BONE HEALTH AND QUALITY OF LIFE IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY

By

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A THESIS

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CERTIFICATE OF APPROVAL

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Abstract

Introduction: The incidence of Duchenne muscular dystrophy (DMD) is 1/3500 male births. This disease is progressive; the life expectancy is 25-30 years of age. Children affected by this disease have higher fracture incidence than children in the general population. The factors that influence development of fractures in children with DMD have not been clearly defined. Health-related quality of life is lower in children with DMD than the general pediatric population. Few risk factors for decreased quality of life have been identified, and the potential effect of fractures on quality of life has not been explored.

Methods: Subjects were recruited from patients with DMD attending Shriners Hospital for Children in Portland, Oregon. Demographic and medical history was gathered from chart review. A thirty-minute survey was conducted with parents using PedsQL and PedsQL Neuromuscular Module to assess health-related quality of life. Data were analyzed using multivariable linear regression with conditional logistic regression for questions arising from the (nested) matched case-control part of the study.

Results: Seventeen of 57 subjects (30%) had a history of fracture. Potential relationships between higher baseline functional status and fracture (OR 0.30; 95% CI: 0.08 – 1.20; p = 0.08), ambulatory status and fracture (OR 4.88; 95% CI: 0.56 – 42.5; p = 0.15), and change of function by at least one level within the year prior to fracture and fracture (OR 3.27; 95% CI: 0.6 – 18.3; p = 0.18) were identified in the setting of a small sample size and wide confidence intervals. Steroid use did not appear to influence fracture occurrence in this sample (OR 0.63; 95% CI: 0.10 – 3.0; p = 0.61). Quality of life scores had a wide range in each sub-domain. History of fracture was associated with lower functional quality of life

scores (9.0 points lower on average; SE 4.4 points; p = 0.05) and approached significance with regard to lower emotional quality of life scores (13.4 points lower on average; SE 7.0; p = 0.06).

Discussion: This study identified potential risk factors for fracture that warrant further investigation, specifically, worse baseline functional status, ambulatory status, and recent change in function in ambulatory children. Our results agree with prior studies suggesting that there is not an increased risk of long-bone fractures for children using chronic corticosteroids. We found that fractures negatively affect quality of life. Preventive measures should target the osteopenia and osteoporosis resulting from disuse in ambulatory children. These have the potential to significantly improve quality of life. Further research into the potential direct effect of DMD on bone remodeling is needed

INTRODUCTION

Duchenne Muscular Dystrophy (DMD)

DMD is a progressive muscle wasting disease, the most common childhood onset muscular dystrophy, with an incidence estimated to be 1 in 3500 live births (Parker 2005). DMD is a condition inherited in an X-linked manner (Parker 2005).

Dystrophin, the protein that is absent or improperly functioning in DMD, is a connecting protein in the muscle cell. It connects the interior of the sarcolemma (the force generating mechanism of the muscle cell) to the membrane of the sarcolemma, and the outer membrane of the cell (Cochrane review, Pescatori 2007). In the absence of dystrophin, the other components of this structure are put under greater stress, specifically the myofibrils and other membrane proteins. This increased stress results in a cycle of cell damage and repair. Eventually the skeletal muscle cannot complete regeneration, leaving a fatty fibrous "scar", which is expressed phenotypically as the generalized skeletal muscle weakness seen in boys with Duchenne (Pescatori 2007).

The first symptoms generally become visible before the age of five, when children present with difficulty rising from the floor and going up and down stairs. The muscle weakness progresses, resulting in loss of independent ambulation between 10-12 years of age and loss of upper extremity function in the late teens (Verhaart 2011). Currently life expectancy is estimated at 25-30 years of age. Death occurs predominantly due to heart and respiratory failure (Verhaart 2011).

Chronic corticosteroid therapy:

There is no curative treatment to date. Corticosteroids have been found to improve muscle strength, prolong walking time, improve cardiac function, and decrease the severity of scoliosis (Houde 2008; Biggar 2006). There are no clear guidelines with regard to when to start corticosteroids, however it has been suggested that the earlier they are started the better the outcome (Bianchi 2003). Additionally, multiple studies regarding dosing (frequency and amount) have been conducted with no clear consensus on which is preferred (Manzur 2008). Children are prescribed corticosteroids depending on parental/patient preference, financial considerations, and side effects. The most common side effects include weight gain, decreased height, behavioral changes, and cataract formation (Manzur 2008; McAdam 2012).

The effect of chronic corticosteroid therapy on bone mineral density is not clear. In those studies that have seen an effect, trabecular bones[1], in particular the vertebrae, appear to be primarily affected, with both decreased bone mineral density and increased fractures occurring in children taking corticosteroids (McAdam 2012; Bianchi 2011; King 2007; Houde 2008). What is less clear is the association between corticosteroids and long bone fractures. Taken as a whole, the literature has not shown an association between chronic corticosteroid use and long-bone fractures (McDonald 2002; Biggar 2004; King 2007).

[1] The primary component of bones in the vertebral column, the pelvis, and the ends of long bones.

Long bone fractures in DMD[2]

Fracture incidence in boys with Duchenne is higher than in the general population, with an estimated incidence of fracture in boys with Duchenne being 30-80/1000 boys with Duchenne aged 6-30/year as compared with 5-36 fractures/1000 children aged 0-16/year[3] (King 2007). Most studies that have been conducted looking at fractures in children with DMD have been retrospective and estimate the prevalence of any occurrence of fracture throughout the child's lifetime (McDonald 2002; Bothwell 2003; Houde 2008). These studies have estimated prevalence rates of fractures of 79/378 (21%) of boys aged 1 – 25 (McDonald 2002)[4], 22/118 (18.6%) of boys aged 9-15 (Biggar 2004), and 47/143 (32.9%) of boys aged 6-30 (King 2007).

Boys with DMD do not recover well from fractures. McDonald et al. (2002) found a fracture prevalence of 21% (79 of 378 subjects aged 1-25). The average age of fracture in this study was 9 years, with fractures occurring most commonly in the 8 to 11 age group[5]. Six of 31 independently mobile patients permanently lost the ability to walk unaided from the time of fracture. Five of these six boys had lower limb fractures. Three of 11 who were using

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[2] Fractures are defined specifically as long bone fractures and vertebral fractures in the literature and clinical records in the DMD population. These have different risk factors and occur at different ages and functional grades (Bothwell 2003; King 2007). This paper concentrates on long bone fractures.

[3] Cheng et al (1993) found a sex ratio of 2.7:1 in favor of boys, suggesting the true incidence for boys in the general population is toward the upper end of this spectrum.

[4] Of note, this study involved two separate methodologies, a chart review and a parental questionnaire. Parental questionnaire was far more effective at identifying history of fracture. In the cohort who received questionnaires, 25.3% had a fracture identified, as compared to 16.8% in the cohort whose fractures were identified from clinical chart review. Other than route of fracture identification, these cohorts were similar (McDonald 2002).

[5] No fractures occurred in any of the 86 males older than age 17.

assistive devices lost the ability to independently ambulate after time of fracture. Only one of these three boys had a fracture of the lower limb. Five of 28 boys who could not independently ambulate reported loss of function following fracture (three reported loss of ability to stand from the wheelchair, one reported increased knee contractures, and one reported increased pain).

Risk factors have not been clearly identified with regard to fracture incidence. The majority of the literature indicates that fractures are occurring throughout the disease course, with the majority occurring during late ambulatory years (McDonald 2002; Douvillez 2005; Houde 2008).

Bone mineral density:

Bone mineral density[6] in boys with Duchenne appears to be lower than that of age-matched controls, specifically in the femur at the younger ages and in the lumbar spine once the boys are no longer ambulatory (Larson 2000). Boys with DMD have femur bone mineral density in the "osteoporotic range" while they are still ambulatory. In a study of 36 boys with DMD who had never been on corticosteroids, Larson and Henderson (2000) found that bone mineral density of the femur was decreased at the earliest measurement (5.5 years), while

[6] Results of measurements of bone mineral density in the growing skeleton are difficult to interpret. First, areal bone mineral density inherently underestimates the bone density of shorter persons (Leonard 2004). Second, as the bone is constantly remodeling, the measurement of bone mineral density is time dependent. Third, studies include difference bones in their measurements. If total body bone mineral density is measured, the most appropriate measurements exclude the head, as cranial development does not occur in the same fashion as the rest of the skeleton (Bianchi 2011). Finally, bone mineral density is measured as degree of deviation from the norm, with the generally accepted rule of 2 standard deviations from the norm indicating osteoporosis. Importantly, what "normal values" are used differ for each study, and are often based on populations previously studied by the authors and not height matched to the subjects.

boys were still ambulatory, and continued to decline throughout ambulatory and non-ambulatory years.

There are multiple mechanisms at work in children with DMD that likely contribute to their decreased bone mineral density including disuse osteopenia, altered calcium and vitamin D metabolism, hormonal imbalance (in particular low growth and sex hormones), a potential direct effect of DMD on bone cells, and chronic use of corticosteroids (Bianchi 2003; Ohshima 2010; Baroncelli 2005; Isaac 2013). The finding that boys with DMD have decreased femur bone mineral density while ambulating at a similar rate to unaffected boys suggests that disuse osteopenia does not fully explain their lowered bone mineral density.

Quality of Life (QOL)

There is no cure for Duchenne muscular dystrophy. Advances in respiratory, cardiac, and orthopedic care have improved survival in recent years (Parker 2005). In any fatal chronic disease of childhood, the importance of understanding the effect of interventions on quality of life is paramount.

Health-related quality of life consists at a minimum of physical, psychological, and social health dimensions. It is thought to be the best representation of patient perceptions of an illness and its treatment on their own functioning and well-being (McDonald 2010). There is limited information in the literature regarding health-related quality of life in boys with Duchenne. Recent studies have found a worse health-related quality of life in both physical and emotional dimensions of daily life compared to children without muscular dystrophy (Baiardini 2011; Uzark 2012). Uzark conducted a cross-sectional study of 203 parents and

117 boys with DMD and found that, by self-report, 57% of their sample aged 8-18 had Psychosocial Health Summary scores below the cutoff point for "significantly impaired QOL" in the general pediatric population. Poor health-related quality of life has been correlated with age, functional grade, lack of independent ambulation, and ventilator use, but not corticosteroid use (Baiardini 2011; Uzark 2012). To this author's knowledge, there is no data on the effect of fractures on health-related quality of life.

Current Study

This study examines the effects of functional status and corticosteroid use on fracture occurrence in children with DMD. It also examines the association between history of fracture and health-related quality of life amongst the population of children with DMD who attend Shriners Hospital for Children in Portland, Oregon. The health care providers at Shriners Hospital for Children provide multidisciplinary services to children with severe neuromuscular disorders. They are a regional referral site and provide bi-annual visits to these children. Routine evaluation includes a visit with a neurologist, orthopedic specialist, cardiologist, physical and/or occupational therapist, geneticist, and social worker.

Significance

Duchenne muscular dystrophy (DMD) is the most common childhood onset muscular dystrophy, with an incidence of 1/3500 live births. This disease is progressive; the life expectancy is 25-30 years of age. The potential impact of fractures on the quality of their shortened lives has not yet been explored. The factors that influence development of these fractures have not been clearly defined.

Research questions

Question 1: What are the effects of functional status and corticosteroids on fracture in children with DMD?

Question 2: What is the effect of history of fracture on quality of life in children with DMD?

METHODS

Study Subjects

This study was approved by the OHSU Institutional Review Board (IRB)[7]. Children were recruited from the MDA clinic at the Shriners Hospital for Children located in Portland, Oregon[8]. Inclusion criteria included 1) open[9] electronic medical record at Shriners Hospital for Children and 2) confirmed diagnosis of DMD by muscle biopsy or genetic test. Exclusion criteria included any additional diagnosed neuromuscular condition. Potential subjects were called a total of three times at each telephone number available on the electronic medical record. Calls were made during weekday mornings, afternoons, and evenings, and weekend mornings. If an answering machine was reached, a message was left describing the purpose of the study and identifying when a second call would be made. A maximum of three messages were left for each subject. A standard telephone script was followed for telephone encounters. If a subject was reached and agreed to participate, the interviewer performed an oral telephone consent approved by the OHSU IRB in January of 2012.

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[7] The OHSU IRB has a high standard for data protection and management. Data was collected and managed using REDCap electronic data capture tools. This is a secure, web-based application designed to support data capture for research studies. Subjects were assigned a random subject number, and subsequently de-identified for analysis. Consent was obtained by telephone with subjects' parents. As quality of life was based on parental proxy-report, subject assent was not required.

[8] For children to have an electronic medical record, they must have been seen at Shriners Hospital for Children at least once between January 2007 and December 2011. Their diagnoses were based on clinical phenotype and genetic testing and/or muscle biopsy and confirmed prior to adding them as potential subjects.

[9] Charts were closed when a patient stopped attending clinic at Shriners Hospital for Children. This could potentially be due to death, moving location, or changing physicians to an adult practioner. The closest clinic that provides a similar service is located in Seattle, WA, 170 miles away.

Measures

Demographic Characteristics

Clinical chart review identified demographic information including subjects' race/ethnicity, subject characteristics including subjects' date of birth and height and weight measurements, and disease specific information including surgical history, diagnosed scoliosis, fractures, corticosteroid use, and functional status progression. Information regarding bone mineral density measurements was not available.

Questionnaire

The survey was developed using an iterative process that began with a comprehensive literature review and discussion with experts in the field of Pediatric Neurology and included numerous rounds of revision based on input from these experts. The survey was then revised based on input from experts in the fields of epidemiology and physical therapy. The question regarding socio-economic status was adapted from the Oregon BRFSS (Behavioral Risk Factor Surveillance System). The final draft survey was piloted with 10 parents, 5 of whom were parents of children with a physical disability. The final English version was translated into Spanish and piloted with one Spanish-speaking parent.

Quality of life questions were drawn from two validated surveys regarding health-related quality of life in children. One module specifically targets children with neuromuscular disorders and a second module is directed toward all children. Both were validated in a population of children with DMD using parental proxy-report (Davis 2010). Parental proxy-report was used due to the age range of children involved in the study and prior literature

indicating that a significant proportion of children with DMD have cognitive impairments (Pane 2012). Previous studies have validated this method and found parental proxy-report calculated means were higher than child self-report calculated means on average (Davis 2010; Uzark 2012). Uzark et al. (2012) determined Internal Consistence Coefficients (ICC) for parental proxy-report and child report in a PedsQL module similar to that used in this study and found parent-child concordance ranged from poor to good, with the highest concordance for the Daily Activities Scale and the lowest concordance for the Emotional Functioning Scale.

The final survey evaluated 5 domains: functional status (progression of disease), information regarding fractures, bone and back pain, medications, health-related quality of life, and a measure of SES (Appendix A). The surveys were conducted over the telephone by a single interviewer from January through September of 2012. Non-response was originally tracked by written record, followed by tracking in an Excel spreadsheet.

Variable classification

- Fractures were identified in the chart review and questionnaire. Parental report was relied upon in analyses, as prior studies have found parental report of fractures to be more reliable than chart review (McDonald 2002).

- Functional status was measured as a modified Brooke/Vignos scale (Brooke 1981), with gross motor function declining on a scale of 1-5 (Table 1). Parental report was preferentially relied upon, other than with regard to stair climbing[10].
- Corticosteroid exposure time was calculated based on parent report.
- BMI-for-age percentiles were calculated using NHANES 2000 census data[11].
- Quality of life scores were scaled to a range of 0 to 100, with 100 indicating the highest quality of life. Six categories were measured, as defined by the previously validated PedsQL and PedsQL Neuromuscular Modules, including:
    - Neuromuscular Function
    - School Function
    - Social Function
    - Emotional Function
    - Family Function
    - Communication

[10] Many parents had difficulty remembering the age at which their child could no longer climb stairs. Their responses were not considered as reliable as their responses for categories where assistive devices were required.

[11] BMI-for-age was calculated based on "Boys age 2 to 20" charts, BMI for boys younger than 2 was not compared, as these results are not reported for the general population. Percentage was rounded to the nearest possible point (3%, 5%, 10%, 25%, 50%, 75%, 90%, 95%, 97%), with those below and above the 3% and 97% rounded to the 3rd and 97th percentiles, respectively.

Missing Data

Some subjects did not respond to the entire survey. If the subject had information on the primary exposure and the outcome, an effort was made to include them in the analyses. Two subjects were excluded from all or part of the analyses:

- Subject 11 did not have information on fractures or quality of life. This subject was not included in either analysis.
- Subject 41 had information on fractures but not on quality of life. This subject was included in the fracture analysis, but not the quality of life analysis.

Many subjects did not respond to particular questions in the quality of life section. Further sensitivity analyses were conducted to determine the effect of this missing data on the results obtained. For a full description of these analyses, please see Appendix B.

Sibling pairs were not adjusted for in the analyses due to the small total number of sibling pairs included in this sample

Statistical Analysis

Data was analyzed using STATA 12.0 by StataCorp LP, College Station, Texas, USA.

- Characteristics of children with fractures

  Characteristics of children with fractures were described with regard to functional status progression and corticosteroid use and compared with sample values.

- Nested Case-Control Design

  To investigate the relationship between functional status, corticosteroid use, and fracture occurrence, a matched case-control design nested within the same sample used above was used. Cases were matched based on age at survey with up to four controls as sample size allowed. Children with age of fracture younger than 5 were not included in the nested case-control analysis. Thirteen cases and 30 controls were included in the final analysis, out of 17 total possible cases and 40 total possible controls. Age for variable measurement was determined based on the cases age at fracture.

  Variables compared included:

  - Functional status one year prior to the age of fracture
  - Corticosteroid use within 6 months of the age of fracture
  - Change in functional status by at least one category (Table 1) within the year prior to the age of fracture
  - Ever being able to climb stairs independently, without the help of a handrail

  Conditional logistic regression was conducted for all variables separately to obtain the crude odds ratio (OR) associated with the risk of fracture. Confounding analysis was completed for all variables, excluding ever able to climb stairs as it was a factor present from birth and therefore could not be affected by the other variables. Variable were adjusted for if, when included, they changed the crude OR of interest

by at least 10% (Figures 19-22). Change in functional status was not included as a potential confounder, as only ambulatory subjects could have a change in functional status.

Multivariate logistic models were made using conditional logistic regression to control for matching with fracture as the outcome of interest. Predictor variables included the exposure of interest and identified confounding variables.

- Quality of life analysis

  To investigate the relationship between quality of life and history of fracture, simple and multivariable linear regression models were built using average quality of life scores for each category as the outcome variables. Sensitivity analyses were conducted to determine the effect of missing questions on the association between independent and dependent variables (Appendix B).

  - Bivariate

    The relationship between history of fracture and average quality of life scores was analyzed with simple linear regression. The relationship between potential confounding variables and average quality of life scores were examined in the same fashion. These variables were selected based on literature review and expert opinion. These included age at time of survey, functional status at time of survey, number of years a child had been non-ambulatory, lifetime corticosteroid exposure, and BMI percent-for-age.

    When independent continuous variables (age and BMI) did not have a linear association with the outcome variable (determined by inspection of locally

weighted scatterplot smoothing plots [lowess] and correlation coefficients), they were analyzed using categorization, with categories determined based on interpretability and equalization of cell counts. When ordinal variables (functional status, number of years non-ambulatory, and steroid exposure) did not have a linear relationship with the outcome variable, each subsequent level was compared to the reference group functioning as a dummy variable.

Bivariate associations were conducted between potential confounding variables and history of fracture. Continuous variables were analyzed using t-test for significance. Categorical variables were analyzed using Pearson's chi-square or likelihood ratio (for variables incorporated in a model).

- Confounding Analysis

The association between history of fracture and each aspect of quality of life was analyzed for the potential confounding effect of each independent variable listed above. Variables were considered confounders and included in the final adjusted analyses if they changed the coefficient of interest by at least 10%.

If subjects did not have complete information regarding independent variables considered to be confounders, their status was categorized as "unknown" and they were included in the analyses.

- Multivariate

A multivariate model was built using the average quality of life score for each category as the outcome and history of fracture and identified confounders as predictor variables. Model diagnostics including residual analysis and outlier identification were conducted.

RESULTS

Respondents

Fifty-eight of 91 eligible subjects participated in the survey (64% response rate)[12]. Response rate for subjects contacted was 95%. Reasons for non-participation were:

- No return call after 3 voicemails (12; 53%);
- Disconnected number (8; 35%); and
- Did not want to participate (3; 13%).

Information gathered by chart review showed that non-responders had a higher mean age, were more often non-ambulatory[13], became non-ambulatory at an older age, had more years of lifetime corticosteroid use, and were less likely to be Caucasian (Table 2). Additionally, more responders had missing data in the chart review (Table 2).

In the responder population, patients older than 15 years had a mean of 23.1 months (SD 30.0) between their last clinic visit and the time of survey, as compared to those younger than 15 years who had a mean of 5.9 months (SD 10.3). Much of the difference in responders versus non-responders described above could be explained by this relationship if

[12] Other potential subjects who were coded as having DMD on record retrieval (19) met exclusion criteria due to closed records (15) or no verification of DMD diagnosis (4).

[13] This comparison was based on functional status identified from chart review. This differed from the information provided by parents (Table 2). As noted in the methods section, functional status categorization used for the rest of the analyses were based primarily on parent interview.

it holds true for the non-responders, as they were older on average than the responders (Table 2). The difference in the race/ethnicity of responders and non-responders may indicate a difference in socio-economic status, resulting in more disconnected telephone numbers.

An effort was made to include Spanish speakers, and all subjects contacted who preferred to interview in Spanish agreed to participate.

Our Sample

Demographics

The average age of the sample at the time of survey was 12.3 years (age ranged from 1.9 – 22 years). Subjects were primarily Caucasian (71%) or Hispanic (17%) (Table 2).

Shriners Hospital for Children draws patients from the state of Oregon, and is the only center in the region that provides a medical home to boys with DMD and other congenital conditions. Subjects represented multiple counties and states, and came from both urban and rural areas (Table 2).[14] This sample was under-representative of those living in the lowest income categories (Table 2).

The majority of respondents were mothers (78%), which is similar to other studies using proxy respondents to quality of life questionnaires (Baiardini 2011; Uzark 2012). The total

[14] Urban/rural classification was based on Oregon Office of Rural Health Urban/Rural definitions. These are defined using zip codes and US census data.

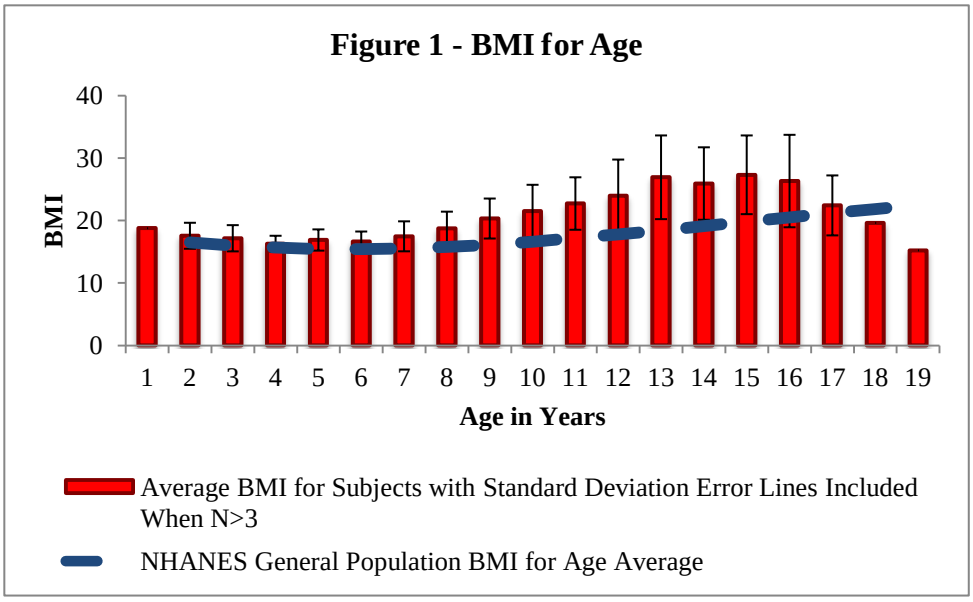
number of children in the home, including the subject, ranged from one to six, with the average number of children in the home being 1.5 (SD 1.3).

Body Mass Index (BMI)

The BMI of the sample population began rising above the national average of general population boys at age 7. Age 7 is also near the time of initiation of corticosteroid therapy for many children with DMD[15]. In this study, as has been reported previously, there was marked variability in BMI amongst subjects[16] (Leung 2011). The difference between average sample BMI and national averages reached a peak of 8.5 points at age 13 (Graph 1).

[15] Age of initiation of corticosteroid therapy varies. Some clinicians encourage initiation when mobility begins to plateau, while others advocate for earlier initiation. The information gathered in this sample regarding initiation is incomplete and imprecise, and so it is not presented here.

[16] Natural history studies indicate that short stature is common in DMD. Although birth weight and length are normal, a gradual slowing of growth is observed, with most patients falling below the 50th percentile for height by age 10 and below the 5th percentile for height by age 18 (Leung 2011). Obesity is common, as is marked variability in weight.



Disease characteristics

Children were diagnosed, on average, at age 3.5 (SD 2.3 years). By age 5, 56.6% could not climb stairs independently, and by age 12 no subjects could climb stairs independently. At diagnosis, 82% of subjects walked without assistance in the community. By age 9, 53.5% could no longer walk without assistance in the community, and by age 13 no subjects could walk without assistance in the community.

The age that boys became non-ambulatory was, on average, 10.0 years (SD 2.7 years). This is a higher mean age at non-ambulatory than samples including only corticosteroid non-users or unclear corticosteroid status and lower than samples including only corticosteroid users (Douvillez 2005; Houde 2008). Our population had a smaller percentage of current

corticosteroid users (59%) and less lifetime corticosteroid exposure than most studies including children of similar ages (Table 2; Bothwell 2003; McDonald 2010), suggesting that this sample was ambulatory longer than might be expected with their lower corticosteroid use.

Long Bone Fractures

Of the 57 subjects with sufficient information, 14 (25%) had suffered one fracture, 2 had had two fractures, and one had experienced four fractures[17]. They had an average age of 9.8 (SD 5.4) at the time of their first fracture. Fractures occurred due to low-force mechanisms (force equal to or less than a ground level fall) in 15/17 cases, with two of those occurring with no contact (Table 3; Figures 2-18).

Functional Status

At the time of their first fracture, boys were ambulatory in 59% of the cases. When compared to age-matched controls, odds of fracture for children that were ambulatory at the age of fracture were 4.88 (95% CI: 0.56 – 42.5) times the odds of fracture for those who were non-ambulatory at the same age, after controlling for the confounding effects of corticosteroid use and whether they were ever able to climb stairs (Table 3; Figure 19).

Forty-eight percent of all boys in the sample could never climb stairs independently, while 13 of the 17 boys who suffered a fracture (76%) could never climb stairs independently (Figures

[17] Chart review found only 53% of the fractures that were identified by parent questionnaire. There were no instances where a fracture was identified on chart review that was not identified by the parent. This was consistent with the results of McDonald et al. (2002) who found a fracture prevalence of 16.8% in chart review and 25.3% on parental questionnaire.

2-18). When comparing only those children in the nested cohort (n=47), odds of fracture were 70% lower for children that were ever able to climb stairs compared to odds of fracture in those who were never able to climb stairs (95% CI: 92% lower – 20% greater; Table 3). This was particularly clear in the boys who suffered fractures before the age of 5, none of whom could ever climb stairs independently (Figures 2-5)[18].

Boys who had suffered a fracture had a recent change in functional status (at least one level within the year prior to the age of fracture) 41% of the time (Figures 2-18). When compared with age-matched controls, boys with a recent change in functional status had odds of fracture 3.27 (95% CI: 0.6 – 18.3) times as great as the odds for boys with no recent change in functional status, after controlling for the confounding effect of corticosteroid use (Table 3; Figure 20).

Corticosteroid Use

At the time of their first fracture, 29% of children with fractures were using corticosteroids. Forty-seven percent of children with fractures had any history of corticosteroid use prior to their first fracture (Figures 2-18). When compared with their age-matched controls, those with fractures had corticosteroid use within the 6 months of their age at fracture 38.5% of the time, while controls had corticosteroid use within 6 months of the cases' age at fracture 56.7% of the time, resulting in an odds of fracture for children that had used corticosteroids 0.63 (95% CI: 0.10 – 3.0) times the odds in children who had not used corticosteroids in the previous 6 months (Table 3; Figure 21).

[18] All fractures in children younger than 5 at time of fracture occurred in the femur, and two of the four went on to develop further fractures (Figures 2-5).

With only 17 children with fractures, no conclusions can be drawn from these results. However, examination of the characteristics of children with fractures and statistical modeling suggest that children may be more likely to fracture if they have a lower baseline functional status (are never able to climb stairs). Additionally, they may be more likely to fracture if they are ambulatory, particularly after a recent change in function.

Quality of Life

Six sub-domains of quality of life were measured, including functional, social, school[19], communication, emotional[20], and family.

Functional

When asked to describe the three most difficult aspects of their child's disease, parents of children of all ages included functional limitations by far the most (64% of respondents; 36%

[19] We did not measure intellectual disability or diagnoses of behavioral difficulties or mental health conditions, nor did we measure whether a child had a current Individual Education Plan (IEP). Therefore, we do not report school functioning scores here, as they would be impossible to interpret in the absence of this data. Intellectual Disability (ID) and Attention Deficit Hyperactivity Disorder (ADHD) are more common in boys with DMD than in boys in the general population (Pane 2012).

[20] Uzark et al. (2012) found parental proxy-report of emotional quality of life to correlate poorly with children's report of their own emotional quality of life, particularly during the teen years. In that study, parents significantly under-reported their child's emotional distress during the teen years, with an overall parent-child ICC of 0.139 for the emotional category, indicating poor agreement (Uzark 2012).

of all aspects identified). Common difficulties identified included weakness (16 respondents), inability to walk (10 respondents), immobility (8 respondents), and excess weight (6 respondents).

Average functional scores ranged from 11.8 – 92.6, with a mean of 59.2 (SD 19.3; Figure 22). Children with a history of fracture had an average score of 47.9 (SD 20.0), with scores ranging from 11.8 – 87.5 (Figure 23). This average was lower than the average for children without a history of fracture (63.6; SD 17.3), with scores ranging from 28.3 – 92.6 (Figure 23).

After adjusting for the confounding effects of age and the number of years a child had been non-ambulatory, children with a history of fracture had a functional quality of life score that was, on average, 9.0 points lower than those without a history of fracture (SE 4.4, $p = 0.04$; Table 5).

Emotional

Average emotional scores ranged from 5.0 – 100.0, with a mean of 62.1 (SD 23.4; Figure 24). Children with a history of fracture had an average score of 48.8 (SD 21.4), with wide ranging scores from 5.0 – 81.3 (Figure 24). This average was lower than the average for children without a history of fracture (67.8; SD 22.1; Table 4), with scores in both categories falling in a similar range (Figure 25).

After adjusting for the confounding effect of age, children with a history of fracture had an emotional quality of life score that was, on average, 13.4 points lower than those without a history of fracture (SE 7.0, $p = 0.06$; Table 5).

Social

When asked to describe the three most difficult aspects of their child's condition, parents of children of all ages described social difficulties more frequently than any other aspect, other than functional difficulties (38% of respondents; 19% of all aspects identified). Common aspects identified included difficulties keeping up with other children (14 respondents) and lack of independence (10 respondents).

Parents described particular barriers to socialization at school being the need for an aid and extra time in the hallway between classes, resulting in isolation. Additionally, parents of teens and young adults noted a particular difficulty finding aids to take their sons to social gatherings with other teens and young adults.

Average social scores ranged from 10.0 – 100.0, with a mean of 58.7 (SD 24.3). Children with a history of fracture had an average score of 48.6 (SD 25.2), with scores ranging from 10.0 – 80.0. This was 14.5 points lower than the average social quality of life score for those without a history of fracture (average 63.1; SD 22.9; $p = 0.05$; Table 4). After adjusting for the confounding effects of age and functional status[21], children with a history of fracture had a social quality of life score that was, on average, 8.7 points lower than those without a history of fracture, however this difference was not statistically significant and had a large standard error of 8.4 ($p = 0.31$; Table 5).

Family

[21] Functional status categories did not have a linear relationship with social quality of life scores. Therefore functional status levels were compared with "climbs stairs independently and/or with the help of a handrail (functional status level 1)" as the reference group (Table 4).

At the end of the survey, parents were asked if they had anything additional to add. Twenty-nine parents (50% of respondents) answered this question. Of these, 14 parents indicated that there were challenges unique to parenting a child with DMD. Specifically, they mentioned difficulties with managing behaviors associated with DMD, medical decision-making with regard to balancing quality of life versus quantity of life, and the effect of their child's condition on his siblings. Three of these parents specifically mentioned feeling socially isolated from their friends and extended family due to their child's condition.

When asked if their child's condition caused problems with their marriage or partner, respondents overall averaged a score of 75/100 (SD 32.7), with a score of 100 indicating that their child's condition never caused problems, and a score of 0 indicating that their child's condition almost always caused problems. Higher marriage scores were associated with higher family quality of life scores. A marriage quality of life score 10 points higher, with all other aspects being equal, resulted in a family quality of life score 2 points higher, on average (SE 0.1; $p = 0.02$).

Average family scores ranged from 10.0 – 100.0, with a mean of 56.5 (SD 23.1). Children with a history of fracture had an average score of 50.0 (SD 22.0), with scores ranging from 10.0 – 90.0. This was 9.2 points lower than the average family quality of life score for those without a history of fracture (average 59.2; SD 23.2; $p = 0.18$; Table 4). After adjusting for the confounding effects of functional status, BMI[22], and the number of years a child had been non-ambulatory, children with a history of fracture had a family quality of life score

[22] BMI did not have a linear relationship with family quality of life scores (Figure 26) and so was categorized based on cell counts and interpretability (Table 4).

that was, on average, 4.3 points higher than those without a history of fracture. This difference was not statistically significant and had a large standard error of 6.7 (p = 0.52; Table 5).

Communication

Of those 29 parents with something to add at the end of the survey, 5 parents indicated that they had specific difficulties with regard to communication with physicians. They felt physicians frequently took away their hope. Additionally, they noted that they often left the physician's office feeling that they needed more information on the disease process and what to expect in the future.

Average communication scores ranged from 0.0 – 100.0, with a mean of 50.5 (SD 36.9). When communication scores were looked at according to history of fracture, the range of scores of children with and without history of fracture remained at 0.0 – 100.0 in each group, with those without a history of fracture having a score 7.4 points lower with a large standard error of 11.1 (p = 0.51; Table 4). This difference decreased to 1.0 points lower with a standard error of 13.2 (p = 0.94) after adjusting for the confounding effects of functional status[23], number of years non-ambulatory, steroid exposure, BMI[24], and age[25].

History of Fracture and Quality of Life

[23] Functional status categories did not have a linear relationship with communication quality of life scores. Therefore functional status levels were compared with "climbs stairs independently and/or with the help of a handrail (functional status level 1)" as the reference group (Table 4).

[24] BMI did not have a linear relationship with communication quality of life scores (Figure 27) and so was categorized based on cell counts and interpretability (Table 4).

[25] Age did not have a linear relationship with communication quality of life scores (Figure 28) and so was categorized based on cell counts and interpretability (Table 4).

There was a wide range of quality of life scores in every sub-domain, and for children with and without a history of fracture. We did find a statistically significant association between history of fracture and lower functional quality of life scores, and an association between history of fracture and lower emotional quality of life scores that approached significance.

DISCUSSION

Functional Status

There was a high prevalence of fractures in our sample (30%), which is consistent with prior studies (McDonald 2002; King 2007). Due to the small sample size we were not able to draw conclusions from our analyses. However, because of the information of functional status progression that we were able to gather, we did identify potential associations that have not been examined by previous literature. Specifically, with regard to functional status, this data would suggest that children with a higher baseline functional status are less likely to fracture. Additionally, children may be more likely to fracture during their ambulatory years, particularly after a recent change in function.

Recent research indicates that DMD may affect bone metabolism independent of skeletal muscle function (Isaac 2013). If this is true, we might expect worse disease related osteoporosis in children with worse muscle function. Our finding that worse baseline functional status may predispose to fracture would support this conclusion. This finding

additionally supports the theory that disuse osteopenia is a primary component of fracture risk, in that children with lower baseline status would be less mobile than their stronger counterparts, resulting in reduced bone mineral density and increased fracture risk.

This was particularly evident in the children with fractures under age 5, all of whom had low baseline functional status. Of particular concern is that all of these children suffered femur fractures, and two of the four went on to suffer further fractures later in life. In this study we were not able to see a clear change in functional status following fracture in these children, which may be due to lack of sensitivity in our measurement technique, the retrospective nature of this research, or a true representation of the functional status of the children. McDonald et al. (2002), however, found that children with fractures of the lower extremity were less likely to return to baseline functional status. This suggests that children who fracture in this younger age group may have more severe consequences associated with their fractures.

The age of diagnosis of DMD in this study was 3.5 years, with diagnosis ranging from 0 – 9 years of age. Other samples have had an even older average age of diagnosis of 4.7 years (Ciafaloni 2009). Because children in the younger age group (less than 5) may not yet be identified as having DMD, any preventive measures would be useless to protect against fractures in this vulnerable group. With this in mind, we have yet another reason to continue to work toward earlier diagnosis of this condition.

Our data suggests that children who are ambulatory, particularly after a recent change in function, are more likely to fracture. Information regarding functional status of boys who

suffer fractures in this population has varied in different samples however, taken as a whole, previous literature would support this finding (McDonald 2002; Douvillez 2005; Houde 2008). The previous differences reported appear to have been a result of the age range of the sample, with samples of older children showing more fractures in non-ambulatory boys. In this study we were able to compare children of the same age at different ambulatory status. By age-matching and examining functional status at the age of fracture occurrence in the cases, we were able to control for recall bias as well as the potential effect of age on fracture occurrence. Additionally, we accounted for the potential confounding effect of worse baseline functional status in our analyses, which has not been done before. Overall, the suggestion from our data that ambulatory children after a recent change in function were more likely to fracture supports previous literature and suggests that this group has a unique risk profile and would benefit from further research in preventive measures targeted at their changing mobility.

Corticosteroid Use

We did not see an increased risk of fracture with corticosteroid use. If anything, our data showed a protective effect of corticosteroids[26]. Our findings support previous literature (McDonald 2002, Biggar 2004, Houde 2008; King 2007) suggesting no association between corticosteroid use and long bone fractures in children with DMD. The mechanisms at work for low bone mineral density in boys with DMD, including disuse osteopenia, hormonal imbalance, altered metabolism, and a potential direct effect of DMD on bone metabolism

[26] The presence of a protective effect is extremely unlikely due to our understanding of the mechanism of action of corticosteroids as well as the lack of similar evidence in other samples. Most likely, this effect is due to sampling error.

(Isaac 2013) result in bones in the osteoporotic range while boys are at their highest functional status (Larson 2000). The additional hit of corticosteroids, although significant in the general population (Van Staa 2003), does not appear to increase an already high risk of fracture in boys with DMD.

Quality of Life

Quality of life scores had a wide range of distribution in all categories. This is encouraging as no one factor, including declining functional status, strongly predicts quality of life scores. Additionally, not all sub-domains of quality of life declined linearly with declining functional status or increasing age, indicating that the multiple factors affecting quality of life are acting in an overlapping and complex manner with the different sub-domains of quality of life. As multiple factors are involved in quality of life there is potential for targeting modifiable factors that decrease scores. This study would suggest that history of fracture is one of the factors that contributes to quality of life scores in boys with DMD, in particular with regard to their functional and emotional quality of life.

It is possible that the decreased functional quality of life is specifically related to a change in function following the fracture. Our functional status scale was not sensitive, and did not examine upper extremity function. This is one potential area for intervention, in that if we are able to improve a child's return to baseline function following the fracture, the effect of fracture on quality of life may be lessened.

The effect of fracture on quality of life may additionally be due to parental or child fear following the fracture. This may result in decreased independence or decreased movement,

or possibly an increased reliance on assistive devices, all of which could impact quality of life. As this was a parent proxy-report, parental guilt with regard to the fracture may have biased the results, in that parents may be more likely to report worse quality of life in those children with a history of fracture due to their own negative feelings about the fracture. Both fear and guilt are areas of potential intervention, if they are found to be contributing to decreased quality of life following fracture. Potential interventions include counseling, improved physician-patient interaction, increased parental and child knowledge regarding osteoporosis and the high-risk of fracture, and increased community support for families.

Generalizability/Comparison with Prior Studies

This study is generalizable to boys with DMD from urban and rural settings who receive medical attention at a children's center. Families who do not receive medical attention at all, or have not recently, are under-represented in this study. Boys who do not receive medical attention likely include boys with worse access to primary care physicians with knowledge of SHC services due to financial or geographic barriers. Boys who have not recently received care likely have lower functional status and are older.

The potential subjects who do not access medical services likely have lower fracture prevalence, as a fracture would generally result with a child being connected with medical services. They may have lower health-related quality of life than boys at a similar age who are connected with the medical system, as they likely have lower functional status due to lack of corticosteroid use and less access to assistive equipment. Therefore, it is possible that addition of these subjects would decrease the association seen in this study regarding

fractures and quality of life.

Overall, our sample is comparable to samples described in previous literature with regard to age, functional status, prevalence and location of long-bone fractures, and quality of life scores (King 2007; McDonald 2002; Bothwell 2003; Douvillez 2005; Houde 2008; McDonald 2010; Baiardini 2011; Uzark 2012). Corticosteroid use was slightly less than seen in other samples. We measured corticosteroid use based on parental report, which resulted in lower total corticosteroid exposure time than measurements based on chart review, which may account for this difference (Table 2).

Strengths and Limitations

One of the major limitations of this study is the small sample size. This is a frequent problem in studies of rare childhood diseases. In our study, it may have limited our ability to identify an association between history of fracture and certain quality of life sub-domains, and between potential risk factors for fracture and fracture occurrence. It additionally could have resulted in identification of an association between exposures and outcome that is not truly present.

A second major limitation is the potential for residual confounding. We did not gather information regarding Intellectual Disability, Attention Deficit Hyperactivity Disorder, or Autism Spectrum Disorder in these boys. These may be acting as residual confounders in the relationship between history of fracture and quality of life. If included, these may weaken the associations seen with regard to history of fracture and quality of life, in that children with these conditions may be more likely to fracture and more likely to have a lower quality of

life. Additionally, we did not have information regarding parental knowledge of osteoporosis in their child. This knowledge may have falsely resulted in a protective effect seen between use of corticosteroids and fracture occurrence, as parents may have been less likely to use corticosteroids in a child with osteoporosis and that child would have been more likely to fracture. This is unlikely, however, as on chart review we found only two boys with information on bone mineral density (DEXA scans) and we only included the child's first fracture, controlling for the potential effect of a fracture on medication preferences.

A third limitation is the potential for recall bias from parental report of functional status. We tried to limit this by using functional status milestones that experts in the field felt the parents would have little difficulty remembering, and comparing parental report to functional status identified on chart review. Overall, chart review appeared to lag behind parental identification of functional status decline (Table 2). Parents of children with fracture were likely better able to identify their child's functional status at the age of fracture than parents of children without fracture. If parents of children without fracture underestimated their child's functional status at the age of fracture, this bias may have resulted in a stronger association seen between ambulatory status and fracture than was actually there.

A fourth limitation is that this study included sibling pairs. We did not adjust for the presence of sibling pairs in this analysis, due to their small overall contribution to the respondents. This could have had an impact on several factors, both outcomes and explanatory factors, as well as on recall bias. It is unclear in which direction this may have biased the results.

A fifth limitation is that we did not have information on parental educational levels. This information may have contributed to our understanding of the variation in quality of life scores. Additionally, parental educational levels may have influenced a child's likelihood of fracture as well as their use of corticosteroids or assistive devices. We were able to examine the effect of socio-economic status, and found no associations between socio-economic status and quality of life or fracture. This agreed with previous research (Uzark 2012), and so we decided not to include this as a potential confounder in the analyses.

The use of proxy-report for quality of life measurement likely resulted in over-estimates of quality of life (Uzark 2012). Previous research has indicated this difference is greatest in psychosocial quality of life measures, such as emotional quality of life (Uzark 2012). This could potentially bias the results toward or away from the null, as parents may be more likely to over-estimate or under-estimate quality of life in boys with a fracture depending on their desire to assuage their own guilt, their estimation of the child's resilience, or the emotional impact of the fracture on the parents. Using child-reported scores would eliminate this source of bias, however would introduce additional bias, in that scores from younger children and children with intellectual disabilities would be difficult to interpret.

One major strength of this study is parental report on corticosteroid exposure time. Chart review and parental report of corticosteroid exposure were frequently inconsistent, and showed that chart review often overestimated the duration of corticosteroid use (Table 2). Corticosteroid exposure time in this study is considered to be a strong reflection of actual corticosteroid exposure time.

A second major strength is the longitudinal nature of this study. We were able to examine functional status progression with regard to fracture occurrence, which allowed us to see that fractures occurred throughout these children's lives, as well as that they appeared to occur more often in boys who were never able to climb stairs, indicating a more severe disease process.

As this is a relatively rare disease, this study does represent one of the larger quality of life studies performed in this population. We have successfully described the relationship between history of fracture and quality of life. Additionally, we have described factors in relation to fractures in these boys that have not been looked at previously.

Preventive Measures

This study adds to the mounting literature identifying areas of potential intervention in children with DMD with regard to fracture prevention. The most obvious area, which will have the greatest effect, is targeting bone health. This research has reinforced the importance of two potential mechanisms of low bone mineral density, specifically disuse osteopenia and a potential direct effect of DMD on bone cells.

Preventive measures that target disuse osteopenia would need to increase the frequency, force, or longevity of muscle use. This could potentially be done by earlier corticosteroid administration, prolonged use of assistive devices prior to wheelchair use, or increased use of "standers" which allow children to weight bear after they are non-ambulatory. All of these need to be balanced with their potential risks, specifically an increased fall risk associated with prolonging ambulation or increasing the number of transfers non-ambulatory children

are subject to. Additionally, parental education in this area regarding the benefits of prolonged, more frequent, and more forceful muscle use may be beneficial. Further research into the independent impact of disuse osteopenia on cortical long bones, specifically with regard to onset, would improve our understanding of how to best target this mechanism.

The research being done into the potential direct effect of DMD on bone remodeling will likely expand our understanding of the role of dystrophin in the cell and the mechanism of this disease. Additionally, it will broaden our understanding of factors involved in bone remodeling and repair. At this point there is no potential therapy targets for this mechanism, other than research regarding overall curative therapy.

Studies have examined bone health in boys with DMD from a metabolic aspect, examining the effect of vitamin D and calcium supplementation on long-bone health and potential fracture prevention. There is limited data in this area. A small study of 33 ambulatory boys with DMD found that intense dietary calcium counseling and Vitamin D supplementation over a period of 2 years either improved bone mineral density or halted the rate of decline (Bianchi 2011). This study was not powered to examine fractures, however they did find fewer children fractured during the two years of treatment (2 fractures) than during the one year of observation (4 fractures).

Additionally, some work is being done examining the potential effect of bisphosphonates (a medication used in adults with osteoporosis) with regard to fracture improvement and prevention, most commonly in non-ambulatory children with vertebral fractures. A few small studies have shown bisphosphonate therapy improves or halts the rate of decline of

bone mineral density in vertebral bones and improves pain associated with vertebral fractures. These studies were limited in that they had no control group and many of the patients were additionally receiving calcium and vitamin D supplementation (Atance 2011; Paksu 2011). They did not examine the potential effect of bisphosphonate therapy on cortical long bones in ambulatory children.

Little research has been done looking at potentially modifying the hormonal balance of children with DMD to prevent bone loss. At this point we do not have a clear understanding of how significant an impact hormonal imbalance is having on bone health, and therefore cannot know to what degree the modification of this would help to prevent fracture occurrence.

Parental education with regard to risk factors for fracture may impact fracture occurrence. Specifically, education regarding the lack of association that has been found in multiple studies between corticosteroids and long-bone fractures, the fact that many fractures occur during ambulatory years, and the fact that many fractures occur during periods of changing functional status (if this is reinforced by further study). This will be particularly useful if more details regarding times of high risk of occurrence can be accrued, as well as data regarding the impact of potential preventive measures on fracture occurrence.

Public Health Significance

In many congenital conditions, including DMD, the life expectancy is increasing. With this comes an increased need to understand the co-morbidities associated with these conditions in young adult and adult life. Osteoporosis is one of those conditions, both in children with

DMD and children with many other chronic conditions that decrease functional capacity. Understanding the impact of interventions on long-term health becomes increasingly important. In this study we have reinforced prior studies which have not found an association between corticosteroid use and long-bone fractures, suggesting that continuing the currently accepted therapy is not putting children at significantly increased risk for future bone complications later in life, and may in fact be helping them by decreasing disuse osteopenia.

Bone health itself is an important issue in multiple populations. These populations include children and adults with chronic conditions that result in decreased use as well as the elderly. This study helps to improve our understanding of the factors involved in bone health, and specifically highlights the negative impact that fractures can have on quality of life.

Finally, the inclusion of quality of life analyses in studies allows a better understanding of the true impact a disease or intervention is having on the population in question. Without understanding the true impact of a particular intervention on a patient's life, physicians are at risk for violating one of the primary aspects that they base their profession on, non-maleficence. The inclusion of quality of life in this study adds to the small but growing number of studies placing importance on the diverse impact variables can have.

SUMMARY AND CONCLUSIONS

This study identifies potential risk factors for fracture that warrant further investigation, specifically worse baseline functional status, ambulatory status, and recent change in function in ambulatory children, highlighting the role of disuse osteopenia and a potential direct effect of DMD on bone cells in fracture risk. Our results agree with prior studies suggesting that there is not an increased risk of long-bone fractures for children using chronic corticosteroids.

We found that fractures negatively affect quality of life, specifically functional and potentially emotional quality of life. Preventive measures should target the osteopenia and osteoporosis resulting from disuse in ambulatory children and the role of DMD on bone remodeling. Successful preventive interventions have the potential to significantly improve quality of life in boys with DMD.

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FIGURES

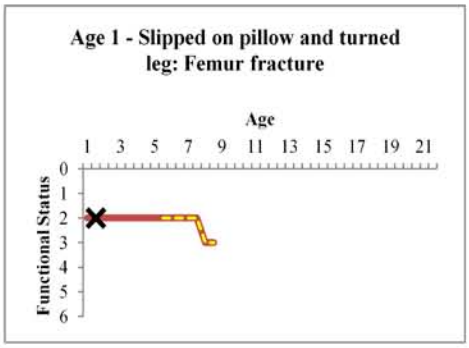


Figure 2: Functional Status Progression Graph for Child with Femur Fracture at Age 1

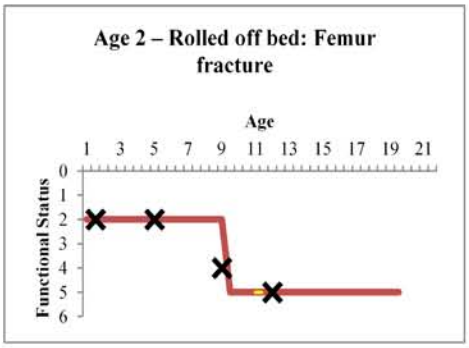


Figure 3: Functional Status Progression Graph for Child with Four Fractures, the First a Femur Fracture at Age 2
Fracture 2 – Tripped on towel and fell: Femur fracture
Fracture 3 – Fell from monkey bars: Tibial fracture
Fracture 4 – Fell on transfer: Tibial and Fibular fractures

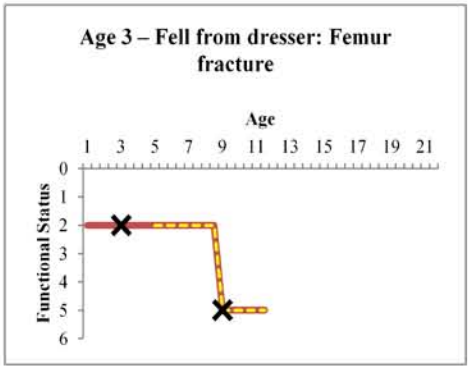


Figure 4: Functional Status Progression Graph for Child with Two Fractures, the First a Femur Fracture at Age 3
Fracture 2 – Fell from wheelchair: Patellar fracture

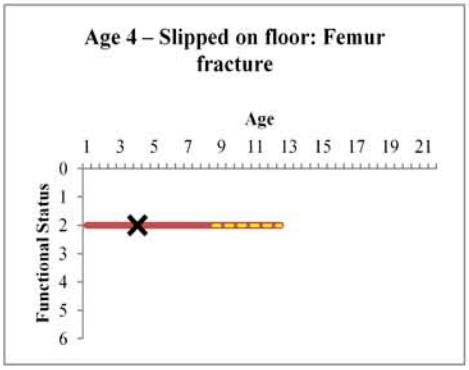


Figure 5: Functional Status Progression Graph for Child with Femur Fracture at Age 4

Key for Functional Status Progression Graphs

Functional Status
1 - Climbs stairs independently or with the help of a handrail
2 - Climbs stairs with help of a handrail and assist, requires assistance to walk for long distances
3 - Cannot climb stairs, does not require assistance to walk in the home
4 - Requires assistance to walk in the home
5 - Non-ambulatory

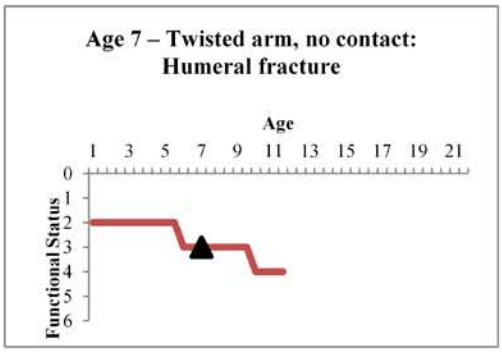


Figure 6: Functional Status Progression Graph for Child with Humeral Fracture at Age 7

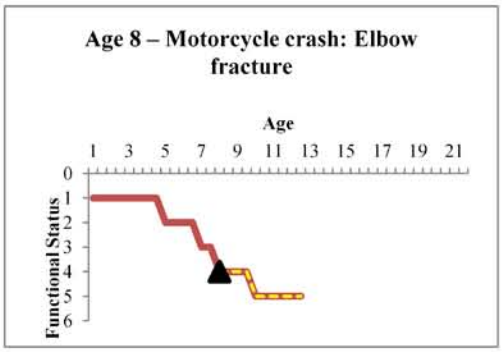


Figure 7: Functional Status Progression Graph for Child with Elbow Fracture at Age 8

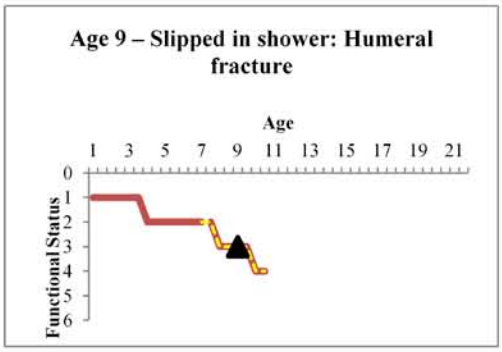


Figure 8: Functional Status Progression Graph for Child with Humeral Fracture at Age 9

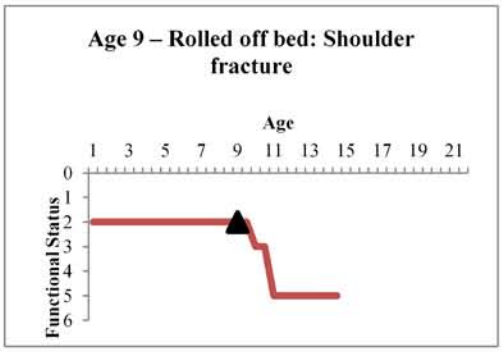


Figure 9: Functional Status Progression Graph for Child with Shoulder Fracture at Age 9

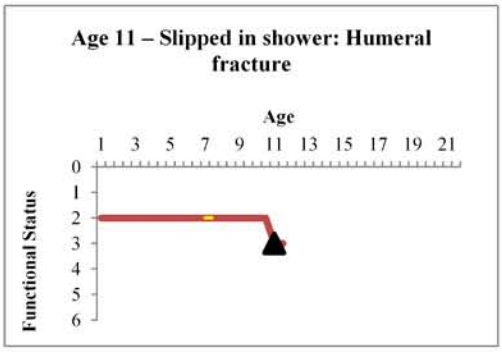


Figure 10: Functional Status Progression Graph for Child with Humeral Fracture at Age 11

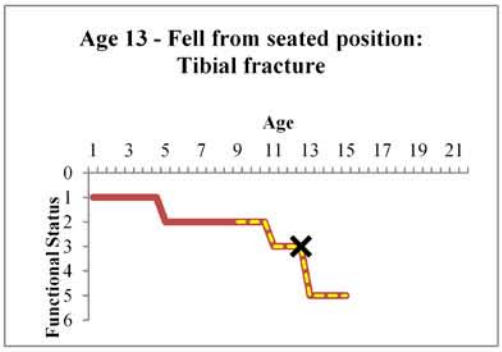


Figure 11: Functional Status Progression Graph for Child with Tibial Fracture at Age 13

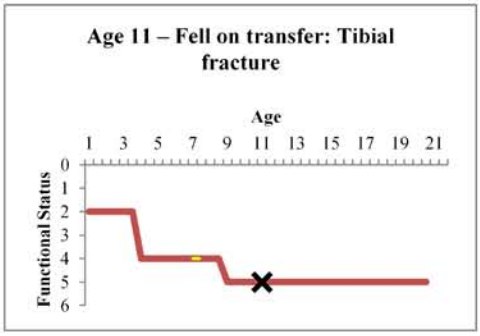


Figure 12: Functional Status Progression Graph for Child with Tibial Fracture at Age 11

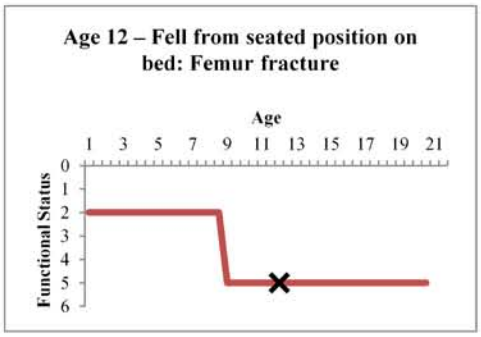


Figure 13: Functional Status Progression Graph for Child with Femur Fracture at Age 12

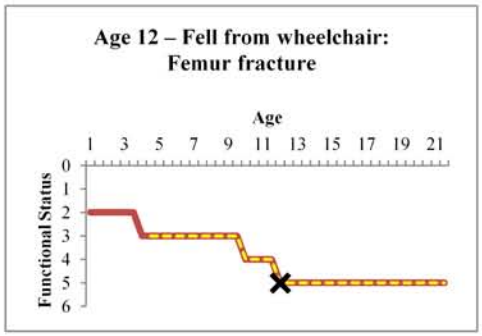


Figure 14: Functional Status Progression Graph for Child with Femur Fracture at Age 12

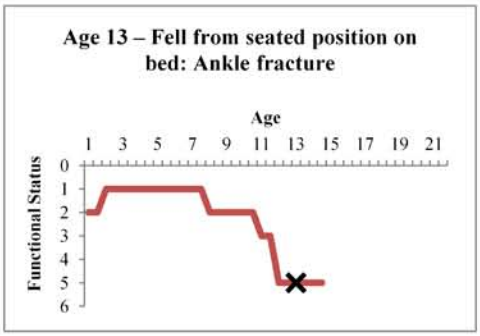


Figure 15: Functional Status Progression Graph for Child with Ankle Fracture at Age 13

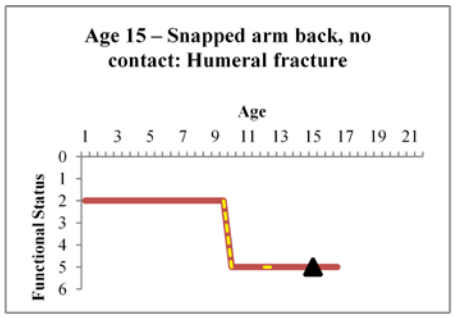


Figure 16: Functional Status Progression Graph for Child with Humeral Fracture at Age 15

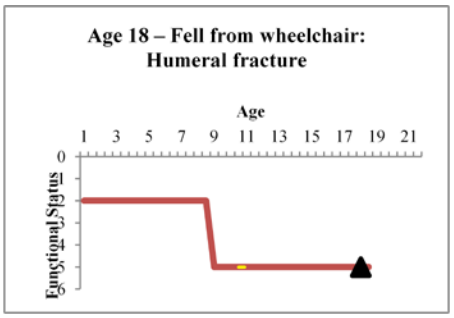


Figure 17: Functional Status Progression Graph for Child with Humeral Fracture at Age 18

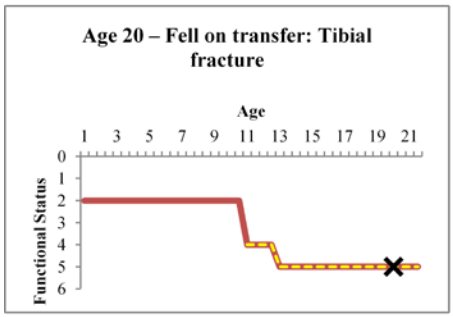
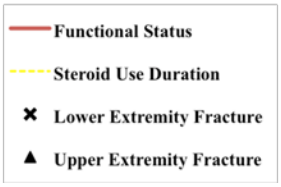


Figure 18: Functional Status Progression Graph for Child with Tibial Fracture at Age 20

Functional Status
1 - Climbs stairs independently or with the help of a handrail
2 - Climbs stairs with help of a handrail and assist, requires assistance to walk for long distances
3 - Cannot climb stairs, does not require assistance to walk in the home
4 - Requires assistance to walk in the home
5 - Non-ambulatory

Key for Functional Status Progression Graphs



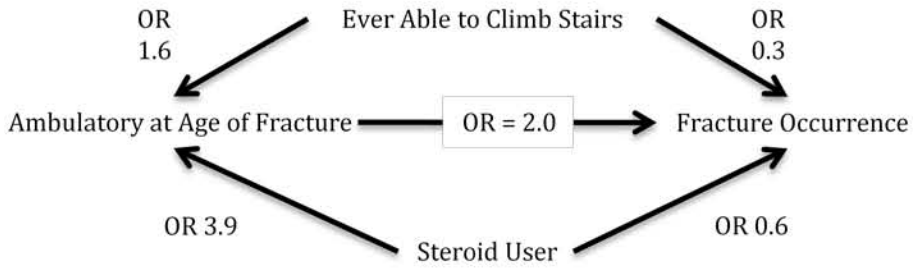


Figure 19: Causal Diagram for Ambulatory at Age of Fracture
Relationship between ambulatory at age of fracture, confounders, and fracture occurrence.
Unadjusted OR: 2.0 (95% CI: 0.4 – 10.4)
Adjusted OR: 4.88 (95% CI: 0.56 – 42.5)

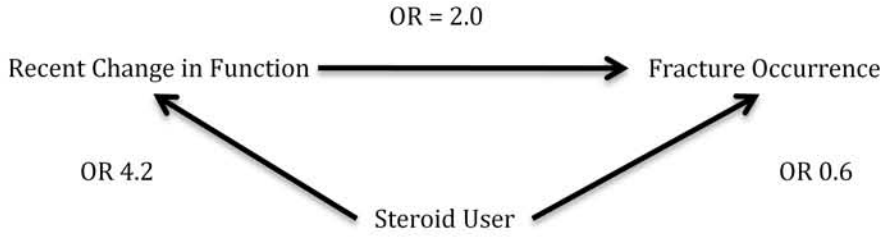


Figure 20: Causal Diagram for Recent Change in Function
Relationship between recent change in function, confounder, and fracture occurrence.
Unadjusted OR: 2.0 (95% CI: 0.5 – 8.4)
Adjusted OR: 3.27 (95% CI: 0.6 – 18.3)

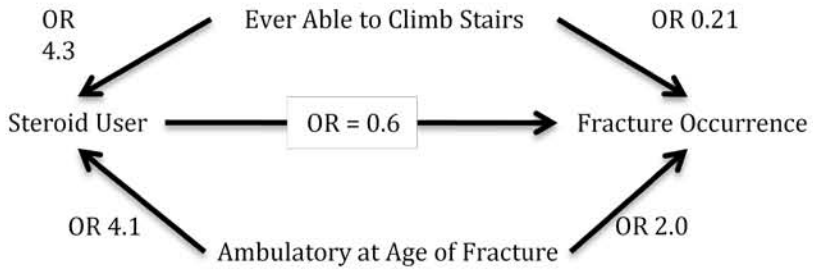


Figure 21: Causal Diagram for Steroid User
Relationship between steroid use, confounders, and fracture occurrence.
Unadjusted OR: 0.6 (95% CI: 0.1 – 2.3)
Adjusted OR: 0.63 (95% CI: 0.1 – 3.0)

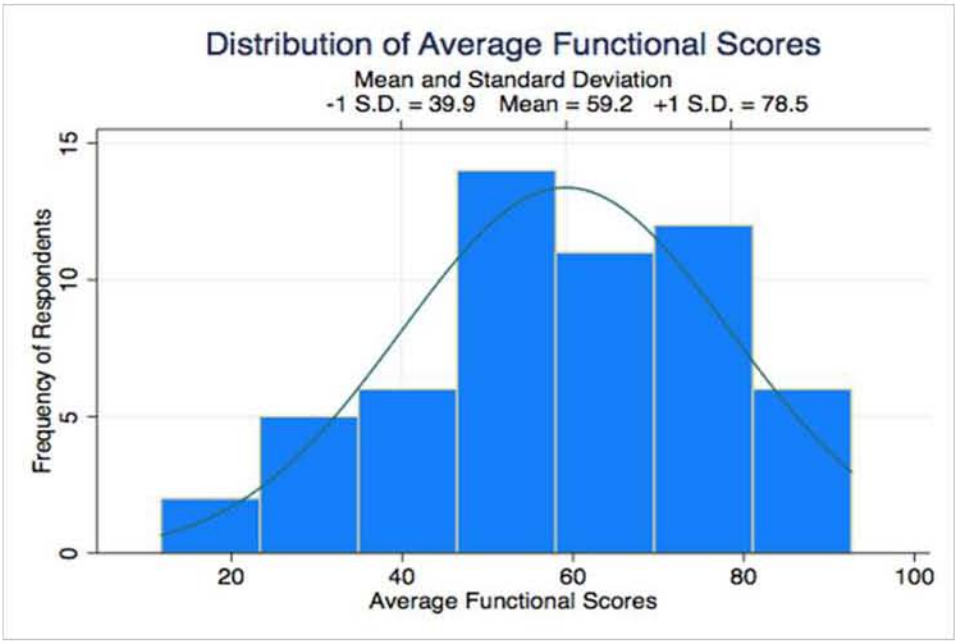


Figure 22: Distribution of Average Functional Scores
Average functional scores for 56 total responders.

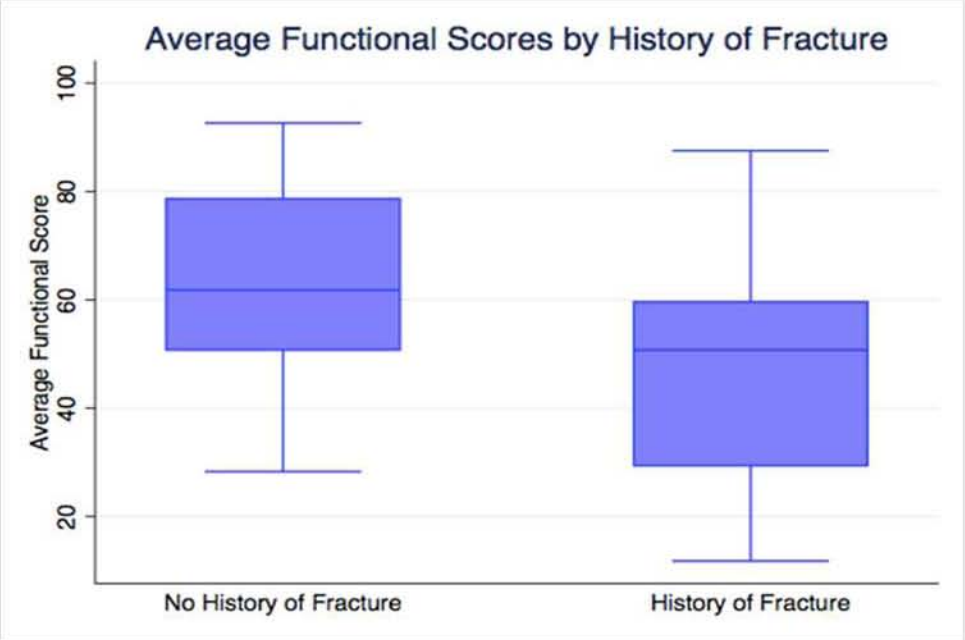


Figure 23: Distribution of Average Functional Scores by History of Fracture
Average functional scores for 56 total responders, 17 with history of fracture, 49 without.

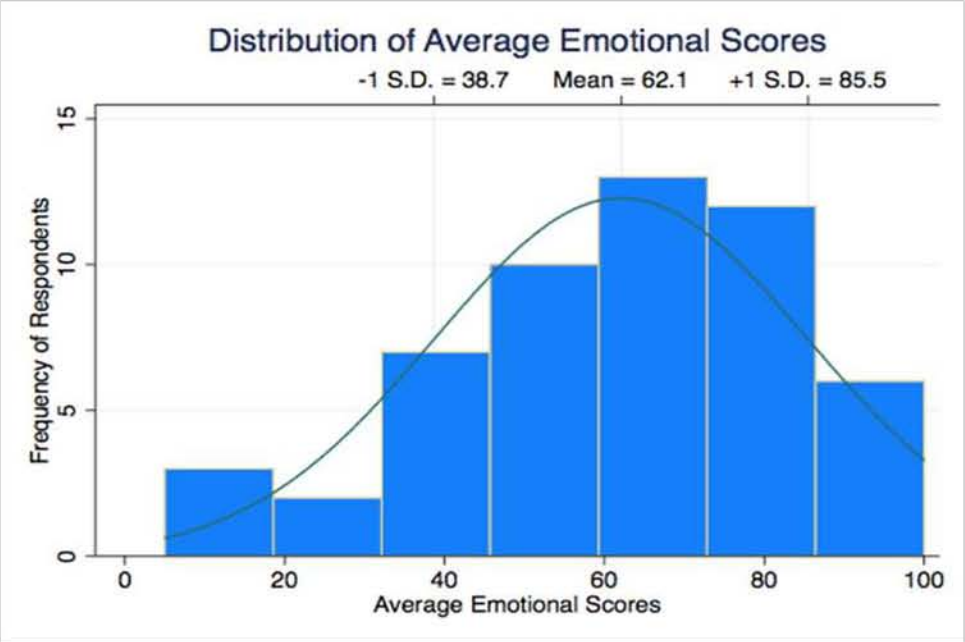


Figure 24: Distribution of Average Emotional Scores
Average emotional scores for 53 total responders.

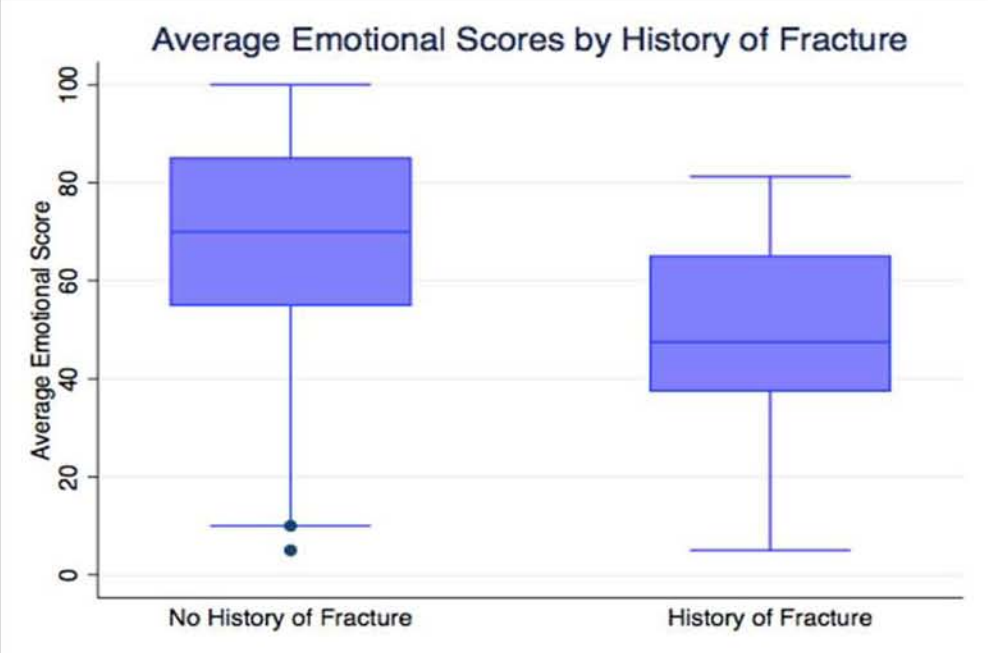


Figure 25: Distribution of Average Emotional Scores by History of Fracture
Average emotional scores for 53 total responders, 17 with history of fracture, 36 without.

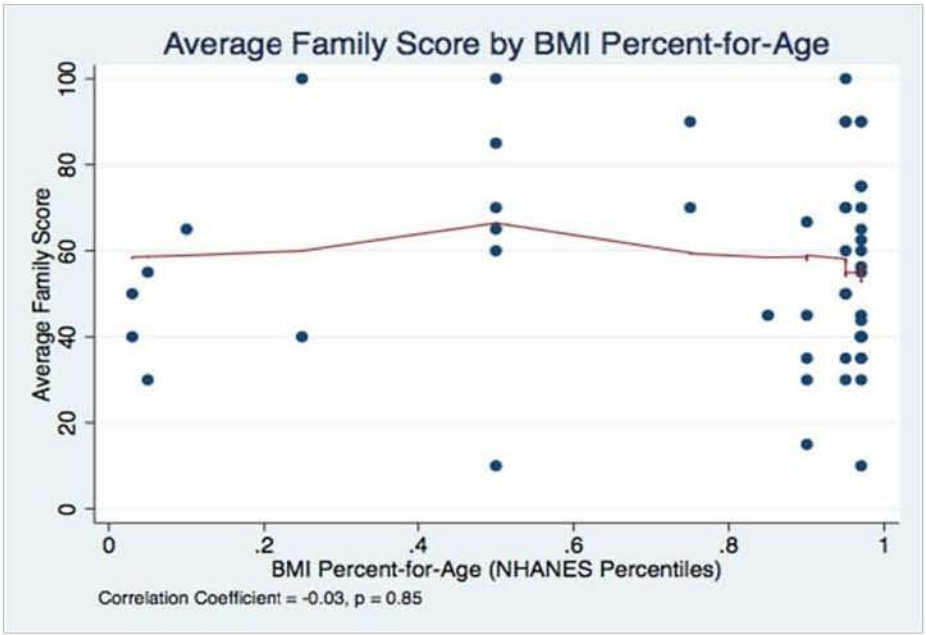


Figure 26: Average Family Score by BMI Percent-for-Age
Average family scores for 55 total responders by NHANES BMI Percent-for-Age.

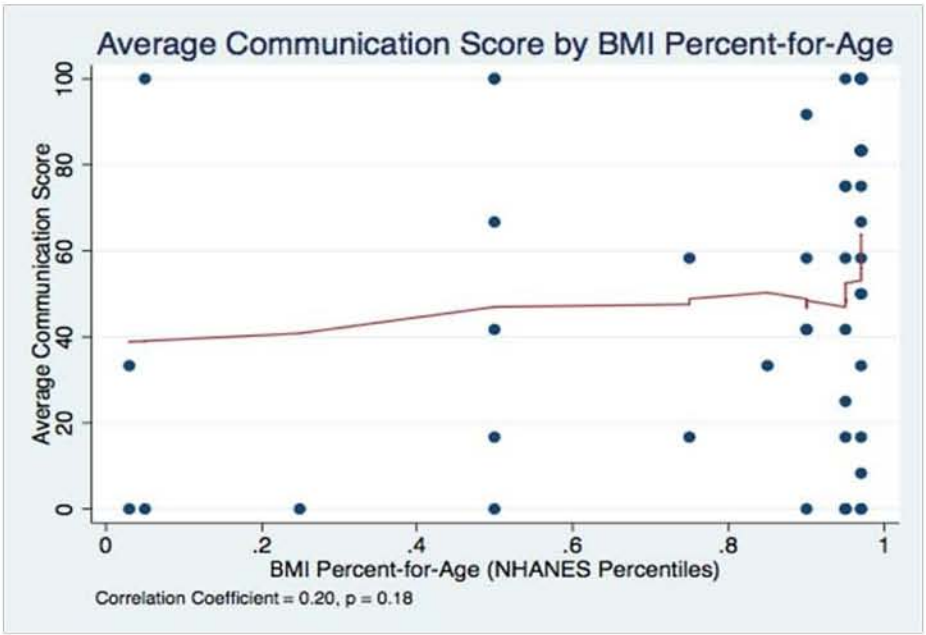


Figure 27: Average Communication Score by BMI Percent-for-Age
Average communication scores for 53 total responders by NHANES BMI Percent-for-Age.

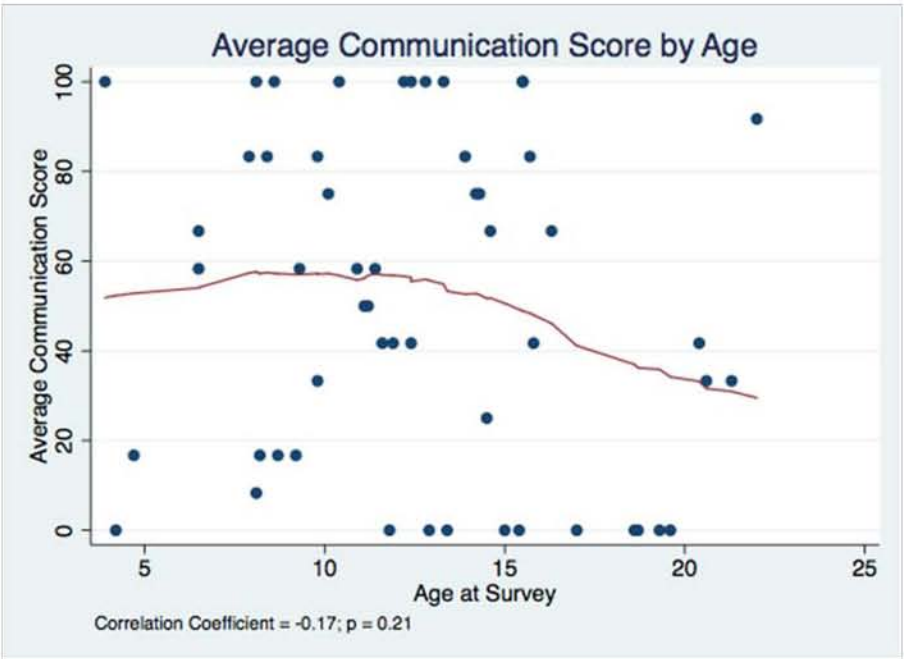


Figure 28: Average Communication Score by Age
Average communication scores for 53 total responders by age at the time of survey.

TABLES

Table 1 - Functional Status Category Definitions

Functional Score	Meaning
1	Climbs stairs independently or with the help of a handrail (Brooke/Vignos 1/2)
2	Climbs stairs with help of railing and assist and/or requires assistance to walk for long distances (Brooke/Vignos 3)
3	Cannot climb stairs, may require assistance to walk, but walks independently in the home (Brooke/Vignos 4-6)
4	Requires assistance to walk in the home, but is ambulatory (Brooke/Vignos 7)
5	Non-ambulatory (Brooke 8-10)

Table 2 - Demographics, Fractures, Steroid Use and Functional Status in Responders and Non-Responders

Comparison of Chart Review Information for Responders and Non-Responders	Responders (n=58)	Non-Responders (n=23)	P
Age (Years)			
Mean (SD)	12.3 (5.1)	14.8 (5.9)	0.07
Race/Ethnicity - n (%)			
White	41 (70.7%)	13 (56.5%)	0.38
Hispanic	10 (17.2%)	6 (26.1%)	
Asian	1 (1.7%)	0 (0%)	
Black	0 (0%)	1 (4.4%)	
Other	5 (8.6%)	3 (13.0%)	
Unknown	1 (1.7%)	0 (0%)	
Annual Household Income from All Sources - n (%)			
< $10,000	2 (3.5%)	--	
$10,000 - $20,000	0 (0.0%)	--	
$20,000 - $25,000	7 (12.1%)	--	
$25,000 - $35,000	7 (12.1%)	--	
$35,000 - $50,000	9 (15.5%)	--	
$50,000 - $75,000	10 (17.2%)	--	
> $75,000	18 (31.0%)	--	
No response	5 (8.6%)	23 (100%)	
Number of Fractures Identified on Chart Review - n (%)			
0	46 (79.3%)	18 (78.3%)	0.76
1	7 (12.1%)	4 (17.4%)	
2	1 (1.7%)	0 (0%)	
Unknown	4 (6.9%)	1 (4.4%)	
Steroid exposure time Identified on Chart Review (Years)			
Mean (SD)	3.9 (3.0)	5.7 (3.3)	0.03
Functional Status Identified on Chart Review - n (%)			
1	15 (25.9%)	8 (34.8%)	0.19
2	10 (17.2%)	2 (8.7%)	
3	3 (5.2%)	1 (4.4%)	
4	3 (5.2%)	0 (0%)	
5	22 (37.9%)	12 (52.2%)	
Unknown	5 (8.6%)	0 (0%)	

Responder Characteristics		
Number of Fractures Identified on Parent Interview - n (%)		
0	40 (69.0%)	--
1	15 (25.9%)	--
2	1 (1.7%)	--
3	0 (0%)	--
4	1 (1.7%)	--
Unknown	1 (1.7%)	
Lifetime Steroid Exposure Identified on Parent Interview (Years)		
Mean (SD)	2.6 (3.1)	--
Age at non-ambulatory Identified on Parent Interview (Years)		
Mean (SD)	10.0 (2.7)	--
Age of Diagnosis (years)		
Mean (SD)	3.5 (2.3)	--
Functional Status Categories (Chart Review and Parent Interview) - n (%)		
Climbs stairs independently or with the help of a handrail	10 (17.2%)	--
Climbs stairs with the help of a handrail and assist, requires assistance to walk for long distances	11 (19.0%)	--
Cannot climb stairs, does not require assistance to walk in the home	4 (6.9%)	--
Requires assistance to walk in the home	2 (3.5%)	--
Non-ambulatory	31 (53.4%)	--
Current Steroid User at Time of Survey - n (%)		
No	23 (39.7%)	--
Yes	35 (60.3%)	--
Other Medications (Subjects Have Used These at Some Point in Their Lives) - n (%)		
Bisphosphonates	1 (1.7%)	--
Vitamin D	19 (32.8%)	--
Calcium	16 (27.6%)	--
Unknown	1 (1.7%)	
Scoliosis		
No	42 (72.4%)	--
Yes	12 (20.7%)	--
Unknown	4 (6.9%)	
History of Surgery - n (%)		
No	44 (75.9%)	--
Yes	10 (17.2%)	--
Unknown	4 (6.9%)	

Current Address - n (%)		
Oregon	34 (58.6%)	--
Washington	8 (13.8%)	--
California	3 (5.2%)	--
Arizona	1 (1.7%)	--
Illinois	1 (1.7%)	--
Montana	2 (3.4%)	--
Vancouver B.C.	1 (1.7%)	--
Unknown	8 (13.8%)	
Urban Zip code - n (%)		
No	12 (20.7%)	--
Yes	22 (37.9%)	--
Unknown	24 (41.4%)	--
Responder - n (%)		
Mother	45 (77.6%)	--
Father	13 (22.4%)	--

Table 3: Characteristics of Children with and without Fractures

Nested Cohort Case Control	Fracture (13)	No Fracture (30)	OR (95% CI)	P	Adjusted OR (95% CI)	P
Age at Time of First Fracture (Years)						
Mean (SD)	9.8 (5.4)	12.8 (3.5)	--	--	--	--
Ambulatory Status One Year Prior to Age of Fracture - n (%)						
Non-ambulatory (reference)	5 (38.5%)	9 (30.0%)	1.0		1.0	
Ambulatory	8 (61.5%)	21 (70.0%)	2.0 (0.4 - 10.4)	0.4	4.88 (0.56 - 42.5)	0.15
Ever Able to Climb Stairs - n (%)						
No (reference)	9 (69.2%)	12 (40.0%)	1.0		1.0	
Yes	4 (30.8%)	18 (60.0%)	0.3 (0.08 - 1.2)	0.1	0.21 (0.04 - 1.02)	0.05
Change in Functional Status Within 1 Year Prior to Age of Fracture - n (%)						
No (reference)	8 (61.5%)	23 (76.7%)	1.0		1.0	
Yes	5 (38.5%)	7 (23.3%)	2.0 (0.5 - 8.4)	0.3	3.27 (0.60 - 18.3)	0.38
Steroid Use Within 6 Months Prior to Age of Fracture - n (%)						
No (reference)	8 (61.5%)	13 (43.3%)	1.0		1.0	
Yes	5 (38.5%)	17 (56.7%)	0.6 (0.1 - 2.3)	0.4	0.63 (0.10 - 3.0)	0.54

	Fracture (17)	No Fracture (40)	P
Bone Involved - n (%)			
Humerus	5 (29.4%)	--	--
Femur	6 (35.3%)	--	--
Tibia	3 (17.6%)	--	--
Elbow	1 (5.9%)	--	--
Ankle	1 (5.9%)	--	--
Shoulder	1 (5.9%)	--	--
Mechanism - n (%)			
No contact	2 (11.8%)	--	--
Ground level fall - seated or lying position	7 (41.2%)	--	--
Ground level fall - standing position	6 (35.3%)	--	--
Fell from height	1 (5.9%)	--	--
Motorcycle crash	1 (5.9%)	--	--
Using Calcium at Time of Fracture - n (%)			
Yes	3 (17.6%)	--	--
No	14 (82.4%)	--	--

Using Vitamin D at Time of Fracture - n (%)			
Yes	3 (17.6%)	--	--
No	14 (82.4%)	--	--
Ever Complained of Bone Pain - n (%)			
No	11 (64.7%)	29 (72.5%)	0.76
Yes	5 (29.4%)	10 (25.0%)	
Unknown	1 (5.9%)	1 (2.5%)	
Ever Complained of Back Pain - n (%)			
No	5 (29.4%)	21 (52.5%)	0.25
Yes	11 (64.7%)	18 (45.0%)	
Unknown	1 (5.9%)	1 (2.5%)	

Whole Sample - Comparison at Time of Survey	**Fracture (16)**	**No Fracture (40)**	**P**
Age at Time of Survey (Years)			
Mean (SD)	15.2 (4.1)	11.0 (4.5)	0.002
Functional Status at Time of Survey - n (%)			
1	0 (0.0%)	10 (25.0%)	0.003
2	1 (6.3%)	10 (25.0%)	
3	2 (12.5%)	2 (5.0%)	
4	2 (12.5%)	0 (0.0%)	
5	11 (68.8%)	18 (45.0%)	
Time between Survey and Most Recent Fracture (Years)			
Mean (SD)	5.0 (3.3)	0 (0)	<0.0001
0	0 (0%)	40 (100.0%)	<0.0001
< 5	9 (56.3%)	0 (0%)	
≥ 5	7 (43.8%)	0 (0%)	
Steroid Exposure (Years)			
Mean (SD)	2.9 (3.9)	2.5 (2.7)	0.66
0	4 (25.0%)	8 (20.0%)	0.56
0 - 1	5 (31.3%)	10 (25.0%)	
1-4	2 (12.5%)	12 (30.0%)	
> 4	5 (31.3%)	10 (25.0%)	
Years Non-Ambulatory			
Mean (SD)	4.6 (4.6)	2.2 (3.7)	0.05
0	5 (31.3%)	22 (55.0%)	0.11
0 - 3	4 (25.0%)	7 (17.5%)	
3 - 9	2 (12.5%)	8 (20.0%)	
> 9	5 (31.3%)	3 (7.5%)	
BMI for Age (NHANES Percentile) - n (%)			
< 10%	2 (12.5%)	2 (5.0%)	0.33
10-75%	3 (18.8%)	9 (22.5%)	
75 - 90%	4 (25.0%)	2 (5.0%)	
90-97%	2 (12.5%)	8 (20.0%)	
>97%	4 (25.0%)	16 (40.0%)	
Unknown	1 (6.3%)	3 (7.5%)	

Table 4 - Bivariate Quality of Life Associations

	Functional (n = 56)		Social (n = 53)		Communication (n=53)		Emotional (n = 53)		Family (n=55)	
	β (SE β)	P	β (SE β)	P	β (SE β)	P	β (SE β)	P	β (SE β)	P
Age (Years)										
Continuous	-2.5 (0.4)	<0.0001	-1.4 (0.7)	0.06	--		-1.9 (0.67)	0.006	-2.5 (0.6)	<0.0001
< 9	--	--	--	--	Ref		--		--	
9 – 12	--	--	--	--	-2.9 (14.9)	0.85	--		--	
12 – 15	--	--	--	--	4.8 (14.9)	0.75	--		--	
> 15	--	--	--	--	-14.7 (14.4)	0.31	--		--	
Functional Status at Time of Survey										
1	Ref		Ref		Ref		Ref		Ref	
2	-1.9 (6.4)	0.80	-7.2 (10.4)	0.50	14.2 (17.6)	0.43	-8.7 (10.3)	0.40	-11.7 (8.4)	0.17
3	-10.7 (8.7)	0.20	2.1 (13.6)	0.90	12.5 (22.8)	0.59	-9.7 (13.5)	0.50	-18.3 (11.1)	0.11
4	-34.6 (11.4)	0.004	-46.7 (17.7)	0.01	-25.0 (29.4)	0.40	-24.7 (17.5)	0.17	-22.1 (14.5)	0.14
5	-27.6 (5.4)	<0.001	-18.9 (8.7)	0.04	-4.0 (14.9)	0.79	-22.4 (8.6)	0.01	-35.6 (6.9)	<0.0001
Ordinal	-7.6 (1.2)	<0.001	--		--		-5.3 (1.8)	0.005	-8.6 (1.5)	<0.0001
Number of Years Non-Ambulatory										
0	Ref		Ref		Ref		Ref		Ref	
0 – 3	-13.0 (5.0)	0.01	-17.7 (8.7)	0.05	7.7 (13.1)	0.56	-11.0 (8.2)	0.18	-27.8 (6.9)	<0.0001
3 – 9	-20.2 (5.1)	<0.0001	-8.4 (9.0)	0.35	-22.6 (13.6)	0.1	-17.7 (8.4)	0.04	-22.6 (7.2)	0.003
> 9	-39.1 (5.6)	<0.0001	-10.8 (10.2)	0.30	-18.4 (14.7)	0.22	-19.0 (9.6)	0.06	-29.9 (7.8)	<0.0001
Ordinal	-12.2 (1.7)	<0.0001	--		--		-7.2 (2.8)	0.01	--	
Steroid Exposure (Years)										
0	Ref		Ref		Ref		Ref		Ref	
0 – 1	-16.4 (7.2)	0.03	14.5 (9.9)	0.15	-38.7 (13.5)	0.006	-16.0 (9.6)	0.10	-3.5 (1.1)	0.70
1 - 4	-0.6 (7.3)	0.90	9.5 (9.8)	0.34	-0.57 (13.3)	0.97	-9.9 (9.3)	0.29	1.1 (9.2)	0.91
> 4	-6.3 (7.2)	0.40	1.4 (9.6)	0.89	9.52 (13.5)	0.48	-6.6 (9.4)	0.48	-8.9 (9.1)	0.33
BMI Percent-for-Age										
< 10%	Ref		Ref		Ref		Ref		Ref	
10-75%	21.9 (10.8)	0.05	-5.7 (16.3)	0.73	11.1 (22.2)	0.62	-16.5 (15.5)	0.29	24.9 (12.9)	0.06
75 - 90%	0.80 (12.1)	0.95	-18.8 (17.5)	0.29	11.1 (23.9)	0.64	-28.3 (16.6)	0.10	-4.3 (14.2)	0.76
90-97%	17.0 (11.0)	0.13	-2.7 (16.3)	0.87	5.8 (21.9)	0.79	-11.0 (15.5)	0.53	20.8 (13.1)	0.12
>97%	18.1 (1.8)	0.08	-7.2 (15.3)	0.64	30.4 (20.2)	0.14	-9.3 (14.6)	0.53	9.13 (12.1)	0.45
Unknown	17.1 (13.2)	0.20	-20.4 (18.9)	0.29	18.8 (26.1)	0.48	-13.8 (18.0)	0.45	16.3 (15.6)	0.30
Fracture										
No	Ref		Ref		Ref		Ref		Ref	
Yes	-15.7 (5.3)	0.005	-14.5 (7.1)	0.05	-7.4 (11.1)	0.51	-19.0 (6.5)	0.005	-9.2 (6.8)	0.18

Table 5 – History of Fracture and Quality of Life Multivariate Adjusted Analysis

Functional Quality of Life	**β (SE β)**	**P**
Whole Sample (n=56) - R-squared for the model: 0.54		
Fracture		
No	Reference	
Yes	-9.0 (4.4)	0.05
Age Centered at 9 Years Old	0.22 (0.74)	0.77
Number of Years Non-Ambulatory	-12.0 (3.0)	<0.0001
Constant	72.8 (2.6)	<0.0001
Social Function Quality of Life		
Whole Sample (n=53) - R-squared for model: 0.21		
Fracture		
No	Reference	
Yes	-8.7 (8.4)	0.31
Functional Status at Time of Survey		
1	Reference	
2	-8.0 (11.4)	0.49
3	5.2 (14.4)	0.72
4	-40.3 (19.8)	0.05
5	-19.6 (13.9)	0.16
Age Centered at 9 Years Old	0.45 (1.26)	0.72
Constant	72.8 (8.3)	<0.0001
Communication Quality of Life		
Whole Sample (n=53) - R-squared for model: 0.48		
Fracture		
No	Reference	
Yes	-1.0 (13.2)	0.94
Functional Status at Time of Survey		
1	Reference	
2	-9.2 (19.6)	0.64
3	25.8 (22.6)	0.26
4	-34.7 (35.3)	0.33
5	5.2 (30.9)	0.87
Number of Years Non-Ambulatory		
0	Reference	
0 - 3	-23.2 (22.6)	0.31
3 - 9	-35.9 (22.4)	0.12
> 9	--	
Steroid Exposure (Years)		
0	Reference	
0 - 1	-44.2 (15.8)	0.008
1 - 4	4.7 (16.2)	0.77
> 4	15.4 (20.0)	0.44

BMI Percent for Age		
< 10%	Reference	
10-75%	26.3 (24.1)	0.28
75 - 90%	15.4 (24.2)	0.53
90-97%	15.1 (24.2)	0.54
>97%	34.3 (21.5)	0.12
Unknown	34.0 (29.0)	0.25
Age at Survey (Years)		
< 9	Reference	
9 - 12	2.7 (17.5)	0.88
12 - 15	12.0 (24.1)	0.62
> 15	0.57 (27.8)	0.98
Constant	38.6 (25.6)	0.14
Emotional Function Quality of Life		
Whole Sample (n = 53) - R-squared for model: 0.20		
Fracture		
No	Reference	
Yes	-13.4 (7.0)	0.06
Age Centered at 9 Years Old	-1.4 (0.7)	0.06
Constant	70.7 (3.8)	<0.0001
Family Quality of Life		
Whole Sample (n = 55) - R-squared for model: 0.50		
Fracture		
No	Reference	
Yes	4.3 (6.7)	0.52
Functional Status at Time of Survey	-7.5 (5.0)	0.14
BMI Percent for Age		
< 10%	Reference	
10-75%	13.3 (12.6)	0.30
75 - 90%	-2.9 (12.9)	0.82
90-97%	16.9 (12.4)	0.18
>97%	3.9 (11.1)	0.73
Unknown	25.5 (13.9)	0.07
Number of Years Non-Ambulatory		
0	Reference	
0 - 3	-4.5 (16.5)	0.79
3 - 9	-5.5 (17.2)	0.75
> 9	-4.6 (16.2)	0.78
Constant	75.8 (16.4)	<0.0001

Appendix A: **Questionnaire**

I. Demographic Information:

A. Subject #__

Although I have this information, I just need to ask you to verify what I have is correct.

What is your son's name? Xx.name

B. Last name

C. First name

And his date of birth?

D. Month of birth

E. Day of birth

F. Year of birth

So that makes Xx.name how old today?

G. Current age

H. What do you consider the three most difficult aspects of Xx.name's condition?

II. Functional Status:

The point of this first section is to get an understanding of the progression of Xx.name's disease, specifically how well he was getting around at the time of his diagnosis, when he entered kindergarten, and again when he entered 2nd grade.

If you have any timelines, diaries, or organized physician records, would you mind pulling them out? They will likely be useful as you are trying to remember dates.

A. **Time point 1: Diagnosis**

These first questions refer to the time of Xx.name's diagnosis.

Can you tell me how old Xx.name was at the time of his diagnosis?

1. Age at diagnosis

2. Year of diagnosis

3. Month of diagnosis

Thinking back to the time he was diagnosed, can you remember where you were living? Was Xx.name going to pre-school or daycare? Do you remember how he was getting to school?

At this time, how well was Xx.name getting around, specifically do you remember if he was able to go up and down stairs on his own?

Did he need to use the railing? If so, did he need the railing a lot, or just a little for balance?

4. Climb up stairs

At this time, was he able to walk around the community on his own?

5. Walk in community

6. Walk in community other

If he did, did he fall down/stumble more than other kids?

7. Fall/stumble

8. Fall/stumble other

Did he need assistive devices out in the community?

9. Assistive devices in community

10. Assistive devices in community other

I'm still referring to the time when he was diagnosed, when he was xx.age years old. At that time, was he able to get around the house on his own?

Did he need assistive devices in the home?

11. Assistive devices in home

12. Assistive devices in home other

If he did need assistive devices, was he able to transfer on his own, or did you need to help him? Did you need to help him a lot or just a little?

13. Transfer

14. Transfer other

And at the time of his diagnosis, was xx.name on steroid medication, such as prednisone or Deflazacort? Which steroid medication as he on?

15. Steroid

And was he on any medication to strengthen his bones at the time of his diagnosis? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate, these are also called bisphosphonates?

16. Bisphosphonates

B. **Time point 2: Kindergarten**

Now I'm going to ask you to remember back to when Xx.name started kindergarten.

Can you tell me how old Xx.name was when he started kindergarten?

1. Age at diagnosis

2. Year of diagnosis

3. Month of diagnosis

Thinking back to when he started kindergarten, can you remember where you were living? Was Xx.name going to pre-school or daycare? Do you remember how he was getting to school?

At this time, how well was Xx.name getting around, specifically do you remember if he was able to go up and down stairs on his own?

Did he need to use the railing? If so, did he need the railing a lot, or just a little for balance?

4. Climb up stairs

At this time, was he able to walk around the community on his own?

5. Walk in community

6. Walk in community other

If he did, did he fall down/stumble more than other kids?

7. Fall/stumble

8. Fall/stumble other

Did he need assistive devices out in the community?

9. Assistive devices in community

10. Assistive devices in community other

I'm still referring to the time when he was diagnosed, when he was xx.age years old. At that time, was he able to get around the house on his own?

Did he need assistive devices in the home?

11. Assistive devices in home

12. Assistive devices in home other

If he did need assistive devices, was he able to transfer on his own, or did you need to help him? Did you need to help him a lot or just a little?

13. Transfer

14. Transfer other

And when he was starting kindergarten, was xx.name on steroid medication, such as prednisone or Deflazacort? Which steroid medication as he on?

15. Steroid

And was he on any medication to strengthen his bones when he started kindergarten? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate, these are also called bisphosphonates?

16. Bisphosphonates

C. Time point 3: Second grade

Can you remember two years after kindergarten, when xx.name was starting second grade?

Where were you living then? What school was Xx.name attending? Do you remember how he was getting to and from school at that point? What activities was he involved with at that point?

Can you tell me how old Xx.name was at the start of second grade?

1. Age at diagnosis

2. Year of diagnosis

3. Month of diagnosis

At this time, how well was Xx.name getting around, specifically do you remember if he was able to go up and down stairs on his own?

Did he need to use the railing? If so, did he need the railing a lot, or just a little for balance?

4. Climb up stairs

At this time, was he able to walk around the community on his own?

5. Walk in community

6. Walk in community other

If he did, did he fall down/stumble more than other kids?

7. Fall/stumble

8. Fall/stumble other

Did he need assistive devices out in the community?

9. Assistive devices in community

10. Assistive devices in community other

I'm still referring to the time when he started 2nd grade, when he was xx.age years old. At that time, was he able to get around the house on his own?

Did he need assistive devices in the home?

11. Assistive devices in home

12. Assistive devices in home other

If he did need assistive devices, was he able to transfer on his own, or did you need to help him? Did you need to help him a lot or just a little?

13. Transfer

14. Transfer other

And when he was starting second grade, was xx.name on steroid medication, such as prednisone or Deflazacort? Which steroid medication as he on?

15. Steroid

And was he on any medication to strengthen his bones when he started second grade? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate, these are also called bisphosphonates?

16. Bisphosphonates

III. Age at changes in function:

These next questions are again looking at the progression of Xx.name's disease, but they're asked in a slightly different way. I'm going to ask you to remember at what age Xx.name stopped being able to perform certain skills, for example when he stopped being able to climb stairs on his own or walk without assistance. Does that make sense?

Can you remember at what age Xx.name could no longer:

1. Climb stairs independently (i.e., all by himself, without any help from a person or the railing)?

2. Climb stairs with the aid of a railing (without significant parental help)?

3. Climb stairs at all (needed to be carried/elevator)?

4. Rise from a chair unaided (he could no longer get off the toilet seat by himself)?

5. Walk without assistance?

6. Walk without assistive devices in the community (for example the grocery store or longer distances)? In other words, how old was he when he first needed a scooter or manual wheelchair?

7. Get around home or school without assistive devices?

8. Walk, but could still stand (i.e., he could help with transfers but could not walk on his own)?

9. And finally, can you remember at what age your son needed the help of a wheelchair fulltime?

IV. Fractures:

Great, thank you! This next section is covering any fractures or broken bones Xx.name has had.

Has he ever broken a bone?

How many times?

1. Number of fracture

Okay, if you don't mind, I'd like to go through them one at a time:

A. First fracture:

1. How old was he when he had his first fracture?

2. Can you tell me what happened? (For example, did he fall or trip? Did he just start complaining of pain? Was it discovered on a routine x-ray?) define for myself what is traumatic vs. atraumatic (fall greater than standing height…

make multiple categories severely moderately mildly

3. What bone was it in?

4. Did he get an x-ray?

5. How was it treated? (Did he require surgery? Did he get a cast or a splint? Did they tell him to simply not use it for awhile?) *Answer with more than one answer*

6. In your opinion, did he eventually fully recover his motor abilities? I.e., did he return to the level of function he had prior to the injury?

7. Was taking steroids at this time? Which steroid medication was he on (for example prednisone or Deflazacort)?

8. Was he taking any medicine to strengthen his bones? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate?

9. Was he taking vitamin D?

10. Was he taking calcium?

B. Second fracture:

1. How old was he when he had his second fracture?

2. Can you tell me what happened? (For example, did he fall or trip? Did he just start complaining of pain? Was it discovered on a routine x-ray?)

3. Did he get an x-ray?

4. What bone was it in?

5. How was it treated? (Did he require surgery? Did he get a cast or a splint? Did they tell him to simply not use it for awhile?)

6. In your opinion, did he eventually fully recover his motor abilities? I.e., did he return to the level of function he had prior to the injury?

7. Was taking steroids at this time (for example prednisone or Deflazacort)?

a. Was he taking Prednisone?

b. Was he taking Deflazacort?

8. Was he taking any medicine to strengthen his bones? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate?

9. Was he taking vitamin D?

10. Was he taking calcium?

C. Third fracture:

1. How old was he when he had his third fracture?

2. Can you tell me what happened? (For example, did he fall or trip? Did he just start complaining of pain? Was it discovered on a routine x-ray?)

3. Did he get an x-ray?

4. What bone was it in?

5. How was it treated? (Did he require surgery? Did he get a cast or a splint? Did they tell him to simply not use it for awhile?)

6. In your opinion, did he eventually fully recover his motor abilities? I.e., did he return to the level of function he had prior to the injury?

7. Was taking steroids at this time (for example prednisone or Deflazacort)?

a. Was he taking Prednisone?

b. Was he taking Deflazacort?

8. Was he taking any medicine to strengthen his bones? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate?

9. Was he taking vitamin D?

10. Was he taking calcium?

D. Fourth fracture:

1. How old was he when he had his fourth fracture?

2. Can you tell me what happened? (For example, did he fall or trip? Did he just start complaining of pain? Was it discovered on a routine x-ray?)

3. Did he get an x-ray?

4. What bone was it in?

5. How was it treated? (Did he require surgery? Did he get a cast or a splint? Did they tell him to simply not use it for awhile?)

6. In your opinion, did he eventually fully recover his motor abilities? I.e., did he return to the level of function he had prior to the injury?

7. Was taking steroids at this time (for example prednisone or Deflazacort)?

a. Was he taking Prednisone?

b. Was he taking Deflazacort?

8. Was he taking any medicine to strengthen his bones? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate?

9. Was he taking vitamin D?

10. Was he taking calcium?

E. Fifth fracture:

1. How old was he when he had his fifth fracture?

2. Can you tell me what happened? (For example, did he fall or trip? Did he just start complaining of pain? Was it discovered on a routine x-ray?)

3. Did he get an x-ray?

4. What bone was it in?

5. How was it treated? (Did he require surgery? Did he get a cast or a splint? Did they tell him to simply not use it for awhile?)

6. In your opinion, did he eventually fully recover his motor abilities? I.e., did he return to the level of function he had prior to the injury?

7. Was taking steroids at this time (for example prednisone or Deflazacort)?

a. Was he taking Prednisone?

b. Was he taking Deflazacort?

8. Was he taking any medicine to strengthen his bones? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate?

9. Was he taking vitamin D?

10. Was he taking calcium?

V. Back/Bone Pain:

These next questions are about bone and back pain. We're interested in if xx.name has experienced bone or back pain, and how severely that pain affected him.

A. Back pain:

1. Has Xx.name ever complained of back pain?

2. Did he get an x-ray to evaluate this pain?

3. Did he get a DEXA scan (bone scan) to evaluate this pain?

4. Did he receive any treatment for it? For example surgery, physical therapy, bone strengthening medication, or pain medication?

5. Do you think this was a major problem, minor problem, or somewhere in between?

B. General bone pain:

1. Has Xx.name ever complained of bone pain?

2. Did he get an x-ray to evaluate this pain?

3. Did he get a DEXA scan to evaluate this pain?

4. Did he receive any treatment for it? For example surgery, physical therapy, bone strengthening medication, or pain medication?

5. Do you think this was a major problem, minor problem, or somewhere in between?

VII. Medications:

Thank you so much, you have been so helpful.

These next questions refer to medications Xx.name is currently taking or has taken in the past.

1. Does Xx.name currently take any steroid medication (for example prednisone or Deflazacort)?

2. If yes, which steroid medication is he currently taking?

3. How long has he taken steroids?

3a. Years

3b. Months

4. If he is not currently taking steroids, has he ever taken steroids? Which steroid medication did he primarily take in the past?

5. How long was he on steroids in total?

5a. Years

5b. Months

6. Does Xx.name currently take any medication to strengthen his bones? Examples of these medications are Fosamax, Actonel, Boniva, alendronate, ibandronate, or risedronate. They are also called bisphosphonates.

7. Has he ever taken one of these medications?

8. Has Xx.name ever taken Vitamin D?

9. Has he ever taken calcium?

10. Has he ever taken Coenzyme Q?

11. Has he ever taken any other herbal supplement or vitamin for his Muscular Dystrophy?

12. If yes, what herbal supplement/vitamin did he take?

13. Has he ever been involved in support groups or therapy?

VII. Quality of Life:

I know that this has been long so far, and thank you for sticking with me. I have one more section of questions now about Xx.name's quality of life. It should take about fifteen minutes. Do you have fifteen more minutes or should I call back at another time?

If yes:

Ok thank you. This last section has questions looking at how Xx.name's disease is affecting his overall life, including school, and how he's doing socially and emotionally. I'm going to ask you questions and I would like you to answer on a five point scale.

This is the scale I would like you to use in regard to how often Xx.name has a particular problem. For example, if I ask "does Xx.name have a problem brushing his hair in the morning," and he can do it most every morning, except a few times he has been too tired, you could answer that he "almost never" has a problem. Does that make sense? Do you have any questions before we begin?

A. About My Child's Neuromuscular Disease (*problems with…)*	**Never**	**Almost Never**	**Some-Times**	**Often**	**Almost Always**
1. Is it hard for Xx.name to breath?	0	1	2	3	4
2. Does Xx.name get sick easily?	0	1	2	3	4
3. Does Xx.name get sores and/or rashes?	0	1	2	3	4
4. Do Xx.name's legs hurt?	0	1	2	3	4
5. Does Xx.name feel tired?	0	1	2	3	4
6. Does Xx.name's back feel stiff?	0	1	2	3	4
7. Does Xx.name wake up tired?	0	1	2	3	4
8. Are Xx.name's hands weak?	0	1	2	3	4

9. Is it hard for Xx.name to use the bathroom?	0	1	2	3	4
10. Is it hard for Xx.name to gain or lose weight when he wants to?	0	1	2	3	4
11. Is it hard for Xx.name to use his hands?	0	1	2	3	4
12. Is it hard for Xx.name to swallow food?	0	1	2	3	4
13. Does it take Xx.name a long time to bathe or shower?	0	1	2	3	4
14. Does Xx.name get hurt accidentally?	0	1	2	3	4
15. Does it take Xx.name a long time to eat?	0	1	2	3	4
16. Is it hard for Xx.name to turn himself during the night?	0	1	2	3	4
17. Is it hard for Xx.name to go places in his equipment?	0	1	2	3	4
B. Communication (*problems with…)*	**Never**	**Almost Never**	**Some-Times**	**Often**	**Almost Always**
1. Is it hard for Xx.name to tell the doctors and nurses how he feels?	0	1	2	3	4
2. Is it hard for Xx.name to ask the doctors and nurses questions?	0	1	2	3	4
3. Is it hard for Xx.name to explain his illness to other people?	0	1	2	3	4
C. About our family resources (*problems with…)*	**Never**	**Almost Never**	**Some-Times**	**Often**	**Almost Always**
1. Is it hard for your family to plan activities like vacations?	0	1	2	3	4
2. Is it hard for your family to get enough rest?	0	1	2	3	4
3. Is money a problem for your family?	0	1	2	3	4
4. Do you think your family has a lot of problems?	0	1	2	3	4
5. Does Xx.name not have access to the equipment that he needs?	0	1	2	3	4
D. School Functioning (*problems with…)*	**Never**	**Almost Never**	**Some-Times**	**Often**	**Almost Always**
1. Does Xx.name have problems Paying attention in class?	0	1	2	3	4

2. Does Xx.name have problems forgetting things in school?	0	1	2	3	4
3. Does Xx.name have problems keeping up with schoolwork	0	1	2	3	4
4. Does Xx.name have problems missing school because of not feeling well?	0	1	2	3	4
5. Does Xx.name have problems missing school to go to the doctor or hospital?	0	1	2	3	4
E. Emotional Functioning (*problems with…)*	**Never**	**Almost Never**	**Some-Times**	**Often**	**Almost Always**
1. Does Xx.name have problems with feeling afraid or scared?	0	1	2	3	4
2. Does Xx.name have problems with feeling sad or blue?	0	1	2	3	4
3. Does Xx.name have problems with feeling angry?	0	1	2	3	4
4. Does Xx.name have trouble sleeping?	0	1	2	3	4
5. Does Xx.name have problems with worrying about what will happen to him?	0	1	2	3	4
F. Social Functioning (*problems with…)*	**Never**	**Almost Never**	**Some-Times**	**Often**	**Almost Always**
1. Does Xx.name have problems with getting along with other teens?	0	1	2	3	4
2. Does Xx.name have problems with other teens not wanting to be his friend?	0	1	2	3	4
3. Does Xx.name have problems with getting teased by other teens?	0	1	2	3	4
4. Does Xx.name have problems with not being able to do things that other teens his age can do?	0	1	2	3	4
5. Does Xx.name have problems with keeping up with other teens?	0	1	2	3	4

G. Parental relationship:

These last questions are a little more personal, and so I just want to remind you that everything you say is confidential and that you don't have to answer any questions that you don't want to.

1. Has xx.name's condition caused problems in your marriage or with your partner?

(Never, almost never, sometimes, often, almost always)

VIII. SES

1. What is your annual household income from all sources? (ask below if prompting is needed)

Is it:

04 Less than $25,000? **If "no," ask 05; if "yes," ask 03** ($20,000 to less than $25,000)

03 Less than $20,000? **If "no," code 04; if "yes," ask 02** ($15,000 to less than $20,000)

02 Less than $15,000? **If "no," code 03; if "yes," ask 01** ($10,000 to less than $15,000)

01 Less than $10,000? **If "no," code 02**

05 Less than $35,000? **If "no," ask 06** ($25,000 to less than $35,000)

06 Less than $50,000? **If "no," ask 07** ($35,000 to less than $50,000)

07 Less than $75,000? **If "no," code 08** ($50,000 to less than $75,000)

08 $75,000 or more

IX. Other

A. Is there something that I didn't ask that you feel is relevant to understanding your son's disease progression or quality of life?

Thank you so much for your help with this! My project team and I will be working on this research for the next year and asking a lot of other parents to answer these same questions. We will then put all of your responses together to improve our understanding of fractures and quality of life amongst boys with muscular dystrophy.

If you would like, once we have looked at all the data, I could send you a summary of what we find. Would that be something that you might be interested in?

If yes:

Ok, if that's so, then would you please give me your address so that I know where to send it to?

Thank you, and thank you again for answering these questions. We're hoping to learn as much as possible about your son's disease, and it's only with your participation that we are able to do any of this research.

Appendix B: QOL Missing Data Sensitivity Analyses

Functional:

15 of 56 subjects did not respond to all quality of life questions regarding neuromuscular function. Five subjects did not respond to five or more questions (subjects 2, 5, 49, 51, and 55). Three questions that participants frequently didn't answer that accounted for the majority (56%) of the skipped questions were questions 10, 13, and 17.

10 – Is it hard for your child to gain or lose weight when he wants to?

13 – Does it take your child a long time to bathe or shower?

17 – Is it hard for your child to go places in his equipment?

Those that missed more questions tended to be younger, of a higher functional group. There tended to be fewer children in the house, and had a slightly lower SES. Their quality of life scores in other categories were similar to those that did not skip any questions, other than their school quality of life, which was significantly higher than those who had not missed any questions.

Those that missed questions 13 and 17 tended to be younger, of higher functional status, and likely did not have equipment. Non-respondents to question 10 did not have an identifiable trend.

Sensitivity Analysis 1: Interpolate responses to Questions 13 and 17 based on the average scores of other children in the same functional category, drop Question 10:

- Whole Sample fracture adjusted for age, number of years non-ambulatory, time since the fracture: β coefficient -6.9; SE 6.3; p = 0.28
- Whole Sample steroid adjusted for age, BMI, number of years non-ambulatory:
    - 0-1 years: β coefficient -8.4; SE 5.7; p = 0.15
    - 1-4 years: β coefficient 2.7; SE 6.1; p = 0.67
    - > 4 years: β coefficient 5.6; SE 6.4; p = 0.39
- Whole Sample BMI adjusted for age, BMI, number of years non-ambulatory:
    - 10-75th percentile: β coefficient 8.5; SE 7.6; p = 0.27
    - 75-90th percentile: β coefficient 0.63; SE 8.2; p = 0.94
    - 90-97th percentile: β coefficient 7.6; SE 7.5; p = 0.32
    - Greater than 97th percentile: β coefficient 7.6; SE 7.0; p = 0.29
    - Unknown BMI: β coefficient 24.9; SE 9.3; p = 0.01

Sensitivity Analysis 2: Exclude all children who didn't respond to five or more questions (Subjects 2, 5, 49, 51, and 55) for a sample n of 51, a non-ambulatory sample n of 28:

- Whole Sample fracture adjusted for age, number of years non-ambulatory, time since the fracture: β coefficient -7.7; SE 6.5; p = 0.24
- Whole Sample steroid adjusted for age, BMI, number of years non-ambulatory:
    - 0-1 years: β coefficient -7.3; SE 6.5; p = 0.28
    - 1-4 years: β coefficient 2.7; SE 6.7; p = 0.69
    - > 4 years: β coefficient 5.7; SE 6.8; p = 0.41

- Whole Sample BMI adjusted for age, BMI, number of years non-ambulatory:
    - 10-75th percentile: β coefficient 16.2; SE 8.8; p = 0.07
    - 75-90th percentile: β coefficient 7.5; SE 9.4; p = 0.43
    - 90-97th percentile: β coefficient 15.1; SE 8.5; p = 0.09
    - Greater than 97th percentile: β coefficient 12.9; SE 8.0; p = 0.12
    - Unknown BMI: β coefficient 30.1; SE 10.2; p = 0.005

Social:

Five of 56 subjects did not respond to all of the quality of life questions regarding social functioning. Three subjects did not respond to any questions (subjects 2, 5, and 55). There was no particular question that stood out amongst the 5 as particularly difficult for parents to answer.

Those that skipped questions did not differ from the others with regard to age, functional status, race, SES, or number of kids in the house. They did have significantly lower communication, emotional, social, and marriage quality of life scores.

No sensitivity analyses were conducted in this group.

Communication:

Six of 56 subjects did not respond to all of the communication quality of life questions. Three subjects did not respond to any questions (subject 2, 5, and 49). There was no particular question that stood out amongst the three as particularly difficult for parents to answer.

Those that skipped questions were significantly younger and of higher functional status. The ages of those that skipped questions ranged from 1.9 – 12.8, with three subjects being younger than 5. They were all ambulatory, with 5/6 still being able to climb stairs. These subjects' quality of life scores across the board were higher for other categories, which is overwhelmingly likely due to their younger age and higher functional status.

No sensitivity analyses were conducted in this group.

Family:

Eight of 56 subjects did not respond to all of the family quality of life. One subject did not respond to any questions (subject 2). All of these eight subjects skipped question 5, which accounted for 69% of all skipped questions.

5 – Does your child have problems with not having access to the equipment that he needs?

Those that skipped questions had significantly better functional status, with 7 of the 8 still being able to climb stairs. They also tended to be younger, with an average age of 9.5 compared with 12.6 (average age of those that did not skip any family QOL questions). They did have significantly higher functional and emotional quality of life scores, and did have higher quality of life scores across all dimensions. Although not statistically significant, the subjects who skipped responses in the family QOL category had a mean family QOL ten points higher than those who did not skip questions.

When question 5 was excluded, the mean decreased 4 points, with a three-point increase in the standard deviation.

Sensitivity Analysis 1: Interpolate responses to question 5 based on average of children in the same functional category.

- Whole Sample fracture adjusted for functional status and age:

  β coefficient 0.51; SE 9.7; p = 0.96

- Whole Sample steroid adjusted for age, BMI, number of years non-ambulatory:
  - 0-1 years: β coefficient 8.8; SE 9.1; p = 0.34
  - 1-4 years: β coefficient 7.6; SE 9.4; p = 0.42
  - > 4 years: β coefficient 26.7; SE 10.6; p = 0.02
- Whole Sample BMI adjusted for functional status, history of fracture, age, steroid exposure:
  - 10-75th percentile: β coefficient 10.0; SE 13.4; p = 0.46
  - 75-90th percentile: β coefficient -7.0; SE 14.2; p = 0.63
  - 90-97th percentile: β coefficient 16.6; SE 13.1; p = 0.21
  - Greater than 97th percentile: β coefficient -0.07; SE 12.1; p = 0.96
  - Unknown BMI: β coefficient 38.1; SE 16.4; p = 0.03

Emotional:

Six of 56 subjects did not respond to all of the quality of life questions regarding emotional functioning. Two subjects did not respond to any questions (subjects 2 and 5). All subjects skipped question 5, which accounted for 43% of all skipped questions.

5 – Does your child have problems with worrying about what will happen to him?

Those that skipped questions did not differ from the others with regard to age, functional status, race, SES, number of kids in the house, or quality of life scores. They did, overall, have lower functional, communication, family, and emotional quality of life, and higher school, social and marriage quality of life, but none of these differences approached statistical significance.

When question 5 was excluded, the mean increased 0.6 points, the standard deviation decreased 0.4 points. The difference was not significant.

No sensitivity analyses were conducted in this group.