays in overall QOL. Exploring factors that are associated with HRQOL would allow us to identify potential determinants of HRQOL that could contribute to improvement of HRQOL. With these gaps of knowledge in mind, the objectives of this thesis are:

1. Describe the QOL and HRQOL in a sample of boys with DMD in Canada from both children's and parents' perspectives.

2. Examine the relationship between QOL and HRQOL**.**

   Hypothesis: QOL and HRQOL will be rated as distinct but related concepts by boys with DMD and their parents.

3. Explore child and family characteristics that contribute to any difference between QOL and HRQOL.

   Hypothesis: Family characteristics relating to social economic status will be associated with the difference between QOL and HRQOL.

4. Explore associations of child and family characteristics with multidimensional measures of HRQOL.

   Hypothesis: Age and ambulation status will be associated with the physical component and the total component of a multidimensional measure of HRQOL; family stress will be significantly associated with the psychosocial component of multidimensional HRQOL.

5. Compare QOL and HRQOL of ambulant boys who were diagnosed recently to those who were diagnosed longer ago.

   Hypothesis: For boys who are still ambulant, those who have been diagnosed before 2012 will have better QOL and HRQOL than those who have been diagnosed after 2012.

6. Compare QOL and HRQOL of boys who have lost ambulation recently to those who lost ambulation longer ago.

   Hypothesis: For boys who are non-ambulant, those who lost ambulation before 2012 will have better QOL and HRQOL than those who lost ambulation after 2012.

Chapter 2

Literature Review

2.1 Methodology of Literature Review

A literature search was conducted in January 2014 in the electronic databases MEDLINE, EMBASE and PsychINFO. Using the following key words: 1) Duchenne Muscular Dystrophy; 2) quality of life OR health related quality of life OR health-related quality of life OR health status..; 3) pediatri* OR paediatri OR teenage* OR adolescent OR child OR child* 4) 1 AND 2 AND 3. Medical Subject Heading (MeSH) terms were used whenever possible. The references of relevant studies were used to identify potential other studies not discovered upon initial search.

Inclusion criteria

Studies were considered for inclusion if: 1) child or parent-reported QOL or HRQOL was the main outcome of the study; 2) study population was specific to or included children with Duchenne Muscular Dystrophy (≤18); and 3) were published in the English language.

2.2 Results

2.2.1 Overview of studies

Nineteen studies were identified that fit the inclusion criteria. The studies were published between 2005 and 2013 and were conducted in the following countries: United States, the Netherlands, Germany, China, Brazil, France, Australia, Italy, and Canada. Thirteen measures of QOL or HRQOL were used; a summary of these instruments can be found in Table 2.1. The majority of the generic instruments used are multidimensional, consisting at least of physical, emotional and social domains, including: KIDSCREEN-52, DISABKIDS, Pediatric Quality of Life Generic Core 4.0 (PedsQL), Child Health Questionnaire-parent report (CHQ), Vecu Sante Percu par l'adolescdent (VSP-A). Some

studies used instruments that examine an individual domain of HRQOL. For example, the Personal Adjustment and Roles Scale-III (PARS-III) focuses only on psychological adjustment and does not include questions pertaining to physical functioning. One of the challenges of summarizing studies is the diversity of the instruments used. There is heterogeneity among the instruments in their purpose and design. For example, all instruments have unique domains, and some have no summary score. This makes it hard to compare results across studies. However, the most commonly used instruments, the PedsQL Generic Core 4.0 and the CHQ-50 Parent Report both have summary physical and psychosocial scores, making them most comparable to one another.

Seventeen of the studies were cross-sectional and two were longitudinal, conducted over the span of nine months and one year. Many studies (N= 8) had single-centre designs and recruited participants through approaching patients in neuromuscular clinics. The sample sizes of the studies ranged from 25 to 287. It should be noted, however, that some of studies' patient populations included adults with DMD or children with other types of neuromuscular disorders (Grootenhuis et al., 2007; Mah et al., 2008; Orcesi et al., 2014; Vuillerot et al., 2010).

Although almost all of the studies of HRQOL in children with DMD are descriptive, some comparative analyses were completed. Four recurring themes were identified among the studies: 1) comparison of HRQOL between boys with DMD and either a healthy control group or a group with another chronic illness; 2) comparison between sub-groups within the paediatric DMD sample; 3) investigation of relationship between clinical measures of function and child or parent reported HRQOL; 4) and comparison and agreement between child self-report HRQOL and parent reported HRQOL. Each of the four themes will be discussed in detail below. A summary of major findings of all studies can be found in Table 2.2.

Comparison to healthy peers or those with another illness

Ten studies compared HRQOL in boys with DMD to a healthy cohort, or children with other chronic illnesses. Four of these studies (Bendixen et al., 2012; Henricson et al., 2013; McDonald et al., 2010; Orcesi et al., 2014) recruited healthy controls along with

their DMD sample, six studies used established normative data from the literature as their healthy controls (Baiardini et al., 2011; Bray et al., 2011; Davis et al., 2010; Elsenbruch et al., 2013; Opstal et al., 2013; Uzark et al., 2012).

Eight studies found that boys with DMD had significantly poorer physical HRQOL than healthy boys and children with other types of chronic illnesses. Five studies reported that boys with DMD had significantly lower psychosocial score than healthy controls (Baiardini et al., 2011; Bendixen et al., 2012; Bray et al., 2011; Davis et al., 2010; C. M. McDonald et al., 2010). None of the studies reported effect sizes, but the differences in physical HRQOL score were consistently larger than differences in psychosocial score.

Houwen-van Opstal et al. (2013) reported that there were no significant differences in HRQOL score between boys with DMD and healthy children, in any of the ten domains of the KIDSCREEN-52, except the physical domain. Elsenbruch and colleagues (2013) divided their sample into child and adolescent groups. In the children's group, all subscale scores as well as the total HRQOL score were significantly lower than the scores of age-matched children with other chronic illnesses ($p<0.05$). In the adolescent group, only the social inclusion subdomain score was significantly lower in boys with DMD compared to normative data ($p<0.01$). Orcesi *et al.* (2014) developed a new HRQOL instrument targeted at young children with neuromuscular illnesses, the Strips of Life with Emoticons (SOLE), which only has an overall score and no domains scores. Compared to healthy boys, the mean score for boys with DMD was significantly lower.

Overall, compared to healthy children or children with other chronic illnesses, boys with DMD had significantly poorer HRQOL scores. This difference is most consistent in the physical domain. In eight out of ten studies, boys with DMD had lower physical HRQOL scores than healthy controls and children with other types of chronic illnesses, and this deficiency was observed in both child self and parent proxy reports. Most of the studies found that the psychosocial scores of boys with DMD are also lower than their healthy peers.

Comparison between subgroups

DMD is a progressive disease with inevitable physical deterioration. Thus, a natural question is whether HRQOL declines with disease progression. This question would most ideally be addressed through longitudinal studies where a group of patients is followed over time. However, as HRQOL in DMD patients is a relatively new area of research, almost all studies are cross-sectional. In cross-sectional studies, patients with different disease severity have been compared to one another. Age is often used as a proxy for disease progression given that generally, older children have more severe illness. Disease groups may also be separated by ambulation status (ambulant or non-ambulant) or ventilation status (does not require ventilation or requires ventilation).

Ten studies compared HRQOL stratified by disease severity. The most commonly used questionnaire was the PedsQL Generic Core 4.0, which has three versions based on age: ages 5-7, ages 8-12, and ages 13-17. In addition, the PedsQL inventory has disease specific modules, including Neuromuscular and DMD modules. Disease specific measures tend to be more sensitive when used to compare HRQOL across disease sub-groups (Eiser & Morse, 2001c).

Three studies used the PedsQL 4.0 Generic Core scale and reported that younger boys had significantly higher physical HRQOL score than older boys (Bray et al., 2010; McDonald et al., 2010; Uzark et al., 2012). In contrast, another study reported that in their sample of boys with DMD, those who were younger than 10 years of age did not report significantly higher physical HRQOL than those who were older (Bendixen et al., 2012). Two studies reported boys who were using wheelchair had significantly lower physical domains scores than boys who were still ambulant (Baiardini et al., 2011; Davis et al., 2010).

There is less consistency across studies that involve assessment of psychosocial HRQOL. Four studies reported that there were no significant differences between older and younger boys in psychosocial HRQOL scores (Baiardini et al., 2011; Bendixen et al., 2012; Bray et al., 2011; McDonald et al., 2010). Similarly, Davis *et al.* (2010) reported that there were no significant differences in psychosocial HRQOL scores between

children who were using wheelchairs and those who were not. In contrast, Hendriksen *et al.* (2009) found that the psychosocial adjustment score was positively associated with age in a survey of parents of boys with DMD ($p<0.001$). As well, Uzark *et al.* (2012) found that children in the oldest age group reported significantly higher psychosocial score than children in younger age groups ($p=0.05$). Mah *et al.* (2008) surveyed the parents of 109 children with various neuromuscular disorders, 24 of whom had Duchenne or Becker Muscular Dystrophy, they found that children on ventilation support had significantly lower physical HRQOL ($p<0.001$) and psychosocial scores ($p=0.028$) compared to children not on ventilation.

Kohler *et al.* (2005) found that in their group of DMD patients, those who were ventilated did not report a significantly lower physical or mental HRQOL scores than those who did not require ventilation. However, the author used the Short Form-36, which was designed to assess HRQOL in adults rather than in children.

In a longitudinal study, Simon *et al.* (2011) followed a group of Boys with DMD over nine months and administered the Life Satisfaction questionnaire every three months, for a total of four times. They divided their sample into four age groups, and found that life satisfaction scores improved significantly in most domains over the follow-up period for boys across all four age groups. However, the authors did not report the actual scores of each age group at each time point but instead reported the average score over four time points for each age group. This makes it difficult to confirm the conclusion these authors drew. One major limitation of the study was that the questionnaire used was designed for adolescents, but was used on children under 12 years of age, who made up majority of the study sample. There was no psychometric evaluation to justify this deviation.

Overall, physical HRQOL in children who are at a more severe stage of the disease is worse than children who are at a less severe stage. Disease severity is proxied by age, and use of assistive devices such as wheelchairs and ventilation. Less consistent is the relationship between disease severity and psychosocial HRQOL. Some studies (Hendriksen et al., 2009; Uzark et al., 2012) found older children reported better psychosocial HRQOL despite having more severe disease, while others (Baiardini et al.,

2011; Bendixen et al., 2012; Bray et al., 2011; McDonald et al., 2010) report there are no significant differences between older and younger children. However, it is worth noting that no conclusions can be drawn on any causal relationship between disease severity and HRQOL due to the cross-sectional nature of most studies. In addition, the studies have generally had small sample sizes precluding more robust analyses such as regression modeling to determine the relative contribution of these disease severity measures.

Correlation with clinical measures

Traditional outcome measurements used in clinical trials of DMD involve quantitative strength and function. With the increasing recognition of the importance of patient-reported outcomes such as HRQOL, some studies have examined the relationship between clinical measures and HRQOL. There are two common groups of clinical measures: measurement of strength and measurement of motor function.

The domains of the KIDSCREEN-52 (Opstal et al., 2013) and the DISABKIDS (Elsenbruch et al., 2013) did not correlate well with clinical measures. The only significant correlations were between the physical domain of the KIDSCREEN-52 and the Vignos scale, a measure of upper body strength ($r=-0.45$, $p=0.01$); and between emotional domain of the DISABKIDS and the Vignos scale ($r=0.5$, $p=0.0490$). McDonald *et al.* (2010) found that only the physical domains of the parent-reported PedsQL 4.0 Generic Core and the Paediatric Outcomes Data Collection Instrument (PODCI) significantly correlated with functional measures. Similarly, in two separate studies, Bray and colleagues (Bray et al., 2010, 2011) found that only the physical domains of the CHQ-50 parent report ($r=-0.38$, $P=0.03$) and the physical domain of the PedsQL correlated with the Vignos scale ($r=-0.17$; $p=0.01$). The 6-minute walk test is a recently adopted outcome measure in clinical trials of DMD (NCT01462292). Henricson *et al.* (2013) found that decline in 6-minute walk test over one year correlated significantly with decline in PODCI score.

Vuillerot *et al.* (2010) examined well-being of a group of 43 adolescents with various neuromuscular disorders, 19 of whom were DMD patients. They concluded that HRQOL does not correlate with motor function.

Overall, it appears that while the physical domains of some HRQOL measures correlates significantly with commonly used clinical measures, neither the psychosocial domains nor the overall HRQOL scores correlated with clinical end points. the examination of the relationship between clinical measures and HRQOL is difficult challenging due to the variety of HRQOL measures and motor strength and function measures being used by investigators, reflecting the early and evolving nature of this area of research.

Comparison and agreement between child report and parent report

It has been well-recognized that assessment of both parent and child perspectives of a child's HRQOL is important, as there are often discrepancies between them (De Civita et al., 2005; Eiser & Morse, 2001c).

Parents generally rate their child's HRQOL lower than children themselves did (Bray et al., 2010; Davis et al., 2010; Hu et al., 2013; Uzark et al., 2012), although no statistical comparisons were conducted in these studies. This difference tends to be greater in the psychosocial domains than the physical domain. Lim *et al.* (2014) and colleagues did find that parents reported significantly lower HRQOL on all domains of the PedsQL 4.0 Generic Core than their sons.

Eight studies included both child self-reports and parent proxy-reports, and of these, five studies examined concordance between child and parent reports. Parent and child concordance is determined by intraclass correlation coefficient (ICC). For the purposes of this review, an ICC of ≤ 0.40 would be considered poor, 0.41 to 0.75 would be considered moderate, and > 0.75 would be excellent (Uzark et al., 2012).

In studies that used the PedsQL Generic Core 4.0 questionnaire (Bray et al., 2010; Davis et al., 2010; Uzark et al., 2012), only the school domain had moderate concordance, while other domains had poor concordance. Davis *et al.* (2010) found that all subdomains of the English PedsQL 3.0 Neuromuscular have poor parent-child concordance. Hu *et al.* (2013) tested the Chinese version of the same questionnaire and found that for 50 child-parent pairs, the ICC of the overall score and subdomains were moderate. Lim *et al.* (2014) found that by both classical test analysis, which examines scale-level agreement, and

Rasch analysis, which examines item-level agreement, there was better concordance between children and parents on the physical scale than psychosocial scale.

Overall, parents tend to rate their child's HRQOL as worse than children themselves do, and the concordance between parent and child is in the poor to moderate range with the majority of domains and total scores in the poor range. The more observable aspects of a child's life, such as the school function tended to yield higher concordance.

Discussion and limitations of previous studies

The existing literature on HRQOL in boys with DMD offers some useful preliminary information, but, there are several limitations that must be taken into account in interpreting the findings. There is heterogeneity across studies with regards to the definition and constructs of QOL and HRQOL. Some measures focus only on individuals' feelings about their well-being (PARS-III, LSI-A), while other instruments are closer to measures of health status in that the questions evaluate the extent of a problem has occurred (CHQ and PedsQL questionnaires). Furthermore, it is difficult to compare the results across measures that have different domains, particularly if they do not have summary score(s). Fortunately, the most commonly used questionnaires are CHQ and PedsQL, both of which have physical and psychosocial summary scores, making it easier to compare the findings.

Many of the studies used convenience sampling and drew participants from local clinic(s). Given the severity of the disease, it is reasonable to assume that almost all boys with DMD are managed at a tertiary-care clinic, thus patients recruited through such clinics are likely representative of the DMD population. However, most studies did not report a response rate and it is unclear whether the respondents differ from those who chose not to participate. Moreover, there has not been a previous study in Canada of boys with DMD. Due to the rarity of DMD, it is difficult to employ a population-based random sampling procedure. A registry based study may be an alternative to population based random sampling.

Most of the studies had relatively small sample sizes, with ten of the 18 studies having a sample size of 50 participants or less. When subgroup comparisons are made, the sample sizes became even smaller. Thus the lack of any significant differences in comparison could be due to insufficient power. Additionally, of all HRQOL measures, only the PedsQL questionnaires has been validated specifically in a paediatric DMD population (Davis et al., 2010). The reliability and validity of other measures in this population is unknown. Some studies have applied questionnaires designed for adults (Kohler et al., 2005) or adolescents (Simon et al., 2011) to children, without any psychometric evaluation of their appropriateness.

Many of the studies did not report their results comprehensively. Some reporting issues include lack of p-value being reported (Opstal et al., 2013), not computing a summary score despite one being available for the questionnaire used and displaying results in graphs with no error bars (Bray et al., 2010).

In four of the studies (Grootenhuis et al., 2007; Mah et al., 2008; Orcesi et al., 2014; Vuillerot et al., 2010), boys with DMD were part of a sample that included children with other types of neuromuscular disorders, making it hard to elucidate specifically the HRQOL of boys with DMD. Some studies excluded boys younger than 8 years old (Davis et al., 2010; Elsenbruch et al., 2013), or boys who have lost ambulation (Henricson et al., 2013; McDonald et al., 2010). The time around initial diagnosis and loss of ambulation, may be particularly vulnerable times for boys with DMD and should receive more focus. Finally, not all of the studies assessed HRQOL from both parent and child perspectives, and only three studies used disease-specific questionnaires (Davis et al., 2010; Hu et al., 2013; Uzark et al., 2012).

A multitude of QOL and HRQOL measures were used. Most studies that used the PedsQL questionnaires designated it as a measure of HRQOL, two studies designated it as QOL (Bendixen et al., 2012; Mah et al., 2008). The KIDSCREEN-52, DISABKIDS, PODCI and TACQoL were considered as HRQOL measures; while the VSPA, LSI-A, Short Form-36 and SOLE were considered to be QOL measures. The CHQ-50 was

considered to be a QOL measure by one study (Baiardini et al., 2011) and health status by another study (Bray et al., 2011).

2.2.2 Conclusions

From the existing literature, it is apparent that the HRQOL of boys with DMD is poorer than that of their healthy peers, particularly in the physical domain. Within the DMD sample, boys with more severe disease consistently reported poorer physical HRQOL than boys with less severe disease; such a difference was not as consistent for psychosocial HRQOL. Similarly, while the physical domains of HRQOL instruments correlated well with clinical measures of functioning, psychosocial domains did not. Finally, the parent and child concordance for most measures of HRQOL was poor. It is important to determine whether these findings can be replicated in future studies that overcome some of the shortcomings of previous work. A comprehensive study that examines QOL and HRQOL from children's and parents' perspectives, using validated generic and disease specific questionnaires and one that spans the entire paediatric DMD age range would help researchers and clinicians gain more insight into the subjective well-being of children with DMD. Furthermore, determining child or family factors that are associated with HRQOL could help clinicians and researchers identify potential risk factors for poor HRQOL and provide appropriate intervention.

Table 2-1 Summary of quality of life and health-related quality of life instruments used by studies reviewed

Instrument	Dimensions/domains	Scoring	Studies
KIDSCREEN-52 Dutch version	Physical, psychological, moods/emotions, self-perception, autonomy, parent relations/home life, financial resources, social support/peers, school environment, social acceptance.	Scores on ten domains No total score	(Opstal et al., 2013)
DISABKIDS German version	Independence, emotion, social inclusion, social exclusion, physical limitation, treatment	Scores on ten domains and total score	(Elsenbruch et al., 2013)
Pediatric Quality of Life 4.0 Generic Core (PedsQL 4.0 Generic) English and Chinese versions	Physical, emotional, social and school functions	Scores on four domains 2 summary scores: Physical score; Psychosocial score (emotional, social and school functions combined) Total score	(Davis et al., 2010; Henricson et al., 2013; Hu et al., 2013; Mah et al., 2008; McDonald et al., 2010; Uzark et al., 2012)
Paediatric Outcome Data Collection Instrument (PODCI) English	Upper extremity, transfer/basic mobility, sports/physical function, pain, happiness, and global functioning	Scores on five domains Global functioning score is mean of all domains excluding happiness.	(McDonald et al., 2010)
TACQoL Dutch	Motor functioning, physical symptoms, social functioning, cognitive functioning, positive emotions, negative emotions, autonomy	Scores on seven domains No total score	(Grootenhuis et al., 2007)
Vecu Sante percu par l'adolescent (VSPA) French	Vitality, leisure, relationship with parents, relationship with friends, relationship with teachers, body image, school performance, physical and psychological wellbeing	Scores on 9 domains No total score	(Vuillerot et al., 2010)
Child Health Questionnaire Parent Form 50 (CHQ-50) English version	Physical Functioning, Role/Social Limitations – Physical, General Health Perceptions, Bodily Pain/Discomfort, Family Activities, Role/Social Limitations – Emotional, Role/Social Limitations– Behavioral, Parent Impact Time, Parent Impact Emotion, Self-Esteem, Mental Health, Behavior, Family Cohesion, Change in health	Scores on 15 domains 2 summary scores: physical and psychosocial No total score	(Baiardini et al., 2011; Bray et al., 2011)

Personal Adjustment and roles Skills Scale (PARS-III) Dutch	Peer relations, dependency, hostility, productivity, anxiety/depression, and withdrawal	Scores on six domains No total score	(Hendriksen et al., 2009)
Life Satisfaction Index for Adolescents (LSI-A) English and Dutch versions	General wellbeing, interpersonal relationship, personal development, personal satisfaction, recreation	Scores on five domains No total score	(Simon et al., 2011)
Short Form 36	Vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health	Scores on eight domains No total score	(Kohler et al., 2005)
Strips of Life with Emoticons (SOLE) Italian	33 individual items that assess how a child feels at different times in a typical day	Total score of all 33 items	(Orcesi et al., 2014)
PedsQL Neuromuscular Module English and Chinese Versions	About My Neuromuscular Disease, communication, About our family resources	3 domain scores Total score	(Davis et al., 2010; Hu et al., 2013)
PedsQL DMD module English version	Daily Activities, Treatment, Worry, communication	4 domain scores No total score	(Uzark et al., 2012)

Table 2-2 Summary of studies reviewed

Citation	Study design and sample characteristics	HRQOL measure used	Major findings
Baiardini et al., 2011	Cross-sectional; DMD sample N=27, mean age 11.4 Neuromuscular clinics in Italy	Child Health Questionnaire 50- Parent Form Parent-report	Parents reported significantly lower physical, psychosocial score than normative sample Use of wheelchairs and ventilation were significantly associated with lower physical functioning HRQOL
Bendixen et al., 2012	Cross-sectional; DMD sample N=50; mean age 8.0 years (range 5-17) healthy sample N=25 Neuromuscular clinic in the United States (Florida)	PedsQL 4.0 Generic Core Self- and parent- report	HRQOL was lower for boys with DMD in the physical, social and school domains, and the overall score. There was no significant difference in the emotional domain Participation level in physical and social activities is not correlated to HRQOL in boys with DMD. Older boys had significantly lower participation level, but not HRQOL than younger boys
Bray et al., 2010	Cross-sectional; DMD sample N=35, mean age 12.5 (range 9-17 Recruited through neurogenetics clinics and community newsletters in Australia	PedsQL 4.0 Generic Core Self- and parent- reports	Parent-child concordance range from poor to modest in different domains, greatest in school domain Self-reported scores significantly correlated with physical domain and Vignos scale Younger boys with DMD had significantly higher physical domain score than older boys

Bray et al., 2011	Cross-sectional; DMD sample N=34, mean age 9.9 (range 5-18) Three urban paediatric hospitals in Australia	Child Health Questionnaire 50-Parent Form Parent-report	Parents reported significantly lower physical, psychosocial score than normative sample and sample of children with Charcot-Marie-Tooth disease Parents experienced greatest stress during disease transition points such as loss of ambulation
Davis et al., 2010	Cross-sectional; DMD sample N=44, mean age 12.9 (range 8-18) Neuromuscular clinics in the United States	PedsQL 4.0 Generic Core and PedsQL 3.0 Neuromuscular modules Self- and parent- reports	Parent and child reported HRQOL significantly lower than normative sample The PedsQL 3.0 Neuromuscular module is reliable and valid measure of HRQOL in the paediatric DMD population Full time wheelchair users had lower physical HRQOL in both generic and neuromuscular specific modules
Elsenbruch et al., 2013	Cross-sectional; DMD sample N=50, mean age 15.4 years (range 8-23) Control derived from 1,152 children with different chronic health conditions Single paediatric neurology clinic in Germany	DISABKIDS chronic generic module for children and adolescents; Short Form-36 for young adults Self- and parent- report	In children, HRQOL score of boys with DMD in all domains were lower than boys with other chronic illnesses. In adolescents, only social inclusion domain had lower score. No correlation between total HRQOL score and Vignos function score.
Grootenhuis et al., 2007	Cross-sectional Muscular dystrophy sample N=40, 36 are DMD patients mean age 12.6 (range 8-17) Dutch Neuromuscular centres	TACQoL children for under 16 year olds TACQoL adult for 16 and older Self-report	Children and adolescents with muscular dystrophy reported significantly lower QOL in 'motor functioning' domain than healthy peers Better 'physical symptoms' score, but worse motor functioning score than healthy peers

Hendriksen et al., 2009	Cross-sectional DMD sample N=287, mean age 10.9 (range 5-18) the Netherland and U.S	Personal Adjustment and Role Skills Scale (PARS-III) Parent report	The PARS-III is a reliable and valid measure in the paediatric DMD population PARS-III total score was not significantly different in DMD compared to males with other chronic medical conditions PARS-III total score positively correlated with increase in age
Hu et al., 2013	Cross-sectional; DMD sample N=56 Mean age 7.54 (range 2-13) Tertiary hospitals in urban China	Chinese version of PedsQL 4.0 Generic Core and Neuromuscular 3.0 module Self and parent-report	The Chinese version of PedsQL 4.0 General core and Neuromuscular is feasible, reliable and valid Agreement between parent and child is moderate.
Henricson et al., 2013	Longitudinal DMD sample N=24 ambulatory boys mean age 7.9 (range 4-12) Controls N=36 Neuromuscular clinics in the United States (California)	PedsQL 4.0 Generic Core PODCI	The 6-minute walk test and the PODCI global scale, and transfer scale declined significantly over one-year interval. One-year change in PODCI scores are significantly correlated with one-year change in 6 minute walk test
Kohler et al., 2005	Cross-sectional DMD sample N=35 mean age 17 (range 8-33)	Short Form-36 Self-report	Neither physical nor mental summary score in DMD patients was not found to be correlated with physical impairment or FVC
Lim et al., 2014	Cross-sectional DMD sample N=63 parent-child pairs Mean age 10.3 (range 5-16) United States	PedsQL 4.0 Generic Core Self and parent-report	Parents reported significantly lower physical and psychosocial HRQOL Classical test theory analysis and Rasch analysis found the agreement between children and parents in physical domain was better than psychosocial domains.

Mah et al., 2008	Cross-sectional Neuromuscular sample N=109, 24 are DMD or Becker MD, mean age 10.5 Single Neuromusclar centre in Canada	PedsQL 4.0 General Core Parent-report	Children who required ventilation had significantly lower overall HRQOL than children not on ventilation
McDonald et al., 2010	Cross-sectional; DMD sample N=52 ambulatory boys (age range 4-17) Control sample N=36 Neuromuscular clinics in the United States	PedsQL 4.0 Generic Core Module PODCI Parent-report	Parent reported HRQOL in both questionnaires are lower than those of controls The physical function domain of PedsQL and of PODCI correlated with age and some clinical measures of strength
Opstal et al., 2013	Cross-sectional; DMD sample N= 40, mean age 11.5 years (range 8-20); Control group N=22,827 Recruited from Dutch Duchenne Parent Database	KIDSCREEN-52 Self-report and parent-report	Apart from physical domain, HRQOL in Boys with DMD not significantly different from that of healthy boys. Significant correlations between physical domain and some functional scales
Orcesi et al., 2014	Cross-sectional; DMD sample N=43 (out of 78 neuromuscular patients) Mean age 8.6 years (range 5-13) Six tertiary centres in Italy	Newly developed Strips Of Life with Emoticons (SOLE) questionnaire Self- and parent- report	DMD patients reported lower QOL than healthy controls No significant correlation found between functional disability and SOLE total score
(Simon et al., 2011)	Longitudinal DMD sample N=95 (age range 5 to 17) Single neuromuscular centre in Brazil	Life Satisfaction Index for Adolescents Self-report	Boys with DMD showed increase in self-perceived QOL in most domains of the Life Satisfaction Index over the nine month period of the study

Uzark et al., 2012	Cross-sectional; DMD sample N=203 mean age 10.4 years (age range 5-17) Neuromuscular clinics in the United States (Michigan)	PedsQL 4.0 Generic Core and DMD module Self- and parent-report	Parent and child reported total and subdomain scores were significantly lower than those of healthy children. Older boys self-reported psychosocial score was significantly higher than that of younger boys. The PedsQL DMD module is reliable and valid
Vuillerot et al., 2010	Cross-sectional; Neuromuscular sample N=43, 19 are DMD Mean age 13.8 years (range 10-17) Single neuromuscular centre in France	Vecu Sante Percu par L'adolescent (self-perceived health states in adolescents) Self-report	Teens with a neuromuscular disorder did not report lower score than nondisabled group QOL scores did not correlate with physical impairment

Chapter 3

Methods

This chapter describes the process of data collection, data management strategies and statistical analyses related to each objective. The properties of the measures and variables used in the study are also reviewed.

3.1 Data Source, Study Design and Data Management

3.1.1 Data source

Participants were recruited through the Canadian Neuromuscular Disease Registry (CNDR), a national registry that collects demographic and medical information from people living with a neuromuscular disease, including DMD, across Canada.

The CNDR was implemented with the objective of fostering collaborative research and facilitating planning of clinical trials. Recruitment at the two lead sites, Calgary and London, began in June 2011. The National Office for the CNDR is based at the University of Calgary in Alberta, Canada. Nine paediatric neuromuscular clinics across Canada are currently enrolling patients with DMD into the registry. Patients are approached for enrollment during routine clinic visits. Upon enrollment, patients indicate whether they want to be contacted for research studies in the future. As part of the registry, demographic and medical information are collected at the initial recruitment visit and then all follow-up visits. At each clinic visit, the treatment team completes the CNDR data collection forms, which are then uploaded onto a secure web-portal. All personnel who complete data entrance at each site are trained by the CNDR national coordinator. As well, there is a detailed data reference manual which outlines the requirement for individual fields. Data entry is reviewed on a weekly basis by the National Office and any errors detected are reported back to the local sites for correction. Finally, data are audited on a regular basis by the National Office (Korngut et al., 2013).

3.1.2 Data collection

Ethics approval was obtained from the Research Ethics Board at Western University and the CNDR. A copy of the approval notice can be found in Appendix A. The CNDR national office coordinated the mail-out to all eligible families who indicated they were interested in participating in research. Due to the confidentiality protocol for the CNDR, only the national office has access to the addresses and identifying information of these families. A set of unique IDs was generated for this study, and only the CNDR national office has the list matching IDs to CNDR data.

Inclusion criteria:

1. Enrollment in CNDR and patient (or parent) has indicated interest to be contacted for research studies
2. Males between ages of 4-18 years of age;
3. A confirmed diagnosis of DMD in the CNDR database. The definition is confirmed by genetic testing or absence of dystrophin on muscle biopsy, and a phenotype consistent with DMD as judged by the treating physician;
4. Availability of primary care giver to complete the parent questionnaire.

Exclusion criteria:

1. Any significant co-morbid medical diagnosis not related to DMD;
2. Inability to comply with study protocol (e.g. lack of language skills to complete questionnaire)

Questionnaires were compiled in London and forwarded to the national office for mail-out in June 2013. There were two separate questionnaire booklets, one for the child to complete as self-report, one for the parent to complete as proxy-report. Parents and children were instructed to complete the questionnaires independently. In the case where the child was unable to complete the questionnaire on his own, parents were instructed to read the questions to their child verbatim and not guide the child in answering the question. Included with the questionnaires were a letter of information for parents and assent letter for children, describing the study (Appendix B). Implied consent was assumed for this study if the participant returned the questionnaires. One week after the

initial mail-out, a reminder postcard was sent out to all families. Four weeks later, a reminder package, containing the same elements as the initial package was sent to those who had not responded. Eight weeks after the initial mail-out, another reminder package was sent to those who had not yet responded. A copy of the reminder postcard and the letter accompanying the reminder package can be found in Appendix C. This method, consistent with the Dillman's Tailored Design method was used to maximize the response rate (Dillman, 1978).

3.1.3 Data management

Questionnaires were initially returned to the national CNDR office at the University of Calgary, Canada where the respondents were cross-referenced against the master list to keep track of who had responded. Returned questionnaires were forwarded from Calgary to London. All data entry was completed at London Health Sciences Centre, Victoria Hospital. Data were entered into Statistical Package for the Social Sciences (SPSS) Statistics 21. Data verification was done by another research assistant, where 10% of the questionnaires were verified. The error rate was less than one percent, and errors were corrected by checking against the original questionnaire.

3.2 Measures

The boys with DMD and their parents completed questionnaires that assessed the child's QOL and HRQOL. The boys and their parents also completed a questionnaire that assessed the child's fatigue. Parents answered additional questions on child characteristics and family information which included demographic information and the Family Inventory of Life Events (FILE) checklist. Instructions were provided at the front of the child and parent questionnaires to aid completion, these instructions can be found in appendices E to G. Parent report version of the various QOL and HRQOL measures, the fatigue measure, the demographic information measure and the FILE can be found in appendices H to N. All measures used are described below.

Apart from child and parent completed information, demographic and medical information recorded in the CNDR database were also obtained, they are described in more detail later in the chapter.

3.2.1 QOL and HRQOL measures

Four different measures were used to measure QOL and HRQOL. The Quality of My Life (QoML) Questionnaire measured both QOL and HRQOL with single-item statements. Three Pediatric Quality of Life Inventory (PedsQL) questionnaires were used as multidimensional measures of HRQOL with various degrees of disease specificity. A visual schematic representation of the QOL and HRQOL measures can be found in Figure 3.1, a summary of all measures used can be found in Table 3.1.

Quality of My Life Questionnaire

The Quality of My Life (QoML) Questionnaire was initially developed to measure overall QOL and HRQOL as distinct constructs in children with rheumatoid arthritis (Feldman et al., 2000). The questionnaire consists of two single-item statements measured on visual analog scales (VAS). The first item states 'overall, my life is…' and the second states 'Considering my health, my life is….'. Answers are marked along a 100mm line for each question, with 0 being 'the worst' and 100 being 'the best'. Child respondents assess their own QOL and HRQOL while parent respondent assess their child's QOL and HRQOL. For this study, an item was removed from the original QoML, which was a question that assesses temporal change in QOL which asks the respondents to indicate 'since the last time I was here my life is…' better or worse, on a 5-point likert scale. This item was removed from this study because the questionnaires were done in a cross-sectional manner and there was no basis for a temporal comparison. Convergent validity of the QoML has been established in the paediatric rheumatology population (Feldman et al., 2000; Gong et al., 2007). The QoML has also been used in other populations, such as children with neurological impairment and children with hemophilia (Mahant et al., 2009; Revel-Vilk et al., 2004). A copy of the QoML can be found in Appendix H.

Pediatric Quality of Life Inventory generic core module and disease specific modules

The PedsQL Inventory is a repertoire of generic and disease-specific modules that measure HRQOL in children and adolescents. All modules in the PedsQL inventory

contain multiple items which are grouped into domains. Each item asks the extent to which an event has been a problem for the child in the past month. For example, a question in the physical domain of the PedsQL 4.0 Generic Core asks 'In the past month, how much of a problem have you had with participating in sports activity or exercise'. Each item is measured on a five-point likert scale that ranges from 0-4 (0=never, 1=almost never, 2=sometimes, 3=often, 4=almost always). All items are reverse scored and linearly transformed into scale out of 100 (0=100, 1=75, 2=50, 3=25, 4=0) such that higher score indicates better HRQOL.

The PedsQL Inventory modules are composed of parallel child-self report and parent-proxy reports, and are divided into three age groups: young child (5-7 years old); child (8-12 years old) and teen (13-18 years old). It should be noted that in our study we administered the young child report to children aged 4 years old (n=6), to increase our sample size, particularly in the number of children who were recently diagnosed. The content of the items is identical, differing in language modified to be developmentally appropriate. For young children's self-report, the 5-point likert scale is reduced to 3-point likert scale, (0=never, 2=sometimes, 4=almost always). Due to the young age of these children, parents were asked to act as interviewers to their child and given specific instructions (Appendix E). Domain scores are computed as a sum of items divided by number of items answered. If more than half of items on a particular domain are missing, the domain score is not calculated. An overall score is calculated as the sum of items divided by total number of items.

Generic Core Module

The PedsQL 4.0 Generic Core module is a generic measure of HRQOL, it has been widely used in healthy children and children with various disorders (Varni et al., 2001; Varni et al., 2003, 2007b). It has been found to be valid and reliable specifically in the paediatric DMD population (Davis et al., 2010). It consists of 23 items, grouped into four domains: eight questions in physical domain, and five questions in each of emotional, psychological and school domains.

In addition to domain scores and the overall score, two summary scores are also calculated. The physical domain score is also the physical summary score, and the emotional, social and school domains make up the psychosocial summary score. The parent proxy-report version of PedsQL 4.0 Generic Core module can be found in Appendix I.

Neuromuscular module

The PedsQL 3.0 Neuromuscular module was developed in particular to measure HRQOL in children with neuromuscular disorders, including those with DMD (Davis et al., 2010). There are 25 items grouped into three domains: About my/my child's neuromuscular disease (17 items), Communication (3 items) and About Our Family Resources (5 items). Each domain generates a score and there is also an overall score. The young child self-report version does not contain the Communication and About Our Family Resources domains. The Neuromuscular module has been tested primarily in a group of children with spinal muscular atrophy (SMA), which is another type of paediatric neuromuscular illness (Iannaccone et al., 2009), as well as a group of 44 boys with DMD and been found to be feasible, reliable and valid (Davis et al., 2010). The parent proxy-report version of PedsQL 3.0 Neuromuscular module can be found in Appendix J.

DMD module

The PedsQL DMD module was developed as a more DMD-specific measure of HRQOL (Uzark et al., 2012). It consists of 18 items, grouped into four domains: Daily Activities (5 items), Treatment (4 items), Worry (6 items) and Communications (3 items). There is no DMD module for young child self-report. It was developed simultaneously with the Neuromuscular module, and has been found to be feasible, reliable and valid (Uzark et al., 2012). The scoring instruction for this module precludes calculation of a total score, however, upon contacting the module developers, it was deemed appropriate to calculate a total score. The parent proxy-report version of PedsQL DMD module can be found in Appendix K.

Missing data

The percent missing for each question in the child-reported PedsQL questionnaires ranged from 2.3% to 8.2%, with most questions having 2-3% missing values. The questions that had a higher missing percentage were deemed 'not applicable' by some children. For example, the question 'how much of a problem have you had with running' was deemed as not applicable by some children who had lost ambulation, some left it blank and wrote 'not applicable' next to the question. Computation of PedsQL domain scores only requires at least half of the questions in a given domain to be non-missing; percent missing of domains scores ranged from only 2.3% to 3.5%. In the parent reported PedsQL questionnaires, the percent missing for each question ranged from 0 to 4.1%. The percent missing for domain scores range from 0 to 2.1%.

Initially, it was found that around 30% (N=25) of boys with DMD and their parents did not complete the Quality of My Life questionnaire. This single-page questionnaire was sent out again, with more detailed instructions, to those who did not complete it initially. A copy of the letter accompanying the additional mail-out can be found in Appendix D. Nine child self-reported QoML and fifteen parent-reported QoML were returned after mailing of single-page QoML questionnaire. Items missing in the demographic portion of the questionnaire were filled if such information could be found elsewhere (e.g. child's date of birth can be obtained from the CNDR). Missing data on the PedsQL were handled according to guidelines of the questionnaire developers.

3.2.2 Child characteristics and family information

Child characteristics

In addition to the QOL and HRQOL questionnaires, boys with DMD and their parents also assessed the child's level of fatigue, which was measured via the PedsQL 3.0 Multidimensional Fatigue module. It has three domains, with six items in each: General Fatigue, Sleep/Rest Fatigue and Cognitive Fatigue. It has been validated in paediatric cancer (Varni et al., 2002) and rheumatology (Varni et al., 2004) populations, among other diseases. It was scored the same as the PedsQL HRQOL modules, where respondents indicated how much of a problem the boy with DMD had with a fatigue-

related event. The scores were then reverse coded so that higher scores indicate less fatigue. A copy of the parent reported PedsQL 3.0 Multidimensional Fatigue module can be found in Appendix L.

The remainder of the child characteristics questions were adapted from the Health Related Quality of Life in Children with Epilepsy Study (Speechley et al., 2012), with permission of the Principal Investigator. Parents were asked to indicate whether their child has a comorbid condition (asthma, cystic fibrosis, diabetes, cerebral palsy, epilepsy or cancer); a developmental or mental condition (developmental delay, a learning disability, Attention Deficit Disorder or Attention Deficit Hyperactive Disorder, Autism, pervasive development disorder or Asperger's syndrome, oppositional defiant disorder, conduct disorder, depression and anxiety); whether child has needed and received extra help with school work (special education, speech language therapy, occupational therapy, medication or therapy for behaviour problems and medication or therapy for emotional problems). Parents were also asked to give their child's month and year of birth. A few questions that were DMD specific were added to this questionnaire: Is your child currently involved in any clinical trials or other research studies for his DMD? Was your child diagnosed with DMD less than one year ago? Is your child able to walk (If no, did your child stop walking less than one year ago or greater than one year ago?)

Family characteristics

The child's family's characteristics were collected through parent questionnaires and included socio-demographic information including parents' current marital status, current employment status, highest level of education completed, household income and other household members who currently reside with the child with DMD. Household income was divided into 13 categories: less than $5000, $5,000-$9,999; $10,000-$14,999; $15,000-$19,999: $20,000-$24,999; $25,000-$34,999; $35,000-$49,999; $50,000-$74,999; $75,000-$99,999; $100,000-$149,999; $150,000-$200,000, over $200, 000, and 'don't know'. Parents also completed the Family Inventory of Life Events (FILE), which was a 71 item of list of potential stressful events that a family may have faced. Each item is answered with either 'yes' or 'no' to indicate whether that particular event has occurred in the past year (McCubbin, 1996). Each item has a corresponding value if it is answered

with 'yes', with higher scores assigned to events causing more stress (e.g. 99=death of child). If an item was answered with 'no', it received a score of zero. The total score was calculated as a sum of all items. The child characteristics and family characteristics questionnaire can be found in Appendix M, and the FILE can be found in Appendix N.

3.2.3 Registry information

Medical information obtained from CNDR database included: forced vital capacity (FVC), left ventricular ejection fraction (LVEF), ambulation status (yes or no), wheelchair use status (never, intermittent, full-time), scoliosis status (yes or no), steroid treatment (never, past use, current use), non-invasive ventilation (yes or no), invasive ventilation (yes or no), cardiac medication (yes or no), type of genetic mutation, and date of genetic test. The child's date of birth was also obtained to confirm date of birth reported by parents. In cases of discrepancy, the date of birth in registry was used.

3.3 Statistical Analyses

For all statistical analyses SAS software version 9.3 was used. A two-sided p-value <0.05 was considered to be statistically significant unless otherwise stated.

3.3.1 Description of sample characteristics

Univariate analyses were used to examine characteristics of the sample (mean and standard deviation for continuous variables, frequencies and percentages for categorical variables). Bivariate analyses (t- and χ^2- tests) were used to determine whether non-respondents were different from respondents on clinical characteristics obtained from the CNDR database.

3.3.2 Describe the QOL and HRQOL in boys with DMD in Canada from both children's and parents' perspectives (Objective 1).

The medians, means and standard deviations of child self-reported and parent proxy-reported QOL and HRQOL scores of boys with DMD were calculated. As references, scores of healthy children (Varni et al., 2003) and scores of a sample of children with SMA, obtained from literature, were also reported.

3.3.3 Examine the relationship between QOL and HRQOL (Objective 2).

The relationship between the single-item measures of QOL and HRQOL were examined with simple linear regression. To ensure that any relationship found between single-item QOL and single-item HRQOL is not due to similarity in design between these two measures (i.e. due to common method variance), the association between QOL and a multidimensional measure of HRQOL (PedsQL Generic Core total score) was examined with Spearman correlation. The association between the single-item measure of HRQOL and multidimensional measure of HRQOL was also examined with Spearman correlation.

3.3.4 Explore child and family characteristics that contribute to any difference between QOL and HRQOL (Objective 3).

Logistic regression was used to assess whether any child clinical or family characteristics distinguished those who rated QOL to be higher than HRQOL from those who did not. We decided to approach this objective by dividing our sample into two groups: boys and parents who rated QOL to be 'much' higher than HRQOL, and children and parents who did not rate QOL to be 'much' higher than HRQOL. QOL was considered much higher than HRQOL if the difference between them was in the top 25% of the sample. There was no guidance from literature on what constitutes a meaningful difference between QOL and HRQOL, thus we made the arbitrary decision, based on the distribution of the values in our sample, to dichotomize our outcome in this manner. The characteristics tested in the multivariable logistic regression are presented in Table 3.1, they were: age of child, fatigue level, ambulation status, presence of at least one mental or developmental disorder, total household income, parental education, and family inventory of life events score. Fatigue score and FILE score were presented in intervals of 10 and 50, respectively, to reflect more meaningful levels of change.

3.3.5 Explore associations of child and family characteristics with multidimensional measures of HRQOL (Objective 4)

To model the relationships of child and family characteristics with HRQOL, multivariable linear regression with backwards elimination was used. Our study was exploratory in nature, given that there was limited past literature on which to base our

selection of variables. As such, various measures of disease severity and other important clinical variables were selected for modeling based on clinical expertise. However, no factors were considered to be primary predictors of interest. Because of the nascent nature of our multivariable analysis, statistical regression (i.e. backwards elimination) was deemed as the appropriate regression method (Tabachnick & Fidell, 2013). Child and family characteristics were first examined individually via simple linear regressions. Those that were significant at the $p<0.30$ level entered the maximum model. After backwards elimination, only the variables that contributed significantly to the regression ($p<0.10$) were kept in the final model. The entrance and retaining criteria for p-values were decided upon after consulting literature and examining the data (Maldonado & Greenland, 1993; Mickey & Greenland, 1989).

The variables that were tested were: age of child, wheelchair status, scoliosis status, steroid usage, forced vital capacity (FVC), left ventricular ejection fraction (LVEF), having at least one developmental or mental disorder, self- or parent-perceived fatigue level (measured by PedsQL 3.0 Multidimensional Fatigue scale), family inventory of life events (FILE) score, annual household income and parent's highest level of education. Clinical factors, such as wheelchair status and FVC, were chosen based on clinical experience and existing literature (McDonald et al., 2010). Demographic factors, namely, parental education and annual household income were included in the regression model as they had been shown to be associated with children's HRQOL (Rueden et al., 2006). The FILE measure had also been shown to be a significant predictor of HRQOL in chronically children, thus it was included as a potential determinant of HRQOL (Speechley et al., 2012). Similarly, fatigue was associated with HRQOL in the pediatric cancer population (Meeske et al., 2004) and thus examined in our sample. A separate set of analyses was carried out to determine the effect of FVC. Data on FVC were available for 67 children, and as SAS uses list-wise deletion, the sample size for the regression analyses would have been reduced to 67. Thus, one set of analyses was done with all variables in the model except for FVC to test for joint effect of these variables, then a separate set of analyses was carried out to assess the effect of FVC in the 67 children with a FVC value. LVEF was another variable that was influenced by list-wise deletion,

however, it did not meet the entrance criteria to enter into the maximum model, and thus was not relevant to the final models. The variables are presented in Table 3.3.

3.3.6 Compare QOL and HRQOL of ambulant boys who were diagnosed recently to those who were diagnosed longer ago (Objective 5).

QOL and HRQOL scores of ambulatory children who were diagnosed after 2012 were compared to ambulatory children who were diagnosed before 2012 using Kruskal Wallis tests.

3.3.7 Compare QOL and HRQOL of boys who lost ambulation recently to those who lost ambulation longer ago (Objective 6).

QOL and HRQOL scores of children who lost ambulation after 2012 were compared to those who have lost ambulation before 2012 with Kruskal Wallis test.

Figure 3-1 Schematic representation of measures of QOL and HRQOL

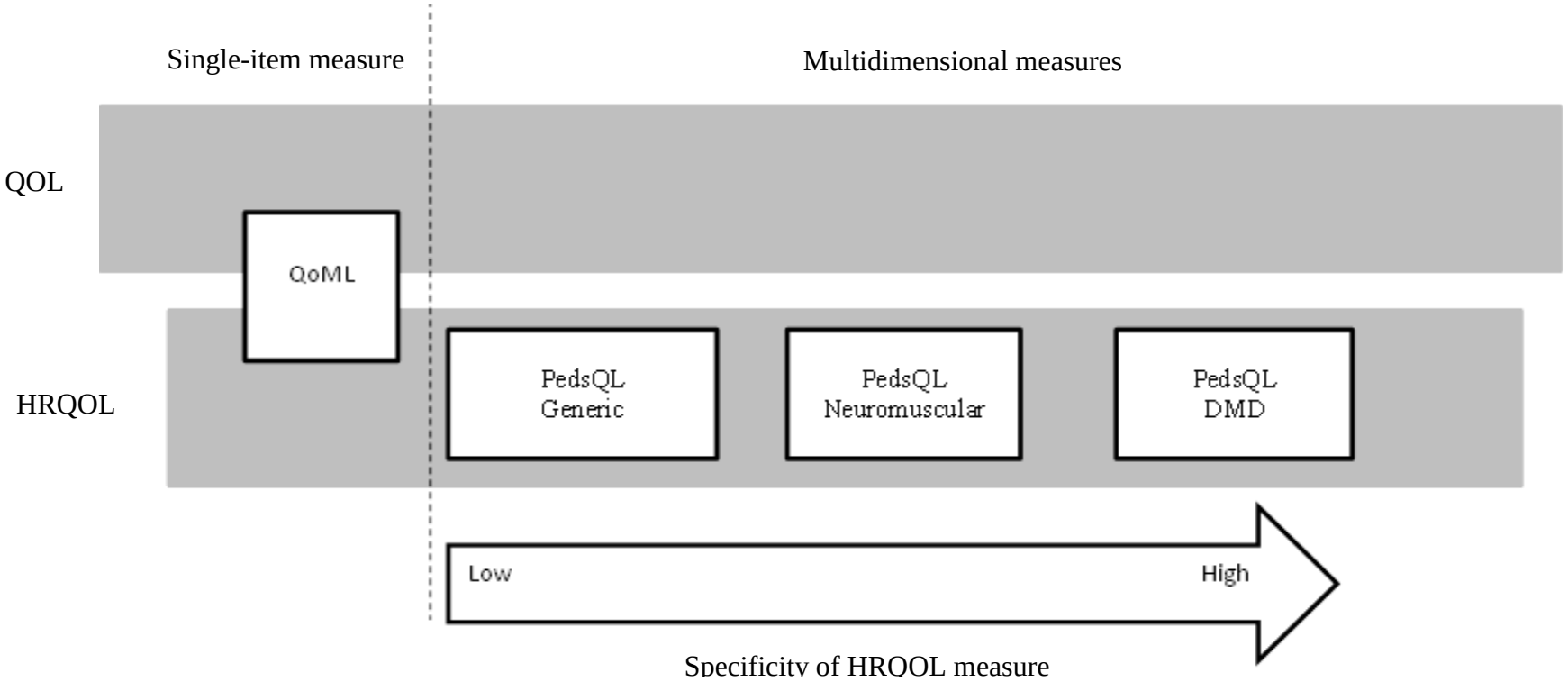

Table 3-1 Summary of child- and parent-reported QOL and HRQOL measures

	Content of questionnaire	QOL or HRQOL measure	Single-item or Multidimensional	Generic or disease specific measure	Scoring
Quality of My Life	"overall, my life is…"	QOL	Single-item	Generic	100 mm VAS between 'the worst' and 'the best'
	"Considering my health, my life is…"	HRQOL	Single-item		
PedsQL 4.0 Generic Core	Physical Emotional, Social and School (make up the psychosocial summary score) 23 items in total	HRQOL	Multidimensional	Generic	How much a problem has…been in the past month, on a scale of 0-4. Items are reverse transformed to score out of 100, higer score indicates higher HRQOL
PedsQL 3.0 Neurmuscular module	About My/my child's neuromuscular disease ; Communication ; About our family resources 25 items in total	HRQOL	Multidimensional	Disease specific	Same as above
PedsQL Duchenne Muscular Dystrophy module	Daily activities ; Treatment Barrier ; Worry; Communication 18 items in total	HRQOL	Multidimensional	Disease specific	Same as above

Table 3-2 Child and family factors tested in multivariable logistic regressions of child or parent rating QOL to be much higher than HRQOL

Clinical factors	Demographic factors
- Age - Fatigue level - Presence of at least one mental or developmental disorder (Yes/***No***)	- Parental education (***no post-secondary education***; post-secondary education) - Annual household income* - Family Inventory of Life Events score

For categorical variables, the reference category is in bold and italicized
*Annual household income was treated as a continuous variable as it had 13 levels

Table 3-3 Child and family factors tested in multivariable regressions with multidimensional HRQOL as outcomes

Clinical factors	Demographic factors
- Age - Fatigue level - Forced vital capacity - Left ventricular ejection volume - Use of steroid (Yes/***No***) - Scoliosis (Yes/***No***) - Presence of at least one mental or developmental disorder (Yes/***No***) - Wheelchair status (***Never used***, intermittent use, permanent use)	- Parental education (***high school or less***; vocational training; post-secondary education) - Annual household income* - Family Inventory of Life Events score

For categorical variables, the reference category is in bold and italicized
*Annual household income was treated as a continuous variable as it had 13 levels

Chapter 4

Results

This chapter presents results of the study corresponding to each objective. The initial section describes the sample characteristics.

4.1 Sample Characteristics

From the Canadian Neuromuscular Disease Registry (CNDR), 176 eligible families were identified. One child was excluded because his parent identified him as having epilepsy, a significant co-morbidity, reducing the total number eligible to 175. Of these, 98 families returned completed questionnaires, for a response rate of 56%. Eight families were lost to follow-up due to incorrect addresses. Both parent and child completed questionnaires in 84 families, 13 families completed the parent questionnaire only and one family returned the child questionnaire only.

The children's clinical and demographic characteristics of are presented in Table 4.1. The average age of the children [mean (SD)] was 10.5 (3.6) years. The majority (72%) of children are ambulant. Over half had at least one mental or developmental disorder, with developmental delay being the most common (23%).

Characteristics of the family are presented in Table 4.2. The majority of parents who completed the questionnaire were mothers, and the mean age of the parent respondent was 43 years. Over half of parent respondents who completed the questionnaire had post-secondary education, and the median household income was in the range of $75,000-$99,000, which is around the national average (Government of Canada, 2013).

Non-respondents

Aggregate clinical characteristics of boys who did not respond were obtained from the CNDR and are compared to those of respondents Table 4.1. Clinical characteristics of non-respondents were not statistically significantly different from the respondents based on these comparisons. However, the boys not in the study sample were older by one year,

on average, and were slightly more likely to have lost ambulation, suggesting they may be at a more severe stage of the disease.

4.2 Describe the QOL and HRQOL of boys with DMD in Canada from both child and parent perspectives (Objective 1).

Child self-report

On the QoML, the median QOL score, as reported by the boys, was 80.0, with a range of 37.8-100, the median HRQOL score was 77, and ranged from 0 to 100. As a reference, the median QOL and HRQOL scores reported by children with rheumatoid arthritis were 93 and 89, respectively.

The child self-reported PedsQL 4.0 Generic Core, the PedsQL 3.0 Neuromuscular Module and the PedsQL DMD Module mean scores, standard deviations and ranges are presented in Table 4.3. As a reference, scores of healthy children and those with another neuromuscular disorder, spinal muscular atrophy (SMA), which were obtained from literature (Iannaccone et al., 2009; Varni et al., 2001), are also presented. Compared to the healthy sample, the score of boys with DMD are lower in all domains of the PedsQL 4.0 Generic Core module, with largest difference in the physical domain, and the smallest in the emotional domain. The PedsQL 4.0 Generic Core total and domain scores comparing boys with DMD and children with SMA were very similar to one another. On the PedsQL 3.0 Neuromuscular module, boys with DMD had higher mean score in "About my neuromuscular disease' domain, but a lower mean score in 'Communication' domain than children with SMA.

Parent proxy-report

On the QoML, the median QOL score of boys with DMD, as reported by their parents, was 72, the scores ranged from 8 to 100. The median HRQOL score was 67, and ranged from 16 to 100. As a reference, the median QOL and HRQOL scores reported by parents of children with rheumatoid arthritis were 90 and 91, respectively (Gong et al., 2007).

The parent proxy-reported PedsQL 4.0 Generic Core, the PedsQL 3.0 Neuromuscular Module and the PedsQL DMD module mean scores, standard deviations and ranges are reported in Table 4.4. As a reference, normative scores of healthy children and those with spinal muscular atrophy, which were obtained from literature (Iannaccone et al., 2009; Varni et al., 2001), were also presented. Compared to the healthy sample, the parent-reported score of boys with DMD are lower in all domains of the PedsQL 4.0 Generic Core module, the difference was largest in the physical domain, and smallest in the emotional domain. Parents of boys with DMD rated their sons to have better physical HRQOL, but worse psychosocial HRQOL than parents of children with SMA. On the PedsQL 3.0 Neuromuscular module, parents of boys with DMD rated their sons to have higher score in 'About my neuromuscular disease' and 'About our family resources' domains, but lower score in 'Communication' domain than parents of children with SMA.

4.3 Examine the relationship between QOL and HRQOL (Objective 2).

The relationship between single-item measures of QOL and HRQOL on the QoML were examined with simple linear regression. On the child self-report, two boys rated their QOL as 100 mm, and HRQOL as 0 mm. These extreme values were deemed as outliers and removed from analysis. Better HRQOL was associated with better QOL (QOL=0.45*HRQOL+44.25, $p<0.0001$). The adjusted R^2 was 0.21. The single-item QOL score did not correlate significantly with the multidimensional PedsQL 4.0 Generic Core total score ($r=0.17$, $p=0.17$). The single-item HRQOL score was significantly correlated with the PedsQL 4.0 Generic Core total score ($r=0.30$, $p=0.01$).

On the parent reported QoML, better HRQOL was associated with better QOL (QOL=0.58*HRQOL+31.00, $p<0.0001$). The adjusted R2 was 0.44. The single-item QOL score did not correlate with multidimensional PedsQL 4.0 Generic Core total score ($r=0.14$, $p=0.21$). The single-item HRQOL score significantly correlated with the PedsQL 4.0 Generic Core total score ($r=0.25$, $p=0.03$).

4.4 Explore child and family characteristics that contribute to any difference between QOL and HRQOL (Objective 3).

Multivariable logistic regressions were run to investigate what child and family characteristics contributed to child and parent respondents rating QOL to be higher than HRQOL. QOL was deemed to be higher than HRQOL if the difference between QOL and HRQOL was in the top 25% of the sample. The factors that entered the logistic regressions were: age of child, ambulation status, fatigue level, parent's highest level of education, total household income and FILE score.

Child self-report

The difference between QOL and HRQOL ranged from 100mm to -46.3mm, the median difference was 0.8mm. QOL was deemed to be higher than HRQOL if it was 14.9 mm or greater than HRQOL. None of the child or family characteristics tested was significantly associated with a child respondent rating his QOL to be higher than HRQOL (Table 4.5). However, children whose parents have post-secondary education were 5.7 times more likely to rate their QOL to be much higher than HRQOL, with a very wide confidence interval (CI: 0.7-237), due to the small sample size.

Parent proxy-report

The median difference between QOL and HRQOL was 0, and ranged from 55mm to -42.5mm. QOL was considered to be higher than HRQOL if it was 9.6mm or higher than HRQOL. None the factors was significantly associated with an increased likelihood of a parent rating their child's QOL to be higher than HRQOL (Table 4.6). However, the lack of significance could be due to the small sample size. For example, the odds ratio of rating QOL to be higher is 4.5, comparing parents of ambulant boys to parents of non-ambulant boys, the confidence interval is from 0.9 to 35.9. As with the child report one factor associated with QOL being higher than HRQOL was parent education level, parents who have post-secondary education were 2.0 times more likely to rate their son's QOL to be higher than HRQOL (CI: 0.6-7.4).

4.5 Explore the association of clinical and demographic characteristics with multidimensional measures of HRQOL (Objective 4)

Regression analyses were carried out on the following HRQOL outcomes in child self and parent proxy-reports: PedsQL 4.0 Generic Core total score, physical summary score, psychosocial summary score, PedsQL 3.0 Neuromuscular Module total score and PedsQL DMD Module total score. Bivariate regression analyses were conducted on each of the explanatory variables and the HRQOL outcomes, and variables that had p-values of less than 0.3 entered the maximum main effects models. The model selected was backwards elimination, variables that had p-values of less than 0.1 stayed in the final model. Two sets of analyses were run, one with FVC in the model, one without.

The child and family characteristics that remained in the final model had p-value less than 0.10. The results of the regression models without and with FVC are presented below (parameter estimate (SE)). The results of models without FVC are presented in Tables 4.7 and 4.8. The assumptions of linear regression were met and the test for collinearity was not significant. Results for each of the HRQOL outcomes in child self-report are presented first, followed by parent proxy-report.

Child report

PedsQL 4.0 Generic Core Total Score

The factors that were significantly associated with the PedsQL 4.0 Generic Core total score were fatigue, intermittent use and full-time use of wheelchair and parent's highest level of education. The R^2 was 0.61. Children who reported less fatigue reported better HRQOL (0.57(0.06)). Compared to children who did not use wheelchair, children who used wheelchair intermittently (-7.47(2.36)) and who used a wheelchair full-time (-15.14(2.46)) had significantly worse overall HRQOL. Compared to children whose parent's highest level of education was high school or less, children who have a parent with college or university education had significantly better overall HRQOL (4.34(2.07)). With FVC added to the model, the factors that remained significant in the final model

were: fatigue (0.62(0.08)), intermittent wheelchair use (-8.53(3.03)) and full-time wheelchair use (-13.11(3.00)). The R^2 for this model was 0.64.

PedsQL Generic Core 4.0 Physical Summary Score

The factors that remained in the final model of the physical summary score were fatigue, intermittent and full-time use of wheelchair. The R^2 was 0.72. The children who reported less fatigue had significantly higher physical summary score (0.46(0.09)). Children who used wheelchair intermittently (-19.92(3.40)) and full-time (-42.41(3.48)) reported significantly lower physical summary scores than children who did not use a wheelchair. With FVC added to the model, the factors that remained significant in the final model were: fatigue (0.47(0.12)), intermittent wheelchair use (-19.86(4.36)) and full-time wheelchair use (-39.35(4.38)). The R^2 for this model was 0.67.

PedsQL Generic Core 4.0 Psychosocial Summary score

The factors that were significantly associated with the Psychosocial Function score were fatigue and annual household income. The R^2 was 0.56. Less fatigue (0.68(0.07)) and higher household income (1.14(0.46)) were associated with better psychosocial HRQOL. FVC did not meet the criteria to enter the maximum model.

PedsQL Neuromuscular Module 3.0 Total Score

The factors that remained in the final model for the Neuromuscular module total score were: age, fatigue, household income and full-time use of wheelchair. The R^2 was 0.76. Older children (0.57(0.27)), those with less fatigue (0.74(0.05)) and higher household income (0.55(0.31)) reported better HRQOL on the Neuromuscular module. Compared to boys who did not use wheelchairs, those who use wheelchair full-time (-12.45(2.25)) reported worse HRQOL. With FVC added to the model, the factors that were significant were fatigue (0.70(0.07)), full-time use of wheelchair (-8.91(2.26)) and total household income (0.80(0.42)). The R^2 was 0.72.

PedsQL DMD Module Total Score

The factors that remained in the final model of PedsQL DMD module total score were fatigue, FILE score, total household income and full-time use of wheelchair. The R^2 was 0.60. The boys who reported less fatigue 0.88((0.09)), whose family had higher FILE score (more stresses) (0.01(0.006)) and higher household income (0.98(0.08)) had significantly better HRQOL on the DMD module. Boys who use wheelchair full-time (-14.3(2.90)) had significantly worse HRQOL than boys not in wheelchair. With FVC added to the model, the factors that remained in the final were fatigue (0.71(0.09)) and FVC (0.40(0.08)). The R^2 was 0.65.

Parent report

PedsQL 4.0 Generic Core Total score

The factors that remained in the final model were fatigue, intermittent use of wheelchair, full-time use of wheelchair, and parent's highest level of education. The R^2 was 0.48. Parents who reported their children to have less fatigue (higher score) also reported better HRQOL (0.53(0.08) for their children on the PedsQL Generic Core module. Compared to parents of children who did not use a wheelchair, parents of children who use a wheelchair intermittently (-9.60(2.9)) or full-time (-8.49(3.2)) reported significantly worse HRQOL for their children. Parents who had post-secondary education reported significantly higher HRQOL (6.77(2.6)) compared to parents whose highest level of education was high school education or less. With FVC added to the model, the factors that remained significant in the final model were: fatigue (0.51(0.10)), intermittent wheelchair use (-9.70(3.68)), full-time wheelchair use (-7.07(3.92)) and parent having post-secondary education (5.57(3.25)). The R^2 for this model was 0.44.

PedsQL Generic Core 4.0 Physical Summary Score

The factors that remained in the final model of the physical summary score were fatigue, intermittent use of wheelchair, full-time use of wheelchair, and parent's highest level of education. The R^2 was 0.25. Parents who reported their children as having less fatigue (0.37(0.2)) also reported better physical summary score for their children. Compared to

parents of children who did not use a wheelchair, parents of children who used a wheelchair intermittently (-15.07(5.5)) or full-time (-18.90(6.0)) reported significantly better HRQOL for their children. Parents who had post-secondary education reported significantly better HRQOL for their children (11.54(4.8)) compared to parents whose highest level of education was high school education or less. With FVC added to the model, the factors that remained significant in the final model were: fatigue (0.34(0.18)), intermittent wheelchair use (-19.27(6.89)) and full-time wheelchair use (-19.94(7.41)). The R^2 for this model was 0.18.

PedsQL Generic Core 4.0 Psychosocial Summary Score

The factors that remained in the final model of the psychosocial summary score were age, intermittent use of wheelchair, fatigue, household income, and having at least one developmental or mental disorder. The R^2 was 0.53. Parents whose children were younger (-0.73(0.3)), who reported their children to have less fatigue (0.58(0.08)) and those with a higher household income (0.81(0.5)), reported better psychosocial summary score for their children. Compared to parents of children who do not have any developmental or mental disorder, parents of children who have at least one disorder reported significantly worse HRQOL (-4.50(2.5) for their children. Compared to parents of children who did not use a wheelchair, parents of children who used a wheelchair intermittently (-4.70(2.6)) reported significantly worse HRQOL. With FVC added to the model, the factors that remained in the final model were fatigue (0.58(0.08), intermittent use of wheelchair (-6.35(2.9)) and parent whose highest level of education is vocational training (9.24(4.4)) or post-secondary education (9.88(3.7)) compared to high school education. The R^2 was 0.53.

PedsQL Neuromuscular Module 3.0 Total Score

The factors that remained in the final model of Neuromuscular 3.0 module total score were fatigue, full-time wheelchair use, and the FILE score. The R^2 was 0.70. Parents who reported their children to have less fatigue (0.62(2.37)) and lower FILE score (less stress) (-0.01(0.004)) also reported better HRQOL on the neuromuscular module. Compared to parents of children who did not use a wheelchair, parents of children who used a

wheelchair full-time (-15.6(2.38)) reported significantly worse HRQOL. With FVC added to the model, the factors that remained in the final model were fatigue (0.72(0.07)), intermittent use of wheelchair (-5.88(2.9)) and full-time use of a wheelchair (-16.9(3.03)). The R^2 for this model was 0.73.

PedsQL 3.0 DMD Module Total Score

The factors that remained in the final model of the DMD module total score were fatigue, full-time wheelchair use, and household income. The R^2 was 0.66. Parents who reported their children to have less fatigue (0.70(0.07)) and who had higher household income (1.27(0.5)) reported higher DMD module score. Compared to parents of children who did not use a wheelchair, parents of children who used a wheelchair full-time (-15.45(2.8)) reported significantly worse HRQOL for their children. In the group with FVC in the model, the factors that remained in the final model were age (-1.19(0.5)), fatigue (0.78(0.08)), FVC (0.25(0.08)), intermittent wheelchair use (6.01(3.1)), and household income (1.09(0.60)). The R^2 for this model was 0.74.

Summary of regression analyses

The factors most consistently associated with HRQOL outcomes were level of fatigue and wheelchair use. Fatigue level was significantly associated with every HRQOL outcome for both child and parent reports, and in greater magnitude than other variables. The use of a wheelchair was associated with all HRQOL outcomes except for child-reported PedsQL Generic Core psychosocial score. In both parent and child reports, parent's highest level of education were significantly associated with the PedsQL Generic Core total score. For both child and parent report, FVC remained in the final model of the DMD module total score.

4.6 Compare QOL and HRQOL of ambulant boys who were diagnosed recently to those who were diagnosed longer ago (Objective 5).

The mean age of boys diagnosed after 2012 was 5.8, of those diagnosed before 2012 was 9.5. The mean self-reported and parent-reported scores of boys diagnosed since 2012

(N=5) were compared against those who were diagnosed before 2012 (N=51) but were still ambulant are presented in Table 4.9. Wilcoxon rank sum test was carried out, and no significant differences were found in any of the scores.

4.7 Compare QOL and HRQOL of boys who lost ambulation recently to those who lost ambulation longer ago (Objective 6).

The mean self-reported and parent-reported scores of boys who lost ambulation after 2012 (N=3) were compared to those who lost ambulation before 2012 (N=20) are presented in Table 4.10. Wilcoxon rank sum test was carried out, no significant differences were found in any of the scores.

Table 4-1 Demographic and clinical characteristics of respondent and non-respondent boys with DMD

Variables	Respondents N=98	Non-respondents N=77
Age (years, SD)	10.7 (3.7)	11.7 (3.2)
Ambulant (%)	72.4	64.0
Wheelchair use: intermittent	25.5	31.0
full-time	23.5	25.0
Currently receiving steroid (%)	80.6	85.7
Scoliosis (%): surgically corrected	4.0	Not available
Not surgically corrected	8.1	
Cardiomyopathy (%)	5.1	6.4
Receive non-invasive ventilation (%)	6.1	2.1
Last FVC mean (SD) (n=67)	78.8 (17.7)	80.5
LVEF mean (SD) (n=72)	64.7 (7.2)	62.4
Co-morbidities	2*	-
Developmental or mental disorder (%)		-
Developmental delay	22.4	
Learning disorder	28.6	
Attention deficit disorder	16.3	
Autism spectrum disorder	10.2	
Oppositional defiant disorder	2.0	
Conduct disorder	0	
Depresion	5.1	
Anxiety	14.3	
Have at least one developmental or mental disorder	55.1	
Participation in clinical trial(%)	28.6	-

*2 boys had asthma, they were kept in the sample as asthma could be a consequence of pulmonary function decline

Table 4-2 Characteristics of respondent families

Variables	Respondents N=98
Age of parent respondent (years, SD)	42.7 (7.0)
Biological parent (%)	91.8
Female (%)	72.0
Married (%)	80.6
Living with spouse or partner	87.8
Mean household size	3.0
Parent's highest level of education (%)	
High school or less	18.3
Vocational	15.3
College/university	61.2
Choose not to answer	4.1
Parent's work status	
Not working	20.4
Working	61.2
Homemaker	16.3
Household income (%)	
<$25,000	12.2
$25,000 - $50,000	18.4
$50,000-$74,999	9.2
$75,000 - $99, 999	16.3
$100,000 –$149,999	16.3
≥$150, 000	19.3
Don't know	6.1
Family Inventory of Life Events score (Mean, SD)	314.3 (260.1)

Table 4-3 Mean self-reported PedsQL Generic Core, Neuromuscular and DMD module scores in boys with DMD, children with spinal muscular atrophy and healthy children

	Boys with DMD		Spinal Muscular Atrophy (Iannaccone et al., 2009)		Healthy (Varni et al., 2001)	
	N	Mean (SD) [range]	N	Mean (SD)	N	Mean (SD)
Generic Core Total score	82	58.3 (15.5) [25.0-97.8]	125	58.7 (14.4)	401	83.0 (14.8)
Physical summary score	82	45.3 (23.8) [3.1-100]	123	43.4 (21.1)	400	84.4 (17.3)
Psychosocial summary score	83	65.4 (15.5) [31.7-96.7]	125	66.6 (16.3)	399	82.4 (15.5)
Emotional	83	66.4 (21.5) [20.0-100]	125	67.0 (23.0)	400	80.9 (19.6)
Social	83	63.3 (18.3) [20.0-100]	125	66.1 (19.5)	399	87.4 (17.2)
School	81	66.7 (19.4) [20.0-100]	124	66.2 (20.9)	386	78.6 (20.5)
Neuromuscular module Total Score	83	72.0 (13.5) [37.0-97.0]	123	67.5 (15.6)	-	-
About my Neuromuscular disease	82	71.7 (13.9) [38.2-98.4]	123	65.9 (16.5)	-	-
Communication	64	63.9 (26.4) [37.0-97.0]	80	70.8 (23.6)	-	-
About our family resources	64	74.9 (20.1) [20.0-100]	80	74.7 (22.2)	-	-
DMD Total Score	64	66.6 (17.8) [26.3-100]	-	-	-	-
Daily activities	64	64.6 (25.0) [15.0-100]	-	-	-	-
Treatment	64	72.6 (24.2) [6.3-100]	-	-	-	-
Worries	64	65.4 (21.9) [16.7-100]	-	-	-	-
Communication	64	63.1 (28.3) [0-100]	-	-	-	-

Table 4-4 Mean parent reported PedsQL Generic Core, Neuromuscular and DMD module scores in boys with DMD, children with spinal muscular atrophy and healthy children

Parent report	Boys with DMD		Spinal Muscular Atrophy (Iannaccone et al., 2009)		Healthy (Varni et al., 2001)	
	N	Mean (SD) [range]	N	Mean (SD)	N	Mean (SD)
Generic Core Total Score	95	51. 9 (16.5) [21.7-93.5]	174	53.4 (14.2)	717	87.6 (12.3)
Physical summary score	95	42.8 (25.7) [0-96.9]	172	36.3 (24.6)	717	89.3 (16.4)
Psychosocial summary score	95	57.2 (15.7) [28.3-95]	174	74.8 (18.2)	717	86.6 (12.8)
Emotional domain	95	62.2 (18.0) [15.0-100]	173	62.2 (17.6)	718	82.6 (17.5)
Social domain	95	50.0 (20.0) [8.3-100]	174	57.4 (17.4)	716	91.6 (14.2)
School domain	95	58.7 (19.5) [25.0-100]	154	63.8 (20.0)	611	85.5 (17.6)
Neuromuscular Module Total Score	96	67.3 (17.0) [25.0-97]	172	59.7 (16.8)	-	-
About my Neuromuscular disease	96	69.2 (17.3) [23.5-100]	176	58.8 (17.7)	-	-
Communication	96	58.0 (28.6) [0-100]	172	67.0 (31.1)	-	-
About our family resources	96	66.7 (23.9) [26.3-100]	176	59.6(22.2)	-	-
DMD Module Total Score	97	61.5 (18.8) [13.9-95.8]	-	-	-	-
Daily activities	97	56.3 (25.5) [0-100]	-	-	-	-
Treatment	96	70.8 (23.5) [6.3-100]	-	-	-	-
Worries	97	60.7 (24.7) [0-100]	-	-	-	-
Communication	93	58.9 (30.2) [0-100]	-	-	-	-

Table 4-5 Results of multivariable logistic regression of rating QOL to be much higher HRQOL on child-reported QoML (N=64).

Parameter	Odds Ratio	95% Confidence Limits
Ambulation	0.6	0.1 - 3.2
Household income	1.0	0.8 - 1.5
Age	1.1	0.8 - 1.4
Parent's highest level of education (post-secondary v.s. not)	5.7	0.7 - 237
Presence of at least one developmental Or mental disorder	0.7	0.1- 2.9
Fatigue score	0.7	0.4 - 1.0
FILE score	0.9	0.7 - 1.0

QOL was considered to be much higher than HRQOL if QOL was 14.9 mm or greater than HRQOL on the VAS (in the top 25%).
Fatigue score: higher fatigue score indicates less fatigue, score was divided by 10 to reflect a more meaninful level of change. The odds ratio is that of child with DMD rating his QOL to be much higher than HRQOL for every 10 unit of increase in fatigue score.
FILE: higher FILE score indicates higher level of family stress experienced in the past year. Score was divided by 50 to reflect a meaningful level of change. Odds ratio represents odds ratio of child with DMD rating his QOL to be much higher than HRQOL for every 50 unit of increase in FILE score

Table 4-6 Results of logistic regression for rating QOL to be much higher than HRQOL on parent-reported QoML (N=74).

Parameter	Odds Ratio	95% Confidence Limits
Ambulation	5.3	0.8 - 35.9
Household income	0.9	0.8 - 1.1
Age	1.0	0.8 - 1.2
Parent's highest level of education (post-secondary v.s. not)	2.0	0.6 - 7.4
Presence of at least one developmental Or mental disorder	0.6	0.1 - 1.3
Fatigue score	0.7	0.5 - 1.0
FILE score	1.0	0.9 - 1.1

QOL was considered to be much higher than HRQOL if QOL was 9.4 mm or greater than HRQOL on the VAS (in the top 25%).
Fatigue score: higher fatigue score indicates less fatigue, score was divided by 10 to reflect a meaninful level of change. The odds ratio is that of parent who rated their child's QOL to be much higher than HRQOL for every 10 unit of increase in fatigue score.
FILE : higher score indicates higher level of family stress experienced in the past year. Score was divided by 50 to reflect a meaningful level of change. Odds ratio is that of parent who rated child with DMD's QOL to be much higher than HRQOL for every 50 unit of increase in FILE score

Table 4-7 Results of backwards elimination models of child and family factors on various child-reported PedsQL measures.

	PedsQL 4.0 Generic Core Total (N=69)	PedsQL 4.0 Generic Core Physical (N=71)	PedsQL 4.0 Generic Core Psychosocial (N=79)	PedsQL 3.0 Neuromuscular Total (N=75)	PedsQL DMD Total (N=59)
Age	N.S.	N.S.	N.S.	0.57 (0.3)	N.S.
Fatigue	0.57 (<0.0001)	0.46 (<0.0001)	0.67 (<0.0001)	0.74 (<0.0001)	0.88 (<0.0001)
FILE score	N.S.	N.S.	N.S.	N.S.	0.011 (0.006)
Household income	N.S.	N.S.	1.14 (0.02)	0.55 (0.06)	N.S.
Wheelchair					
Never (ref.)	---	---		---	---
Intermittent	-7.47 (0.002)	-19.92 (<0.0001)	Did not enter maximum model	N.S.	N.S.
Full-time	-15.14 (<0.0001)	-42.41 (<0.0001)		-12.4 (0.0004)	-14.51 (<0.0001)
Steroid	N.S.	N.S.	N.S.	N.S.	N.S.
≥1 developmental or mental disorder	N.S.	N.S.	N.S.	Did not enter maximum model	Did not enter maximum model
Parental education					
≤ High school (ref.)	---	Did not enter maximum model	Did not enter maximum model	Did not enter maximum model	Did not enter maximum model
Vocational	N.S.				
Post-secondary	4.34 (0.04)				

FVC was not included in models to maximize sample sizes

Parameter estimate and p-value of factors that remained significant (p<0.10) in the final model after backwards elimination are presented

N.S. - Not significant after backwards elimination;

The variables scoliosis and LVEF did not meet criteria to enter maximum model for any of the HRQOL outcomes, they are not presented in the table. Binary variables (coded as Yes/No) are steroid and presence of at least one developmental or mental disorder, the reference group is "No". Multilevel categorical variables are wheelchair status and parental education, the reference category is indicated as 'ref.' Parameter estimates in continuous variables indicates amount of change in HRQOL for one unit change in the explanatory variables.

Table 4-8 Results of backwards elimination models of child and family factors on various parent-reported PedsQL measures.

	PedsQL 4.0 Generic Core Total (N=85)	PedsQL 4.0 Generic Core Physical (N=85)	PedsQL 4.0 Generic Core Psychosocial (N=85)	PedsQL 3.0 Neuromuscular Total (N=88)	PedsQL DMD Total (N=90)
Age	N.S.	N.S.	-0.73 (0.030)	0.62	N.S.
Fatigue	0.53 (<0.0001)	0.37 (0.02)	0.57 (<0.0001)	0.62 (<0.0001)	0.7 (<0.0001)
FILE score	N.S.	N.S.	N.S.	Did not enter maximum model	N.S.
Total household income	N.S.	N.S.	0.82	N.S.	1.27 (0.011)
Wheelchair					
Never (ref.)	---	---	---	---	---
Intermittent	-9.60 (0.0099)	-16.27 (0.007)	-4.7 (0.08)	N.S.	N.S.
Full-time	-8.49 (0.0101)	-19.94 (0.002)	N.S.	-15.6 (<0.0001)	-16.10 (<0.0001)
Scoliosis	N.S.	Did not enter maximum model	N.S.	Did not enter maximum model	Did not enter maximum model
≥1 developmental or mental disorder	N.S.	N.S.	-4.46 (0.074)	N.S.	N.S.
Parental education					
≤ High school (ref.)	---	---	---	Did not enter maximum model	Did not enter maximum model
Vocational	N.S.	N.S.	N.S.		
Post-secondary	6.78 (0.010)	11.54 (0.02)	N.S.		

FVC was not included in models to maximize sample sizes.
Parameter estimate and standard error of factors that remained significant (p<0.10) in the final model after backwards elimination are presented.
N.S. - Not significant after backwards elimination
The variables steroid and LVEF did not meet criteria to enter maximum model for any of the HRQOL outcomes, they are not presented in the table.
Binary variables (coded as Yes/No) are steroid, scoliosis and presence of at least one developmental or mental disorder, the reference group is "No". Multilevel categorical variables are wheelchair status and parental education, the reference category is indicated as 'ref.'. Parameter estimates in continuous variables indicates amount of change in HRQOL for one unit change in the explainatory variabels.

Table 4-9 QoML and PedsQL 4.0 Generic Core scores of ambulatory boys who were diagnosed recently and those who have been diagnosed for longer a period

	Diagnosed after 2012 (N=5)	Diagnosed before 2012 (N=51)
Child report		
QoML Overall	80.9 (24.1)	79.8 (18.1)
QoML Health	75.3 (31.2)	76.4 (20.8)
PedsQL Generic Core Total	69.7 (7.3)	60.0 (14.6)
PedsQL Generic Core Physical	65.6 (7.0)	51.4 (20.5)
PedsQL Generic Core Psychosocial	72.1 (12.0)	64.6 (14.9)
PedsQL Neuromuscular	81.42 (4.92)	73.2 (11.7)
Parent report		
QoML Overall	76.1 (13.9) n=2	69.9 (18.6)
QoML Health	76.8 (16.4)	67.9 (21.5)
PedsQL Generic Core Total	54.6 (13.2)	54.3 (16.4)
PedsQL Generic Core Physical	40.8 (18.0)	47.5 (23.3)
PedsQL Generic Core Psychosocial	63.8 (11.1)	57.9 (15.4)
PedsQL Neuromuscular	77.3 (12.9)	72.5 (13.2)
PedsQL DMD	66.4 (16.7)	67.1 (15.9)

Table 4-10 QoML and PedsQL Generic Core 4.0 scores of non-ambulatory boys who lost ambulation recently and those who have been non-ambulant for a longer period

	Lost ambulation after 2012 (N=3)	Lost ambulation before2012 (N=20)
Child report		
QoML Overall	69.3 (26.8)	80.12 (18.3)
QoML Health	51.0 (40.3)	69.07 (25.6)
PedsQL Generic Core Total	35.5 (6.7)	52.19 (14.2)
PedsQL Generic Core Physical	11.5 (9.3)	25.24 (19.6)
PedsQL Generic Core Psychosocial	48.3 (9.3)	66.88 (17.3)
PedsQL Neuromuscular	50.0 (17.4)	73.24 (11.7)
PedsQL DMD	48.6 (23.2)	62.01 (20.4)
Parent report		
QoML overall	46. 4 (34.9)	71.79 (16.7)
QoML health	40.7 (17.8)	72.89 (17.6)
PedsQL generic core total	35.9 (15.3)	45.59 (14.3)
PedsQL generic core physical	31.3 (43.3)	32.31 (30.1)
PedsQL generic core psychosocial	38.3 (9.3)	54.09 (16.1)
PedsQL Neuromuscular	37.3 (6.8)	53.63 (16.1)
PedsQL DMD	35.2 (15.3)	48.32 (19.9)

Chapter 5

Discussion

This chapter will provide interpretations of study findings and place them in the context of existing literature. Clinical and research implications of some results, as well as the strengths and limitations of the study are discussed. Finally, conclusions and potential future research avenues are presented.

5.1 Summary of Results

5.1.1 Describe the QOL and HRQOL of boys with DMD in Canada from both child and parent perspectives (Objective 1).

When compared to children with rheumatoid arthritis and their parents, respectively, those with DMD and their parents reported poorer QOL and HRQOL (Feldman et al., 2000). This was to be expected given DMD is a life limiting disease whereas rheumatoid arthritis is not usually viewed in that manner. For both DMD and rheumatoid populations, parents' ratings were lower than children's self-assessment, this difference was more pronounced in the DMD population in this study.

Three measures from the PedsQL Inventory were used as multidimensional measures of HRQOL. The results in our sample were similar to those reported by others (McDonald et al., 2010; Uzark et al., 2012). From the generic measure, HRQOL was worse in boys with DMD than healthy children. The biggest difference was found in the physical domain. This is not surprising considering the hallmark of the disease is progressive muscle loss. This was also found to be the case by other studies (Baiardini et al., 2011; Bendixen et al., 2012; Bray et al., 2011; Davis et al., 2010; Elsenbruch et al., 2013; McDonald et al., 2010; Opstal et al., 2013; Uzark et al., 2012). Within the psychosocial summary in the Generic Core module, the social domain was the most impacted, this was also in line with findings of other authors (Bendixen et al., 2012; Elsenbruch et al., 2013; Hu et al., 2013; Uzark et al., 2012). Furthermore, the social domain was also the only one out of the psychosocial domains that fell below the significantly impaired cut-off score, which was designated as one standard deviation below the population mean (Varni et al.,

2003). It is likely that diminished social HRQOL in boys with DMD is partially due to their physical limitations, but social function could also be a reflection of the high level of cognitive deficits in this population, impacting the boys' ability to communicate with others of similar age.

Across all measures QOL and HRQOL, parents' ratings tended to be lower than boys' self-reports, which has been consistently observed across a number of paediatric chronic illnesses (Ingerski et al., 2010; Upton et al., 2008). There could be a number of explanations for this observation: children likely do not understand the long term implications of their disease to the same extent their parents do, may have adjusted to their disorder over time, or may have different concerns than their parents when it comes to factors that influence HRQOL or QOL. Parents may also let their own worries and fear about their child's disease influence their assessment of their child's HRQOL.

Spinal muscular atrophy (SMA) is another type of paediatric neuromuscular illness, and is a good comparison group for DMD. Like DMD, SMA is characterized by progressive muscle weakness, however, muscular degeneration occurs at an earlier age and much more severely. On the other hand, children with SMA are not affected cognitively to the extent of boys with DMD. On the PedsQL 3.0 Neuromuscular module, both boys with DMD and their parents reported higher scores in "About my neuromuscular disease" domain, but lower scores in the "Communication" domain than children with SMA and their parents. This is consistent with the symptomology of the two diseases, there is a higher prevalence of cognitive disability in DMD which could further impact the boys' ability to communicate and socialize with others (Cotton et al., 2001). Children with SMA are not impacted cognitively but have more severe physical symptoms (Iannaccone et al., 2009). In our sample, 51% of parents indicated their child with DMD has a developmental delay and/or learning disorder, and 10% of parents indicated their child has autism spectrum disorder, all of which could have a negative influence on the child's communication skills. However, it should be noted that we did not directly measure the cognitive ability of our sample, and any relationship between cognitive ability and HRQOL is speculative.

Lastly, the more disease-specific PedsQL 3.0 Neuromuscular module was better at discriminating between boys with DMD and children with SMA than the Generic Core module, as the differences between the two groups were more pronounced on the Neuromuscular module than Generic Core module. This was to be expected for disease-specific measures (Eiser & Morse, 2001a; Quittner et al., 2003), which are designed to be more sensitive to differences within a disease group.

5.1.2 Examine the relationship between QOL and HRQOL (Objective 2).

Single-item measures of QOL and HRQOL were rated as distinct but related concepts by both the boys with DMD and their parents. This was also found to be the case by Feldman *et al.* (2000), who found that in a group of children with rheumatoid arthritis, HRQOL explained 30% of the variability in QOL. In our sample, HRQOL explained 21% and 44% of the variability in QOL in child- and parent-reported measures, respectively. Our results supported our hypothesis that boys with DMD and their parents consider QOL and HRQOL to be distinct but related concepts. QOL and HRQOL were significantly related to each other, but for both child and parent reports, over 50% of the variability in QOL were not explained by HRQOL. It is also likely that the association between these two single-item measures of QOL and HRQOL is partially due to common-method variance, specifically because of common scale format and anchoring (Snow et al., 2013). Thus, to further investigate the relationship between QOL and HRQOL, we also tested the association between the single-item QOL and a multidimensional HRQOL, the PedsQL 4.0 Generic Core module, and found that they were not significantly related to one another. However the lack of association between these two measures could be due to differences in their design - QOL is a single-item measure whereas the PedsQL 4.0 Generic Core module is a multidimensional measure. We investigated the relationship between two measures of HRQOL (one single-item and one multidimensional), and found they were significantly associated with one another. It appears that when asked to ‘consider their health’ on the QoML, boys with DMD and their parents considered aspects of the child’s life that are more or less aligned with domains measured by the multidimensional HRQOL. Whereas, when the respondents are

rating the broader, overall QOL, they may be thinking less about their health, or were considering aspects of their lives other than health-related domains. This theory is also supported by our and Feldman's finding that HRQOL explained less than 50% of the variability in QOL.

In the qualitative debriefing that took place during the development of the QoML, factors such as relationship with family and friends were identified, in addition to health, as being important in determining overall QOL (Feldman et al., 2000). People place different values on various aspects of their health and life, leading to different assessments of QOL in relation to HRQOL. Those lacking in health may have other aspects of their lives that 'make up' for that health deficit. Our results support the notion that QOL and HRQOL are regarded as related constructs by boys with DMD and their parents, and suggest there are factors outside of HRQOL that contribute to QOL.

5.1.3 Explore child and family characteristics that contribute to any difference between QOL and HRQOL (Objective 3).

On the QoML questionnaire, QOL and HRQOL were both measured on VAS scales. We explored factors that were associated with the difference between single-item measures of QOL and HRQOL. More specifically, we investigated child and family characteristics that could potentially contribute to boys with DMD and their parents rating QOL to be higher than HRQOL.

For both child self and parent proxy-reports, no factors were found to be significantly associated with a respondent rating their QOL to be higher than HRQOL. However, the lack of significance is likely due lack of statistical power given the small sample size. By child report, children whose parents had post-secondary education were 5.2 times more likely to rate their QOL to be much higher than children whose parents did not have post-secondary education, even though the relationship was not significant. Parental education has been found to be a factor significantly associated with child's HRQOL in a group of children with sickle cell disease (Panepinto et al., 2005).

We divided our sample into two groups: those who rated QOL to be much higher than HRQOL and those who did not. In the latter group, the heterogeneity is greater as we

grouped those who rated QOL to be slightly higher than, equal to, and lower than HRQOL together. The extent of heterogeneity could have reduced the power and contributed to the wide confidence intervals.

5.1.4 Explore the association of child and family characteristics with multidimensional measures HRQOL (Objective 4).

We explored child and family factors associated with multidimensional measure of HRQOL from the PedsQL Inventory. Due to the exploratory nature of our study, we did not anticipate any specific factor as a primary predictor of interest. Instead we used backwards elimination to elucidate a subset of variables that are associated with HRQOL which could inform future research. By both child and parent reports, the factor that was consistently associated with HRQOL was fatigue. Fatigue was associated with every HRQOL outcome, and in greater magnitude than other factors; boys and parents who reported greater fatigue reported worse HRQOL. Fatigue has not been examined closely in the DMD population, as far as we could determine from the literature. Thus, the strong relationship between fatigue and HRQOL came as an unexpected, but not an overly finding.

Muscle fatigue is a physiological consequence of muscle degradation in DMD; decreased lung and heart function all could contribute to weakness and fatigued muscles (Angelini & Tasca, 2012). Fatigue can also be thought of as a subjective experience and measured as such. The PedsQL 3.0 Multidimensional Fatigue module was initially designed to measure fatigue in paediatric cancer patients and was found to be feasible, reliable and valid (Varni et al., 2002). It has also been validated in a variety of other chronic illnesses (Huang et al., 2013; Marcus et al., 2009; Meeske et al., 2004; Varni et al., 2004). Fatigue manifests itself both physically and mentally, and is multidimensional in nature. A confirmatory factor analysis supported the existence of three domains in the PedsQL 3.0 Multidimensional Fatigue Scale: the general, sleep/rest and cognitive domains (Varni et al., 2013).

Other studies have also reported associations between fatigue and poorer QOL or HRQOL in children with chronic illnesses. In a group of paediatric cancer survivors,

fatigue was the only factor significantly associated with both physical and psychological HRQOL (Meeske et al., 2007). Fatigue has consistently been identified as an important, if not the most important factor associated with HRQOL (Eddy & Cruz, 2007; Huang et al., 2013) in children with various chronic illnesses.

Fatigue in neuromuscular disorders has been mostly studied in adults, and samples have, to our knowledge, not included DMD patients. Fatigue is a common complaint of adult patients with neuromuscular illnesses, it was reported by 60% of a cross-sectional sample of adults with common neuromuscular disorders (Kalkman et al., 2005). In other studies of adults with neuromuscular illness, fatigue was one of the factors associated with HRQOL (Burns et al., 2012; Oksuz et al., 2009). In a study of people with muscular dystrophies, pain and fatigue were found to be independently associated with lower physical function and greater depression (Alschuler et al., 2012).

Because fatigue is such a common manifestation in neuromuscular illnesses, some neuromuscular disease-specific HRQOL measures contain a fatigue-related component. For example, the Individualized Neuromuscular QoL questionnaire for adults has a fatigue domain (Rose et al., 2012). In our study, it was noted that the PedsQL of fatigue module and the PedsQL Neuromuscular module share two of the questions, which renders them not completely independent from each other. However, given the strong significance in every other module, where there were no identical questions, we believe this is a robust finding. We also examined whether there were any associations between fatigue and other clinical variables. By parent proxy-report, there were no significant associations between fatigue and any of the clinical variables such as age and FVC. In contrast, by child report, children who were using a wheelchair intermittent had significantly greater fatigue than children not using a wheelchair. Perhaps boys who are just transitioning into wheelchair use struggle with trying to maintain ambulation when they maybe too weak to do so. This is a well-recognized clinical issue often resulting in pain and falls. Taken together, fatigue was clearly a significant factor negatively impacting HRQOL of boys with DMD, and this is an important novel finding which potentially contributes to advancing research and improving clinical care for DMD patients.

Another factor consistently associated with HRQOL was wheelchair use. Boys who were in wheelchairs, had poorer HRQOL than boys not in wheelchairs across all HRQOL measures, with the exception of psychosocial summary score. The negative disease milestone of transition to full time wheelchair use is of particular focus to boys, their families and clinicians and so this finding is not surprising in the clinical context. This result is similar to other studies that found significant associations between clinical measures of strength and physical HRQOL, but not psychosocial HRQOL (Bray et al., 2010, 2011; McDonald et al., 2010). These results suggest that while progression of DMD severely impacts physical aspects of a child's life, it does not necessarily impact the emotional aspects of a child's life, at least, not to the same degree as the physical aspect.

Age was only associated with the PedsQL 3.0 Neuromuscular module, and no other HRQOL measures. This was a somewhat surprising result as age is often considered a proxy for disease severity and one would speculate that it would be associated with HRQOL. The fact that age did not remain significantly associated with most measures of HRQOL could be the result of adjusting for other factors such as wheelchair usage. In unadjusted analyses, by parent proxy-report, age was related to all measures of HRQOL; by child report, age was related to PedsQL 4.0 Generic core total and physical summary score, and the Neuromuscular module score. In other studies (Davis et al., 2010; Uzark et al., 2012), older boys with DMD had poorer physical HRQOL than younger boys, but not worse psychosocial HRQOL.

Having at least one developmental or mental disorder was negatively associated with parents' report of their child's psychosocial HRQOL is consistent with other literature (Panepinto et al., 2005). A study of children with epilepsy also found that presence of cognitive problems was predictive of poorer HRQOL (Speechley et al., 2012).

FVC appears to be a significant factor only in the PedsQL 3.0 DMD module is consistent with the physical manifestation of the disease. Loss of respiratory function is an important aspect of DMD, and its association with the DMD module highlights the sensitivity of the PedsQL 3.0 DMD module to the disease itself.

Due to the exploratory nature of our study, we used multivariable regressions where all the explanatory factors were treated as equals. Alternatively, structural equation modelling, and more specifically, path analysis, would allow us to investigate the relationship between the explanatory variables in a more sophisticated manner and potentially establish a more causal relationship between these variables and the outcome. For example, a potential path could be that FVC or ambulation status affects fatigue level, which in turn affects HRQOL.

5.1.5 Compare QOL and HRQOL of ambulant boys who were diagnosed recently to those who were diagnosed longer ago (Objective 5).

We compared HRQOL of boys who were diagnosed more recently (after 2012) with those who had been diagnosed for longer (before 2012) but who were at the same plateau phase of the disease (i.e. who were still ambulant). During this phase, the health condition of these boys stays relatively constant. Thus we hypothesized that boys who were diagnosed more recently and their parents would report worse HRQOL than boys who have been diagnosed for longer who have had more to time to adjust to the diagnosis. This was not what we found. Within the ambulatory group, there were no differences in any of the HRQOL outcomes between boys who were diagnosed after 2012 and boys who had been diagnosed for longer. This did not support our hypothesis that the boys more recently diagnosed would have worse HRQOL, even on the psychosocial HRQOL. The fact our results did not support our hypothesis was not as surprising in child-report as it is for parent proxy reports. When these boys were diagnosed, they were very young and thus they may not have had the cognitive capacity to comprehend the impact of their disease and what their future holds. But for the parents this is often a devastating time and the clinical experience is that parents seem to be more affected, emotionally, than the child himself because parents are able to envision their child's future and how DMD will impact it. It should also be noted that any interpretation of results must be done with caution as the samples sizes are small. It might also be worthwhile, in the future, to compare the HRQOL of parents whose boys were recently diagnosed to that of parents whose boys who had been diagnosed for longer.

5.1.6 Compare QOL and HRQOL of boys who lost ambulation recently to those who lost ambulation longer ago (Objective 6).

Loss of ambulation is considered a major transition point in the course of DMD. In the non-ambulatory group, there were no statistically significant differences between boys who lost ambulation within the last year and boys who have been non-ambulant for longer than one year. However, the lack of significance could be due to small sample sizes, as there were only 3 boys who lost ambulation within the past year. The boys who lost ambulation over one year ago had much better HRQOL than boys who lost ambulation more recently, even though the differences were not significant. It seems that loss of ambulation is a particularly distressing event for the boys with DMD and their parents. This was found to be the case by Bray et al. (2011) who reported that parents of boys with DMD reported that their son's transition to wheelchair had a very negative emotional impact, and that their emotional coping was disrupted at time of loss of ambulation. It is also possible that as time passes, there is some adjustment in the HRQOL after the first year as the child stays in the long period of non-ambulation plateau.

5.2 Implications

This study examined QOL and HRQOL in a sample of boys with DMD across Canada. It demonstrated the feasibility and some of the challenges of using a nation-wide registry, the CNDR, and mail-out questionnaires to conduct research studies. A national, clinic based registry is a valuable research tool for studies of this nature. The ability to engage a broad representative sample of patients from different clinics and regions is reassuring for generalizing the results to the larger DMD population. Further, the ability to use accurate data collected in the clinic confers more confidence in study results than patient driven web-based registries available in other countries. Of particular importance to the generalizability of patient reported outcomes such as QOL and HRQOL, is the ability to compare respondents to non-respondents and determine if any significant differences exist. A registry based study can provide this valuable information.

This study replicated previous findings that HRQOL in boys with DMD are poorer than that of healthy children, from both children's and parents' perspectives. Also in line with other studies, we found that the social aspect of HRQOL in boys with DMD are affected more than emotional and school aspects. Given this knowledge, efforts can be made to enhance the social HRQOL of boys with DMD. For example, these boys may participate in social skills training program to improve their abilities to interact with others. Furthermore, teachers and education assistants can develop programs and scenarios that encourage more seamless participation of boys with DMD alongside their typically developing classmates. Finally, school-based education programs may also be implemented to reduce stigma, improve knowledge and attitudes toward boys with DMD. Such programs have found success with epilepsy (Martiniuk et al., 2007).

To our knowledge, this is the first study that explores the relationship between QOL and HRQOL in the DMD population, and one of very few studies that have addressed these concepts in the child health realm. The finding that QOL and HRQOL are distinct but related concepts corroborates the findings of Feldman *et al.* (2000). This finding emphasizes the need to recognize QOL as a more holistic representation of the child's subjective experiences. Such recognition can help clinicians to more effectively guide families of boys with DMD in making disease management decisions that will have the most beneficial impact on the lives of these boys, not just their health. In addition, this finding highlights the importance of continued investigation into the relationship between QOL and HRQOL. For example, a qualitative study may be carried out where boys with DMD and their parents are asked how their ideas of QOL and HRQOL differ. Information from this type of study could drive further cross-sectional and longitudinal studies that include a more comprehensive dataset to better understand the contributions of various factors to QOL and HRQOL.

This study identified fatigue as a potentially modifiable factor associated with a number of HRQOL outcomes, which was an unexplored concept in DMD. The formal assessment of fatigue has not been a focus of standard clinical care for children with DMD either, and our conclusions suggest that it warrants much more attention from clinicians. Modifying school and home schedule to ensure adequate rest, and improving sleep

hygiene could also lead to reduction of fatigue. The higher level of fatigue in boys who use wheelchair intermittent compared to those use wheelchairs full-time suggest that earlier initiation of full-time wheelchair use could reduce fatigue, and if families and clinicians are more aware of the impact on HRQOL then this may become a more palatable intervention. Other implications for clinicians arise from this study, placing increasing importance on understanding factors that contribute to fatigue. For example sleep apnea is a commonly reported problem in children with DMD (Polat et al., 2012) and contributes to daytime sleepiness and fatigue, perhaps earlier monitoring of sleep quality can be initiated to reduce fatigue.

Even though this was a cross-sectional study, it supported the paradigm that loss of ambulation is an extremely stressful event. Perhaps in addition of providing the boys with DMD with wheelchair support, emotional support, such as referral to a counselor could also be provided. Anticipatory guidance about wheelchair is likely lacking currently in the clinics as so much of the focus is on preventing loss of ambulation, and real discussion and planning about wheelchair use is often neglected. The knowledge that HRQOL of boys who lost ambulation seem to be better in those who have been non-ambulant for longer period of time, and that advancing age is not necessarily associated with a progressive decline of HRQOL, could also offer hope to children and parents who do not recognize that their HRQOL does not precipitously fall over time.

The Food and Drug Administration has mandated that patient-reported outcomes such as QOL and HRQOL be included as endpoints of clinical trials. A number of promising therapies for DMD are in various stages of clinical trials. In order to be able to interpret these forthcoming results, minimally clinically important differences (MCID) need to be established to understand the magnitude of change that is meaningful to patients. MCIDs of QOL and HRQOL measures are important on their own, and they also help to establish clinical meaningfulness of other commonly used endpoints such as 6-Minute Walk Test through associating changes in these endpoints to changes in HRQOL outcomes. Our study provided a profile of HRQOL at different stages and set the foundation for longitudinal studies in order to establish MCIDs.

Our identification of fatigue as a potential determinant of HRQOL suggests that perhaps fatigue could be measured alongside HRQOL in future clinical trials. Inclusion of fatigue measures would help us determine whether the treatment in question has an effect on fatigue as well as HRQOL. Longitudinal study involving both fatigue and HRQOL measures would also establish magnitude of change in fatigue that corresponds with a meaningful change in HRQOL. Furthermore, since fatigue appears to be such an important factor associated with HRQOL in boys with DMD, and fatigue is a multidimensional measure, future research should explore specific aspects of fatigue that contribute most to HRQOL. Doing so would enable clinicians to target a specific aspect of fatigue (e.g. sleep/rest fatigue) that might have the biggest impact on improving HRQOL in boys with DMD. Finally, the relationship between fatigue and other clinical endpoints such as 6-Minute Walk Test and strength measures could be established in future studies to compare sensitivity of clinical endpoints to changes in disease severity

Our study showed support for the notion that QOL and HRQOL are distinct but related concepts and we believe this finding could have implications for clinical trial outcomes. There is a theory that QOL tend to stay more stable than HRQOL over time (Cummins, 1998), as people tend to maintain a state of homeostasis in their lives. Thus, in clinical trials, if we have both QOL and HRQOL measures, we would expect HRQOL may change more in response to the treatment. Having a measure of QOL could serve as a reference point, and help us better interpret changes in HRQOL.

5.3 Strengths and Limitations

There are several strengths of our study. This study offered one of the most comprehensive examinations of QOL and HRQOL in the pediatric DMD population to date. It was one of the first that used a national registry to recruit patients and thus is made up of a more representative sample than studies that recruited their participants from a single clinic. This study used a variety of measures that ranged from general to disease-specific and included both child self-report and parent proxy-report, to capture the most complete perspective possible. This study is the first to examine child and family factors associated with HRQOL via multivariable regressions. We identified a potentially modifiable clinical factor, fatigue that could lead to improvement of HRQOL

in this population. Finally, this was the first study that explored the relationship between QOL and HRQOL, providing empirical evidence for the distinction between these two concepts.

This study also had a number of limitations. The cross-sectional nature of the study did not allow for causal relationships to be established. Also, the QoML measure has not been validated in the DMD population, nor has it been used, to our knowledge, in young children. A study found that only 42% of kindergarten aged children (5.0-6.8 years of age) were able to complete VAS scales satisfactorily on their own (Shields et al., 2003). In the young children group in our sample, 50% (N=13) of the QoML measures were not filled (returned blank). Of the young children who did complete the QoML measure, the majority had checked the box beside 'this form with filled out by my parent'. Presumably, for these children, their answers were physically marked on the VAS by their parents. This brings forth another limitation, which is that due to the mail-out nature of our study, we cannot be sure of the extent to which parents 'helped' their boys completes their questionnaire. We had provided instructions for children and parents to complete their questionnaires independently, and if the child does require help with reading comprehension, that the parent does not influence their child's answers. However, it is still possible that some parents had some influence over their child's responses. One way of examining this potential issue is to compare the concordance between children and parents in our sample to studies where one can be sure children and parents completed HRQOL assessments independently. For example, some studies had their participants complete the questionnaires in clinics under the supervision of research assistants (Davis et al., 2010; Uzark et al., 2012). If the concordance in our sample is significantly higher than those of other studies, it might suggest that parents had 'helped' their children complete their questionnaires. Another potential limitation is the accuracy of the CNDR information. Registry updates are reliant upon individual clinics, and clinical information is supposed to be updated each time a patient visits clinic. Due to limited resources at some sites, not all patients have the most updated information. Thus, some of the clinical characteristics in our study, despite our best efforts, were out of date (e.g. FVC was more than a year old). However, the majority of the patients did have up-

to-date information in the registry, particularly with regards to major disease milestones such as transition to intermittent and full-time wheelchair use.

Lastly, our response rate of 56% is not ideal, generating a concern regarding the generalizability of our results. This concern is somewhat alleviated by the use of a registry to recruit participants, which allowed for their comparison to non-participants on a number of characteristics such as age and ambulation status. There were no statistically significant differences between the two groups in any of these characteristics, suggesting that our respondents are fairly similar to those who did not respond. However, as the non-respondents were slightly older and more likely to have lost ambulation, it is possible that the non-respondents are at a more severe stage of the disease than boys who did respond. Therefore, it is possible that the QOL and HRQOL are somewhat overestimated in our sample, especially in the physical domain.

A possible reason for our response rate could be related to our recruitment method. Per policies of the CNDR, we, as the study investigators, could not have direct contact with families who did not respond to our questionnaires. This lack of direct contact may have limited our response rate as it has been shown that contacting potential participants before sending the questionnaire and contacting non-respondents directly increased final response rates (Edwards, 2002).

5.4 Conclusions and Future Work

QOL and HRQOL of boys with DMD as judged by self-report and parent-report, are worse than the healthy population, and children with other types of chronic illnesses. Domains related to physical function were affected more than domains related to psychological and social functioning. It appears that QOL and HRQOL are related constructs, but there are factors outside of HRQOL that contribute to the QOL of boys with DMD. Further research is needed is to elucidate these factors. Fatigue has emerged as a clinically amendable factor associated with HRQOL and warrants further attention from clinicians and researchers. Lastly, it appears that loss of ambulation is particularly difficult event for the boys and their parents, but there is evidence that HRQOL potentially improves over time.

We are currently in the process of extending our cross-sectional project into a two-year longitudinal project and have already begun the process of collecting data for the second time point. We will be able to track temporal changes in QOL and HRQOL in our sample of boys with DMD, and be able to explore the relationship between QOL and HRQOL over time. Finally, we will be able to establish more causal relationships between potential determinants of HRQOL and HRQOL outcomes.

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Appendices

Appendix A Ethics Approval

Western Research

Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Craig Campbell
File Number:103358
Review Level: Delegated
Approved Local Adult Participants:0
Approved Local Minor Participants:50
Protocol Title: Understanding Quality of Life and Health Related Quality of Life in Children Affected by Duchenne Muscular Dystrophy
Department & Institution: Schulich School of Medicine and Dentistry\Epidemiology & Biostatistics,London Health Sciences Centre
Sponsor:
Ethics Approval Date: February 06, 2013 **Expiry Date:**June 30, 2014
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Instruments		
Instruments		
Instruments		
Western University Protocol		2012/12/18
Assent	assent letter with letterhead	
Caregiver Letter of Information & Consent	Letter of information with letterhead	
Instruments	updated demographics questionnaire	2013/02/05

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

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

Signature

Ethics Officer to Contact for Further Information

This is an official document. Please retain the original in your files.

Appendix B Letter of Information and Assent Letter

Children's Hospital
London Health Sciences Centre

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

Investigators: Dr. Craig Campbell and Dr. Kathy Speechley, Department of Paediatrics, Children's Hospital, London Health Sciences Centre, and Sally Wei, 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 and health related 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 (www.CNDR.org). The purpose of this letter is to provide you with information required for you to make an informed decision regarding participation in this research. Quality of life research allows healthcare workers to better understand the challenges children with DMD and their families face, and lead to better clinical care of these children.

Males between the ages of 4-18 with a confirmed diagnosis of DMD, who have been in the care of a parent for at least 6 months, are eligible for this study. Individuals with any significant medical problems not related to DMD, who are unable to complete the study protocol because of an inability to read and write English or French are not eligible to participate. 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 some questionnaires that are for your parent to complete separately from you, some that you can complete together and some that you should complete on your own. 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) then, of course, you may ask your parents to help you. If you do get help please do your best to answer the question using your own feelings. There are no right or wrong answers for these questionnaires because they ask about how you feel about your life and your health. For the parent questionnaires we ask that all the forms be completed by the same parent, and it does not matter if this is your mother or father. We would ask that once the questionnaires are complete that you place them in the included, pre-posted envelope and send them back to us.

Consent:

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

Risks:

There are no known risks or discomforts associated with participating in this study. However, if you do experience any problems or discomfort, you may discontinue the task at any time.

Benefits:

You may not directly benefit from participating in this study, but 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. You will not be compensated for your participation in this research. 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.

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 Dr. Craig Campbell,

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

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

Children's Hospital
London Health Sciences Centre

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 this study is 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.

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 test, and there are no right or wrong answers.

3. **Will the study help you?**
   No, this study will not help you directly but 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 the teachers, your family or someone else.

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.

Appendix C Reminder Postcard and Letter

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 and we will get another one in the mail to you today.

Craig Campbell, MD
Paediatric Neurologist
Department of Paediatrics

About 4 weeks ago a questionnaire 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.

The responses of participants who have already returned their questionnaires include a wide variety of experiences with Duchenne Muscular Dystrophy(DMD). We think 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 questionnaire has 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 study number will identify 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, but 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.

Sincerely,

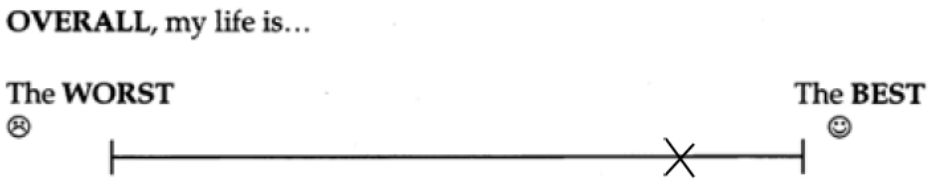
Craig Campbell, MD
Paediatric Neurologist
Department of Paediatrics

Appendix D Quality of My Life Questionnaire Follow Up Letter

Thank you so much for participating in our research study "**Quality of Life and Health Related Quality of Life in Children with Duchenne Muscular Dystrophy**". Your feedback has helped us better understand the experiences of children and families living with Duchenne muscular dystrophy (DMD) and learn how to best support children with DMD.

When reviewing the responses we noticed that you did not answer two of the questions in Section 1 of the questionnaire, these questions are essential for us to gain a comprehensive understanding of the quality of life in children with DMD. If it was your intention to leave these questions blank, please disregard this letter. However, we have seen that a number of people left these questions blank, leading us to believe that the way the questionnaire was set up, led to some confusion about how to complete that section. We have revised the instructions for these two questions to clarify and attached the questions again here.

The questions asks you to rate your (the child with DMD) quality of life by marking an "X" along a line, between "the worst" and "the best". For example, if someone feels his/her quality of life is great, he/she will put the "X" closer towards "the best".



On the next page you will see two similar but different questions so please place an "X" on the line for both questions "OVERALL, my life is…" and "Considering my HEALTH, my life is…".

There are two pages with the same questions: one to be completed by you (the person with DMD) to rate your quality of life; one to be completed by your parent to indicate their opinion of your quality of life. Please indicate who completed the questionnaire by checking the box(es) beside "This form was filled out by". Once done, please return by mail using the pre-addressed envelope.

Thank you again,

Craig Campbell

Appendix E Instructions for Young Child Report

INSTRUCTIONS

TO PARENTS:

1. Due to the young age of your child, we ask that you act as "interviewer" to your child. Please carefully follow the instructions for each section of the questionnaire. While helping your child complete the questionnaires, please indicate **his** answers, without your input. Do not interpret the question for him. Repeat the item to him exactly as written. Ask him to answer the item according to what *he thinks the question means*. If he has trouble deciding on an answer, ask him to choose the response that comes closest to how he feels.

2. Certain questions may look alike or even identical to each other, please try to answer all of the questions on each page.

3. If your child is unable to complete the questionnaire, even with some help from you, please indicate this by checking this box. ☐ And please return this booklet along with the parent questionnaire.

Appendix F Instructions for Child and Teen Reports

INSTRUCTIONS

1. Please answer these questions on your own.
2. There is no right or wrong answer. If you are unsure how to answer a question, please give the best answer you can. Write any comments you may have on the page beside the question or at the end of questionnaire.
3. Answer questions by checking the appropriate box or circling the appropriate number. Please answer questions thinking of the **past month**.
4. Certain questions may look alike or even identical to each other, please try to answer all of the questions on each page.

TO PARENTS:

1. If your child is unable to read the questions, you may read the questions to him. While helping your child complete the questionnaires, please indicate **his** answers, without your input. Do not interpret the question for him. Repeat the item to him exactly as written. Ask him to answer the item according to what *he thinks the question means*. If he has trouble deciding on an answer, ask him to choose the response that comes closest to how he feels.
2. If your child is unable to complete the questionnaire, even with some help from the parent, please indicate this by checking this box. ☐ And please return this booklet along with the parent questionnaire.

Appendix G Instructions for Parent Reports of All Age Groups

INSTRUCTIONS

1. Throughout this questionnaire when we refer to "your child", we are referring to your child with Duchenne muscular dystrophy.
2. Most of the questions in this booklet ask about your son's health and well-being. A few of the questions ask about your own and your family's health and well-being. Your individual answers will remain strictly confidential.
3. Answer questions by checking the appropriate box or circling the appropriate number. Please answer questions thinking of the **past month**.
4. Certain questions may look alike or even identical to each other, please try to answer all of the questions on each page.
5. There is no right or wrong answer. If you are unsure how to answer a question, please give the best answer you can. Write any comments you may have on the page beside the question or at the end of the questionnaire.

Appendix H Quality of My Life Questionnaire

For the first two questions, place an "X" along the line to indicate your child's quality of life

Quality of My Life

Some of the children who come to see us feel that their life is not that great, while others think that their life is O.K. How about you?

OVERALL, my life is…

The **WORST** ☹ — The **BEST** ☺

Considering my **HEALTH**, my life is …

The **WORST** ☹ — The **BEST** ☺

Check one or both boxes.
This form was filled out by

Me: ❑

My parent: ❑

Other: ❑
(please explain)

Date: □□□□/□□/□□
(Year/Month/Day)

Appendix I Pediatric Quality of Life 4.0 Generic Core Module

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other children not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Appendix J Pediatric Quality of Life Inventory 3.0 Neuromuscular Module

*In the **PAST MONTH**, how much of a **problem** has this been for your child …*

ABOUT MY CHILD'S NEUROMUSCULAR DISEASE (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for my child to breathe	0	1	2	3	4
2. My child gets sick easily	0	1	2	3	4
3. My child gets sores and/or rashes	0	1	2	3	4
4. My child's legs hurt	0	1	2	3	4
5. My child feels tired	0	1	2	3	4
6. My child's back feels stiff	0	1	2	3	4
7. My child wakes up tired	0	1	2	3	4
8. My child's hands are weak	0	1	2	3	4
9. It is hard for my child to use the bathroom	0	1	2	3	4
10. It is hard for my child to gain or lose weight when he or she wants to	0	1	2	3	4
11. It is hard for my child to use his or her hands	0	1	2	3	4
12. It is hard for my child to swallow food	0	1	2	3	4
13. It takes my child a long time to bathe or shower	0	1	2	3	4
14. My child gets hurt accidentally	0	1	2	3	4
15. My child takes a long time to eat	0	1	2	3	4
16. It is hard for my child to turn him or herself during the night	0	1	2	3	4
17. It is hard for my child to go places with his or her equipment	0	1	2	3	4

COMMUNICATION (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for my child to tell the doctors and nurses how he or she feels	0	1	2	3	4
2. It is hard for my child to ask the doctors and nurses questions	0	1	2	3	4
3. It is hard for my child to explain his or her illness to other people	0	1	2	3	4

ABOUT OUR FAMILY RESOURCES (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for our family to plan activities like vacations	0	1	2	3	4
2. It is hard for our family to get enough rest	0	1	2	3	4
3. I think money is a problem in our family	0	1	2	3	4
4. I think our family has a lot of problems	0	1	2	3	4
5. My child does not have the equipment he or she needs	0	1	2	3	4

Appendix K Pediatric Quality of Life 3.0 Duchenne Muscular Dystrophy Module

*In the past **ONE** month, how much of a **problem** has your child had with…*

DAILY ACTIVITIES *(PROBLEMS WITH...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Trouble eating with a fork and knife	0	1	2	3	4
2. Difficulty writing or drawing with a pen or pencil	0	1	2	3	4
3. Difficulty putting his/her clothes on	0	1	2	3	4
4. Using the toilet without assistance	0	1	2	3	4
5. Needing more time to complete tasks	0	1	2	3	4

TREATMENT *(PROBLEMS WITH...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Taking medicines	0	1	2	3	4
2. Physical therapy or daily exercise causing pain	0	1	2	3	4
3. Difficulty being responsible for medicines or physical therapy	0	1	2	3	4
4. Difficulty managing his or her muscle problem	0	1	2	3	4

WORRY *(PROBLEMS WITH...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Worrying about his or her muscle problem	0	1	2	3	4
2. Worrying about whether or not medicines are working	0	1	2	3	4
3. Worrying about his or her family	0	1	2	3	4
4. Worrying about needing help from others	0	1	2	3	4
5. Worrying about not being accepted by others	0	1	2	3	4
6. Worrying about being treated differently than others his/her age	0	1	2	3	4

COMMUNICATION *(PROBLEMS WITH...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty telling the doctors and nurses how he/she feels	0	1	2	3	4
2. Difficulty asking the doctors and nurses questions	0	1	2	3	4
3. Difficulty explaining his/her muscle problem to other people	0	1	2	3	4

Appendix L Pediatric Quality of Life 3.0 Fatigue Module

*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
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(PROBLEMS WITH...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(PROBLEMS WITH...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

Appendix M Demographic and Medical Questionnaire

The following questions ask you about some other health experiences your child may have had:

1. 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:		

2. Has your child ever been diagnosed with any of the following developmental disorders:

	No	Yes
Developmental delay		
A learning disability		
Attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD)		
Autism, pervasive developmental disorder (PDD) or Asperger's syndrome		
Oppositional defiant disorder		
Conduct disorder		
Depression		
Anxiety		

3. For each of the following please provide two answers, 1) whether your child has ever needed and 2) whether your child has ever received:

	1) Needed		2) Received	
	No	Yes	No	Yes
Extra help with school work (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, please specify:				

4. Is your child currently involved any clinical trials or other research studies for his DMD?

☐ Yes ☐ No

5. Was your child diagnosed with DMD less than a year ago?

☐ Yes ☐ No

6. Is your child able to walk?

☐ Yes ☐ No

If no, did your child stop walking

☐ Less than 1 year ago ☐ Greater than one year ago

7. When was your child born?

☐☐ / ☐☐

MONTH YEAR

The following questions ask you about your family structure:

8. Are you:

☐ Male ☐ Female

9. Who lives with your child currently?

Person	Their relationship to your child	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

10. 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

11. 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)

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12. What is the highest grade of school you have completed?

- ☐ less than 8 years
- ☐ 8-12 years
- ☐ completed high school
- ☐ completed vocational/technical training
- ☐ completed college/university
- ☐ completed graduate school
- ☐ choose not to answer

13. What is your age?

☐☐

14. What is your current marital status? (check one box only)

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

15. Are you currently living with a spouse or partner?

☐ Yes ☐ No If no, go to question 17

16. 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

17. What is the highest grade of school your spouse/partner has completed?

- ☐ less than 8 years
- ☐ 8-12 years
- ☐ completed high school
- ☐ completed vocational/technical training
- ☐ completed college/university
- ☐ completed graduate school
- ☐ choose not to answer

18. In which category is your total yearly household income before taxes? (check one box only)

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

19. 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, Super-annuation
- ☐ Dividends and interest on bonds, deposits, and saving certificates
- ☐ Other government sources such as welfare, mother's allowance, etc.
- ☐ Other sources(s), please specify: _____

Appendix N Family Inventory of Life Events

Over their life cycle, all families experience many changes as a result of normal growth and development of members and due to external circumstances. The following list of family life changes can happen in a family at any time. Because family members are connected to each other in some way, a life change for any one member affects all the other persons in the family to some degree.

*"**FAMILY**" means a group of two or more persons living together who are related by blood, marriage or adoption. This includes persons who live with you and to whom you have a long term commitment.*

Please read each family life change and decide whether it happened to any member of your family - **including you** - during the past 12 months and check **Yes** or **No**.

Did the change happen in your family:	During the Last 12 Months **Yes**	**No**
I. Intrafamily Strains a. Increase of husband/father's time away from family		
b. Increase of wife/mother's time away from family		
c. A member appears to have emotional problems		
d. A member appears to depend on alcohol or drugs		
e. Increase in conflict between husband and wife		
f. Increase in arguments between parent(s) and child(ren)		
g. Increase in conflict among children in the family		
h. Increased difficulty in managing teenage child(ren)		
i. Increased difficulty in managing school age child(ren) (6-12 yrs)		
j. Increased difficulty in managing preschool age child(ren) (2.5-6 yrs)		
k. Increased difficulty in managing toddler(s) (1-2.5 yrs)		
l. Increased difficulty in managing infant(s) (0-1 yr)		
m. Increase in the amount of "outside activities" which the children are involved in		
n. Increased disagreement about a member's friends or activities		
o. Increase in the number of problems or issues which don't get resolved		
p. Increase in the number of tasks or chores which don't get done		
q. Increased conflict with in-laws or relatives		

Did the change happen in your family:	During the Last 12 Months Yes	No
II. Marital Strains a. Spouse/parent was separated or divorced		
b. Spouse/parent had an "affair"		
c. Increased difficulty in resolving issues with a "former" or separated spouse		
d. Increased difficulty with sexual relationship between husband and wife		
III. Pregnancy and Childbearing Strains a. Spouse had unwanted or difficulty pregnancy		
b. An unmarried member became pregnant		
c. A member had an abortion		
d. A member gave birth to or adopted a child		
IV. Finance and Business Strains a. Took out a loan or refinanced a loan to cover increased expenses		
b. Went on welfare		
c. Change in conditions (economic, political, weather) which hurts the family investments		
d. Change in agriculture market, stock market, or land values which hurts family investments and/or income		
e. A member started a new business		
f. Purchased or built a home		
g. A member purchased a car or other major item		
h. Increased financial debts due to over-use of credit cards		
i. Increased strain on family "money" for medical/dental expenses		
j. Increased strain on family "money" for food, clothing, energy, home care		
k. Increased strain on family "money" for child(ren)'s education		
l. Delay in receiving child support or alimony payments		
V. Work-Family Transitions and Strains a. A member changed to a new job/career		
b. A member lost or quit a job		
c. A member retired from work		
d. A member started or returned to work		
e. A member stopped working for extended period (e.g., laid off, leave of absence, strike)		
f. Decrease in satisfaction with job/career		
g. A member had increased difficulty with people at work		
h. A member was promoted at work or given more responsibilities		
i. Family moved to a new home/apartment		
j. A child/adolescent member changed to a new school		

Did the change happen in your family:	During the Last 12 Months	
	Yes	**No**
VI. Illness and Family "Care" Strains a. Parent/spouse became seriously ill or injured		
b. Child became seriously ill or injured		
c. Close relative or friend of the family became seriously ill		
d. A member became physically disabled or chronically ill		
e. Increased difficulty in managing a chronically ill or disabled member		
f. Member or close relative was committed to an institution or nursing home		
g. Increased responsibility to provide direct care or financial help to husband's and/or wife's parents		
h. Experienced difficulty in arranging for satisfactory child care		
VII. Losses a. A parent/spouse died		
b. A child member died		
c. Death of husband's or wife's parent or close relative		
d. Close friend of the family died		
e. Married son or daughter was separated or divorced		
f. A member "broke up" a relationship with a close friend		
VIII. Transitions "In and Out" a. A member was married		
b. Young adult member left home		
c. Young adult member began college (or post high school training)		
d. A member moved back home or a new person moved into the household		
e. A parent/spouse started school (or training program) after being away from school for a long time		
IX. Family Legal Violations a. A member went to jail or juvenile detention		
b. A member was picked up by police or arrested		
c. A member ran away from home		
d. A member dropped out of school or was suspended from school		

Curriculum Vitae

Name: Yi Sally Wei

Post-secondary Education and Degrees:

The University of Western Ontario
London, Ontario, Canada
2007-2012 BSc in Biochemistry

The University of Western Ontario
London, Ontario, Canada
2012-2014 MSc in Epidemiology and Biostatistics

Honours and Awards:

Western Research Graduate Scholarship
The University of Western Ontario, London, Ontario
2012-2014

Graduate Student Quality of Life Initiative
Children's Health Research Institute , London, Ontario
2013-2014

Presentations:

Canadian Neurological Sciences Federation 49th Congress (oral)
June 2014

Canadian Society of Epidemiologists and Biostatistics Conference (poster)
May 2014

London Health Sciences Centre Paediatrics Department Research day (oral)
May 2014

London Health Research Day (poster)
March 2014

Epidemiology Department Student Research Day (oral)
September 2013