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Title Page:

Quality of life and psychosocial wellbeing in youth with neuromuscular disorders who are wheelchair users: A systematic review.

Running Head: Wellbeing in Neuromuscular Disorders

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TITLE:

Quality of life and psychosocial wellbeing in youth with neuromuscular disorders who are wheelchair users: A systematic review

ABSTRACT

Objective: To investigate quality of life (QoL) and psychosocial wellbeing in youth with Neuromuscular Disorders (NMD) who are wheelchair users.

Data Sources: Medline, Embase, CINAHL and PsycINFO (January 2004 to April 2016) and reference lists of retrieved full-text papers.

Study Selection: Peer-reviewed studies were included when data describing self-reported QoL and psychosocial wellbeing could be separately understood for those using wheelchairs and aged 12-22 years old. 2058 records were independently screened and potentially eligible papers were obtained and examined by all reviewers. Twelve observational and three qualitative studies met the inclusion criteria.

Data Extraction: Population representativeness, measurement tools and outcomes, where possible with comparison groups. Two reviewers independently appraised studies for risk of bias to internal validity and generalisability.

Data Synthesis: Heterogeneity of measurement and reporting precluded meta-analysis. Data were cross-sectional only. Compared to same age typically developing peers, physical QoL was scored consistently and significantly lower in youth with NMD, whilst psychosocial QoL was not. Psychosocial QoL was highest in youth non-ambulant since early childhood and in those recruited via single tertiary specialist clinics. Mental health and social participation could not be compared to same age populations.

Conclusions: Despite low physical QoL, psychosocial QoL in youth with NMD appeared comparable to same age peers. The psychosocial wellbeing of younger adolescents on degenerative disease trajectories appeared most compromised, though the longitudinal impacts of growing up with NMD on mental health and social participation are unknown. Interpretation was hampered by poor description of participant age, gender and physical ability, lack of population based recruitment strategies and inconsistent use of age appropriate measures. Understanding of self-reported QoL and psychosocial wellbeing in youth with NMD transitioning to adulthood is limited.

Keywords: Adolescent, Youth, Neuromuscular Diseases, quality of life, mental health, social participation

Abbreviations:

CMD	Congenital Muscular Dystrophy
DMD	Duchenne Muscular Dystrophy
MD	Muscular Dystrophy
NMD	Neuromuscular Disorders
NIV	Non Invasive Ventilation

QoL Quality of Life

SMA Spinal Muscular Atrophy

INTRODUCTION

Neuromuscular Disorders (NMD) are genetically acquired rare diseases causing severe muscle weakness [1, 2]. Spinal Muscular Atrophy Type II (SMA II) and Duchenne Muscular Dystrophy (DMD) are examples of more common NMD that necessitate wheelchair dependence in early childhood or adolescence respectively [3, 4]. Cognition is unaffected in most; youth with DMD are at higher risk of specific learning disabilities and/or autistic spectrum traits if their disease causing mutation occurs in the latter third of the dystrophin gene[4, 5]. Co-morbidities in multiple body systems result from progressive muscle weakness and compromise physical health and life expectancy [6, 7].

Best practice health management [4, 8, 9] including steroid use in individuals with DMD, spinal fusion and non-invasive ventilation (NIV) can optimise physical health [9, 10] and potentially extend life expectancy well into adulthood [11]. The self-reported wellbeing of young adults with NMD ranges from severely compromised [12] to comparable with typically developing populations [13, 14], where outcomes appear mediated through empowered autonomy and optimally supported social participation [15, 16].

The adolescent period is an important precursor to adult life. Development of independence in preparation for adult autonomy challenges the psychosocial wellbeing of typically developing adolescents [17, 18] and presents even greater challenges to adolescents with NMD who are wheelchair users. Physical dependence and health issues often increase through adolescence due to growth spurts and the progressive nature of many NMD, compromising participation and expectations for autonomy [14, 19]. The development of self-management skills for new or established health interventions is a concern for all adolescents with chronic health conditions [20, 21]. Uptake of respiratory support such as NIV is one such challenge for those with respiratory muscle weakness [22, 23]. Though NIV has significant benefits to physical health [24], it signifies additional dependence and may have both positive [25] and negative impacts on Quality of Life (QoL) [26, 27]. A deeper understanding is needed of the psychosocial aspects of adolescence in youth with NMD [28, 29].

The concepts of QoL and wellbeing encompass domains of an individual's perception of their health, happiness and life satisfaction [17, 30]. Reporting of QoL in youth with NMD is commonly by parent proxy, who consistently score their child's QoL lower than the children themselves [31, 32]. There is a need for deeper understanding of QoL and psychosocial wellbeing in the period of adolescence from the perspective of young people themselves [28, 29], to inform how youth may be best supported to achieve and maintain optimal wellbeing as they transition to adulthood.

This purpose of this review was to synthesise literature describing self-reported QoL and psychosocial wellbeing in youth with NMD who are wheelchair users, where possible compared with other groups of youth.

METHODS

The conduct of this systematic review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA-P 2015) [33] and was registered with the PROSPERO international prospective register of systematic reviews (CRD 42014015501).

Search Strategy

Medline, Embase, CINAHL and PsycINFO databases were searched utilising database specific Medical Subject Headings (MeSH) and pre-defined keywords. Search terms utilised in Medline are presented as an example in Supplemental Appendix 1. Subject headings were exploded and all subheadings included to encompass all related search terms and ensure exhaustiveness. Search yields for each search terms were combined within each category with "OR", and with "AND" across the categories of population (age – youth, adolescence) AND population (diagnosis - neuromuscular disorders) AND outcome

(wellbeing). Search yields were limited by year of publication since 2004 to account for advances in best practice care experienced by youth with NMD over the past decade. The complete search strategy of the electronic databases was conducted on January 15th 2015, and updated on 5th November 2015 and 7th April 2016 to identify new articles.

Additional literature was sourced by screening the reference lists of full text papers reviewed and through consultation with researchers and clinicians of the Australasian Neuromuscular Network (www.ann.org.au).

Study Selection Criteria

Peer reviewed full text papers of any study design published in English were included if: (1) *Population* – participant age or mean age was 12-22yo (representing the age range commonly used in Australian terminology of "young person" and "youth" [34]); if a broader age range was studied, data on 12-22yo participants could be separately extracted; participants were diagnosed with a NMD; data for non-ambulant youth with NMD could be extracted; and (2) *Outcomes* included self-reported data describing QoL, mental wellbeing and social participation.

Study selection

Figure 1 illustrates the selection process. Two authors (VT & JD) independently screened the citations by titles and abstracts for relevance to the inclusion criteria. Potentially relevant citations were combined and discrepancies were included in the full text review. Potentially eligible full text papers were retrieved and examined by all authors during a group review. Disagreement or ambiguities were resolved by discussion and consensus.

Data extraction and synthesis

Information regarding study methods (design, participants, recruitment, outcome measures) and results (including normative or similar sample comparison, descriptive statistics) were extracted by VT. Data extraction and synthesis were refined through regular discussion of all authors. Heterogeneity of data collection and reporting precluded the opportunity to synthesize similar outcomes in a meta-analysis.

Risk of bias assessment and quality appraisal

In keeping with the recommendations of Higgins and Green [35] (http://handbook.cochrane.org/ Section 8.5.3., accessed 10.11.14) and Shamliyan *et al* [36], a non-scoring quality assessment tool was utilised to assess each paper's internal validity and generalisability. Four criteria (Table 1) were adapted from the STROBE quality appraisal checklist [37] and risk of bias assessment tools specific to observational [38] and prevalence studies [39], being selection and response bias, use of valid and reliable outcome measures, and interpretation bias. Two authors (VT and SP) independently assessed studies for risk of bias as high, low or uncertain. The assessments considered the risk of material bias rather than any bias defined as bias of sufficient magnitude to have a notable impact on the results or conclusions of the trial, recognizing that subjectivity is involved in any such judgement. Differences were resolved by consensus. Studies were not excluded based on their risk of bias.

RESULTS:

Study selection

The search strategy identified 1839 unique papers, of which 1763 papers were agreed as ineligible based on title and abstract screening (Figure 1). Screening the reference lists of the remaining 76 papers yielded one further potentially eligible paper. Full text assessment led to the exclusion of 62 papers, reasons being that they did not include or separately report 12-22year old participants' data (38) or data for those with NMD (9), did not include or describe participants' ambulatory status (9), reported proxy-rated outcomes only (5) or could not be sourced (1). All authors reached consensus for the 15 papers that met the inclusion criteria.

Study characteristics – Methods

Designs included 11 cross-sectional observational surveys, 1 mixed observational and qualitative study, and 3 qualitative studies. One study was a survey conducted internationally [40] and three each were conducted in Australia[41-43] and the United States [44-46]. Nine studies recruited through tertiary clinics [43, 44, 47-53], five studies through multiple sources [40-42, 46, 54] and one study did not report their participant source [45].

Participants

A total of 411 youth were recruited across the 15 studies, with participant numbers in individual studies ranging from 4 [43] to 58 [52] (see Supplemental Appendix 2). The majority were boys (n=376, 91%) and living with DMD (n=at least 339, 82%), with 9 of the 15 studies recruiting only youth with DMD. Four studies mentioned the exclusion of youth with cognitive impairment[41, 47, 51, 53], though only one of these indicated how intellect was assessed[41] and none specified numbers excluded. Youth with reading and writing difficulties were assisted in one study, though numbers were not specified[44]. Two studies each did not specify individual diagnosis [42, 54] or gender [43, 54].

One quantitative [53] and two qualitative studies [42, 45] specifically recruited youth aged between 12-22 years old. In the eight studies that recruited participants with a larger age range, data of 12-22 year olds could be separately extracted [40, 43, 46-49, 54]. In the remaining 4 studies [41, 44, 50, 52] participants' mean age fell within the specific age range of this review, with the age of outliers ranging from 8 [44] to 25 years old [50].

Five studies described all participants as wheelchair users [40, 45, 47-49] and three recruited only boys with DMD of whom the majority were wheelchair users [41, 44, 46]. Two studies recruited by functional dependence on NIV [43, 50], one included only those with compromised sitting ability having undergone spinal fusion [52] and all three reported extremely low physical scores, hence they were assumed to include only non-ambulant participants. One study that did not specify wheelchair use recruited only 11-17 year old participants living with DMD[51]. As loss of loss of ambulation in DMD typically occurs around age 13 years old [4], the study was included since the majority were likely using wheelchairs. Vuillerot *et al* [53] grouped participants by functional ability as classified on the Motor Function Measure (MFM), where a score of >80 indicated wheelchair dependence and applied to two of the three groups in this study.

The proportion or participants who underwent spinal fusion, or used steroid and NIV interventions were inconsistently described and investigation of relationships with QoL or wellbeing outcomes was not possible. Extracted data are presented in Tables 2, 3 and 4.

Outcome Measures used

The 12 quantitative studies utilised a variety of outcome measures. Two generic QoL measures were most commonly used: the Pediatric Quality of Life Inventory™ 4.0 Generic Core Scales (PedsQL™; http://pedsql.org/index.html) and the SF-36 (http://www.sf-36.org/) in four studies each. Two used the disease specific PedsQL™ 3.0 NMD Module [44] and PedsQL™ 3.0 DMD Module [46]. A further four QoL measures were utilised in one study each: two were generic for children and adolescents (TAC-

QoL [54] and VSP-A [53]), one specific for children with chronic health conditions (DISABKIDS [47]) (though these data were presented in figures only and could not be extracted), and one disease and age specific to adolescents with DMD [Life Satisfaction Index for Adolescents (LSI-A) [51]].

Study Characteristics – Risk of Bias

Assessment of bias in each study is presented in Table 5. Eight studies were assessed as at risk of selection bias due to incomplete reporting of sampling strategy, including a lack of description of how potential participants were approached [41, 44-46, 48, 49, 51, 54]. All studies were assessed as at risk of response bias, as no study compared responders and non-responders and none reported a population based sample.

Use of outcome measures with unverified validity and reliability for the population with NMD compromised the internal validity of four studies [40, 51, 52, 54] (see Table 2 and Table 3): Grootenhuis *et al* [54] excluded the social functioning domains in the TAC-QoL from analysis due to unsatisfactory scale structure and reliability in 12-15 year olds; the LSI-A used with 44 participants with DMD by Simon *et al* [51] had undergone pilot study validation in only 15 youth; Suk *et al* [52] used SF-36 results for 13-16 year old participants though the measure is only validated for those aged 17 years and older, and Janssen *et al* [40] measured social participation utilising de novo questions.

Risk of interpretation bias appeared low in four quantitative [41, 44, 46, 53] and two qualitative studies [42, 45] who clearly reported the steps taken in their analysis process and which were assessed to be appropriate for their data.

Findings – Quality of Life

Measures of QoL that included physical function domains found poorer QoL for youth with NMD compared to typically developing youth [41, 43, 44, 46, 47, 49, 50, 52-54]. Young *et al* [43] and Read *et al* [50] reported the lowest physical QoL scores, reflective of their study population including NIV users only.

Two studies utilising the PedsQL reported lower but not significantly different psychosocial QoL for youth with NMD compared to typically developing youth [41, 44]. The SF-36 QoL mental health status sub-domain did not show significant differences from the norm [47, 49, 50, 52]. Psychosocial QoL sub-domains were highest in youth with more severe physical disability, including those with relatively unchanging NMDs non-ambulant since early childhood and those dependent on NIV [43, 53, 54]. These participants also reported higher school functioning [43, 53], body image [53], relationships with teachers [53], academic performance [53] and cognitive functioning [54] than peers with NMD with less physical impairment [53] or same age typically developing peers [54]. Two younger NIV users rated their social and school functioning on the PedsQL well above the norms for all comparison groups [43] , whereas 10 slightly older NIV users rated their social function on the SF-36 at 31% lower than the normative population [50].

Emotional and social functioning scores were lower in younger participants with DMD [41, 46, 49, 51] than youth with DMD in late adolescence [46, 51], young men with DMD who were NIV users [49] and youth with relatively non-progressive, severe NMDs [43].

Emotional, social and school functioning mean scores on the PedsQL were higher in participants recruited from a single tertiary specialist clinic [44] than those recruited from multiple sources [41, 46]. Emotional functioning scores on the SF-36 were reported higher in Swiss [49] and Korean [52] participants than in United Kingdom participants [50].

Findings – Mental Health and Social Participation.

No clinical depression or neuroses were found utilising the Hospital Anxiety and Depression Scale [50] and the Beck Depression Inventory [47], though three of 34 participants in the latter study (12.5%) aged 17-23 years old reported mild-moderate subclinical depressive symptoms. In response to de novo

questions, six of 10 participants aged 12-25 years old reported previous psychological problems for which four families had sought help [50]. The type, age of onset and extent of these problems were not described.

No studies utilised standardised measures of social participation. De novo questions utilised by Janssen *et al* [40] broadly described the proportion of 24 youth with DMD aged 8 -19 years old participating in school (83%), recreation (89% sport, 92% hobby), and employment (66% working).

Findings – Adolescents' qualitative accounts

Three qualitative studies [42, 45, 48] reported positive and negative accounts of psychosocial wellbeing (Table 4). Hamdani *et al* [48] described four participants as NIV users, but no other descriptors of steroid, spinal fusion or NIV uptake were reported in any of these studies. Mid-adolescent boys identified practical and interpersonal barriers to independent socialisation including assisted toileting [42]. Slightly older participants appeared ambivalent about expectations for social independence, resisting talking, thinking about or practically preparing for the future [48]. Participants experienced growth in their sense of identity and confidence through participation in a disease specific social group [42]. In order to maintain positive psychological states, participants preferred to focus on living well in the present [48]. Pehler and Craft-Rosenberg [45] explored participants' accounts of longing for missed activities, relationship and to be seen as a person, finding that spirituality was protective factor to ameliorate such sense of longing.

DISCUSSION

This systematic review sourced 12 cross-sectional quantitative and three qualitative papers that described QoL and psychosocial wellbeing in youth with NMD who are wheelchair users. Quality of life was poor when the measure included a domain rating physical ability. Psychosocial QoL was rated higher by older than younger adolescents living with DMD, and highest by adolescents with NMD manifest in early childhood. Mental health and social participation could not be compared with other populations.

Physical wellbeing domains of QoL

It is not surprising that youth with NMD living with severe physical limitations scored lower QoL than their typically developing peers in all studies that used QoL measures rating physical ability within a physical health domain [41, 43, 44, 46, 47, 49, 50, 52-54]. Individuals living with NMD do not perceive physical ability as important in the physical domain of QoL; ease of mobility, vitality, pain and fatigue were identified as more important [55]. These components are captured in the French VSP-A measure utilised by Vuillerot *et al* [53], who compared QoL in youth with NMD amongst each other grouped by physical ability. The 'disability paradox' holds true in these participants, with the most severely disabled NIV dependent youths scoring their physical wellbeing higher than their more physically able peers [56]. Though Vuillerot *et al* [53] describes that one third of participants were diagnosed with relatively non-progressive NMDs and two-thirds with rapidly progressive NMD (such as DMD), the proportion of diagnoses within each functional group was not specified. Whilst the importance of physical ability to QoL may be different in those living with progressive disease, it is also likely that youth with similar cognitive ability and physical limitations have similar experiences navigating development of physical, emotional and social autonomy.

Psychosocial domains of QoL – mental health and emotional wellbeing

The trends identified in emotional and social functioning scores across studies warrant a careful look at the dynamic nature of QoL experienced by youth with NMD on different disease trajectories. Though 15%[57] to 38%[58] of younger boys with DMD are at higher risk of specific learning disabilities and/or autistic spectrum traits, none of the studies sourced in this review mentioned the prevalence of cognitive impairment amongst participants nor the number of such individuals excluded. Possible impact on QoL in these individuals with DMD remains unknown. The majority of youth with DMD are

cognitively able to participate in mainstream education[5] and likely to experience social limitations due to physical disability similarly to other youth with NMD. The wide-ranging scores of emotional functioning between youth with severe NMD manifest in early childhood and those with on progressive disease trajectories possibly relate to different experiences of identify formation and different anxieties about uncertain futures.

Emotional functioning was lower in younger youth with DMD where some still had walking ability albeit limited [41, 49, 51, 53], compared with those older and fully wheelchair dependent [51, 53] and using NIV [49]. The higher emotional functioning scores in older youth with DMD may reflect a 'response shift' where, once the 'new' status of being non-ambulant and requiring respiratory support is accepted, individuals get on with their lives [13, 46]. It is unknown how preparation for the anticipated loss of ambulation and need for NIV in DMD may influence an individual's acceptance. Notwithstanding, 'acceptance' is a dynamic process, made more difficult during adolescence when changing body image and formation of identify are known to be risk factors of mental health disorders in typically developing youth [59]. Interestingly, the most severely disabled youth with NMD scored better than their abler peers in domains of body image, school and social functioning [43, 53]. It is possible that youth with relatively unchanging, severe disabilities manifest in early childhood perceive wheelchair and NIV use as part of their identity and may be more accepting of their limitations, especially if they have never known a different physical status. High scores in school functioning may be because they prioritise intellectual achievement when their disability precludes them from physical achievement. The comparatively abler youth in the studies by Young *et al* [43] and Vuillerot *et al* [53] may have scored lower on body image and emotional and social functioning if they perceive themselves in a 'void' - identifying themselves neither with their typically developing, physically able nor with their severely disabled, intellectually high achieving peer group.

Boys with DMD managed with steroid medication face the additional challenge of delayed puberty. Though current medical management slowing of DMD disease trajectory benefits their physical health, anecdotal evidence suggests that the concomitant short stature and delayed puberty can impact the psychosocial wellbeing of these young men [60]. Delayed puberty is associated with emotional symptoms in typically developing 13-18 year old boys [61]. Little is known about how the timing of physical changes during adolescence impacts on identity formation in youth with degenerative NMDs, and in turn psychosocial wellbeing, nor if boys have different experiences to girls.

Living with an uncertain disease course and shortened lifespan no doubt impacts the emotional wellbeing youth with NMD. Measured in the PedsQL™ 3.0 DMD Module, one in five youth with DMD reported 'frequently' being worried about their families and what was going to happen to them [46]. Though concerning, this incidence of worry and stress does not appear higher than in typically developing youth, where 29% without a probable serious mental illness are concerned about their level of stress [62], followed by study and body image. The two studies that specifically measured depression did not find clinically significantly symptoms, but four of their ten NIV users had previously sought help for psychological problems [50]. The interplay between family and individual mental health alluded to by Read *et al* [50] is confirmed in the recent publication by Landfeldt *et al* [63], who found that individuals with DMD whose parents self-reported depression and anxiety were at higher risk of mental health issues. It is concerning that up to 70% of parents were recorded as experiencing anxiety and depression [63]. Hence, whilst high emotional functioning scores in possibly emotionally well-supported populations indicate a resilience amongst youth with NMD [49, 64], more careful measurement of mental health and emotional wellbeing is needed to identify times of vulnerability both for themselves and their families.

Social participation

The three qualitative studies exploring the adolescents' perspective reflected both positive and negative accounts of mental wellbeing and social participation [42, 45, 48]. Optimal wellbeing and social participation in youth with NMD who are NIV users is possible, though published accounts are of single

cases only [16]. As social connectedness with peers with similar life experiences is a powerful enhancer of physical and mental wellbeing in other groups living with disability [65, 66] , the low scores in QoL leisure and social participation domains for youth with NMD across studies sourced in this review are of concern.

Severe physical disability necessitates significant additional support to enable social participation [13]. Participants recruited via single tertiary clinics [43, 44, 49] reported social participation scores closest to typically developing same age peers, yet participants recruited from a broader geographical area [41, 46] reported lower on the same PedsQL measure. It is possible that adolescents cared for in specialist centres receive greater expert, individualised emotional support to optimise physical health and opportunities for participation [67, 68]. Convenience and opt-in sampling means that the QoL and wellbeing even in these studies may be over-representative of those best supported and socially connected with capacity to participate in research. Wellbeing of the most vulnerable and socially disconnected may be still be severely compromised and unknown.

Limitations and directions for future research

A risk of selection bias is acknowledged through inclusion of only English language papers. However, this risk was mitigated to a certain extent as included papers represented different countries, languages and cultural contexts.

The lack of a standardised international definition of youth and adolescence led to the decision for this review to use the 12-22 year old age as per US & Australian terminology [34], which excluded studies with a mean age under 12 [69, 70] and over 23 years old [71]. Data reported in these studies were very similar to those included and were unlikely to have changed our findings.

The variable descriptors of wheelchair use, best practice health management strategies (steroids, spinal fusion and NIV), proportions of gender and diagnostic groups [53, 54] and absent descriptors of cognitive ability made it difficult to understand possible correlations to QoL and wellbeing. The inclusion of youth experiencing different disease trajectories can be argued as a limitation as well as a strength. Though youth living with conditions such as DMD experience more rapid deterioration in physical ability, their experience of adolescence, wheelchair use and multiple health interventions to manage muscle weakness is shared with those with other NMDs. Consistent descriptors of functional ability have advanced specificity in cerebral palsy research [72] and have been proposed and recommended for use in NMD [4, 73]. Only one [40] of six studies included and published since 2011 utilised the functional descriptors recommended by Bushby and Connor [73]. Adoption of standardised descriptors of functional ability will strengthen understanding of possible correlations between function, changes in function, uptake, for example, of NIV and QoL and wellbeing outcomes across diagnostic groups and gender in this population.

Limitations in the assessment criteria for the risk of bias reflect the difficulty discriminating reporting quality from methodological quality [36]. Notwithstanding, our checklist identified a need for clearer reporting of recruitment strategies, methods that recruit greater participant numbers and use of age and population validated QoL measures [55].

Recent collaborative efforts in rare disease research have shown that focus on an age range need not compromise participant numbers. Landfeldt *et al* [31] recruited 154 youth with DMD aged 12-15 years old who were wheelchair users via the international TREAT-NMD database (http://www.treat-nmd.eu/). Unfortunately, this paper could not be included in this current review as results were reported as a combined score across ages (<5 to >30 years old) [31]. Future studies need clearer reporting specific to age groups to enable deeper understanding of wellbeing in developmentally unique age periods.

The variety of QoL assessment instruments currently in use precluded the pooling of results. Most measures utilised in studies in this review had shortcomings in construct and content validity, such as involvement of the population of study in the design of the measure. Whilst the DISABKIDS Chronic Generic Measure DCGM-37 was recently appraised as having strongest evidence to support its measurement properties in children with neurodisability [74], the single study sourced utilising the DISABKIDS [47] presented data in figures only that could not be extracted. Efforts to construct and validate disease and age specific instruments with involvement of patient stakeholders are ongoing [55], with the PROMIS [75] and SOLE [76] outcome measures being recent examples.

No studies specifically investigating social participation were sourced despite use of keyword search terms. This is surprising, given social participation is an identified priority in youth with NMD [15] and the value of social connectedness to long term health and wellbeing is known [65, 77]. Future longitudinal research utilising standardised measures to describe the social worlds of adolescents growing up with progressive, chronic illness is necessary to aid deeper understanding of how health care supports and interventions impact on adolescents' short and long term wellbeing [78].

CONCLUSION:

This review demonstrated that there is value in grouping adolescents across NMD diagnostic groups, whose similar cognitive ability and physical limitations lead to similar experiences in navigating development of physical, emotional and social independence. Youth with NMD do not rate their psychosocial QoL significantly lower than same age typically developing peers, providing reassurance for those living with degenerative NMDs that despite severe physical disability and NIV use, life with average to above average cognitive ability can be good.

Trends across age and diagnosis highlighted that psychosocial wellbeing of younger adolescents with NMD on degenerative disease trajectories appears most at risk during periods of significant change to physical ability, when development of sense of self and social connectedness are also compromised. Changes over time are currently unknown. The opt-in recruitment method used by all studies in this review likely skews the representation to those who are coping well and have the capacity to participate in research.

There is little information around the mental health and social participation of youth with NMD, nor about the psychosocial wellbeing of those cared for outside of specialist clinics or who did not opt-in to studies. Future longitudinal studies with clearer reporting of age, gender and physical ability, an attempt at population based recruitment strategies and use of age appropriate, standardised measures are needed to enhance understanding of how interventions impact and maintain wellbeing of youth with NMD in transition from adolescence to adulthood.

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Figure 1 PRISMA flow diagram of study selection

Highlights:

1. Some groups of youth with NMD on degenerative disease trajectories and in different countries report psychosocial QoL lower, but not significantly, to typically developing peers.
2. Challenges to identify formation and body image may compromise wellbeing in younger adolescents with DMD, but changes over time in the same population are not known.
3. Information about mental health and social participation in youth with NMD is currently restricted to those cared for in specialist clinics and cannot be compared to other populations.

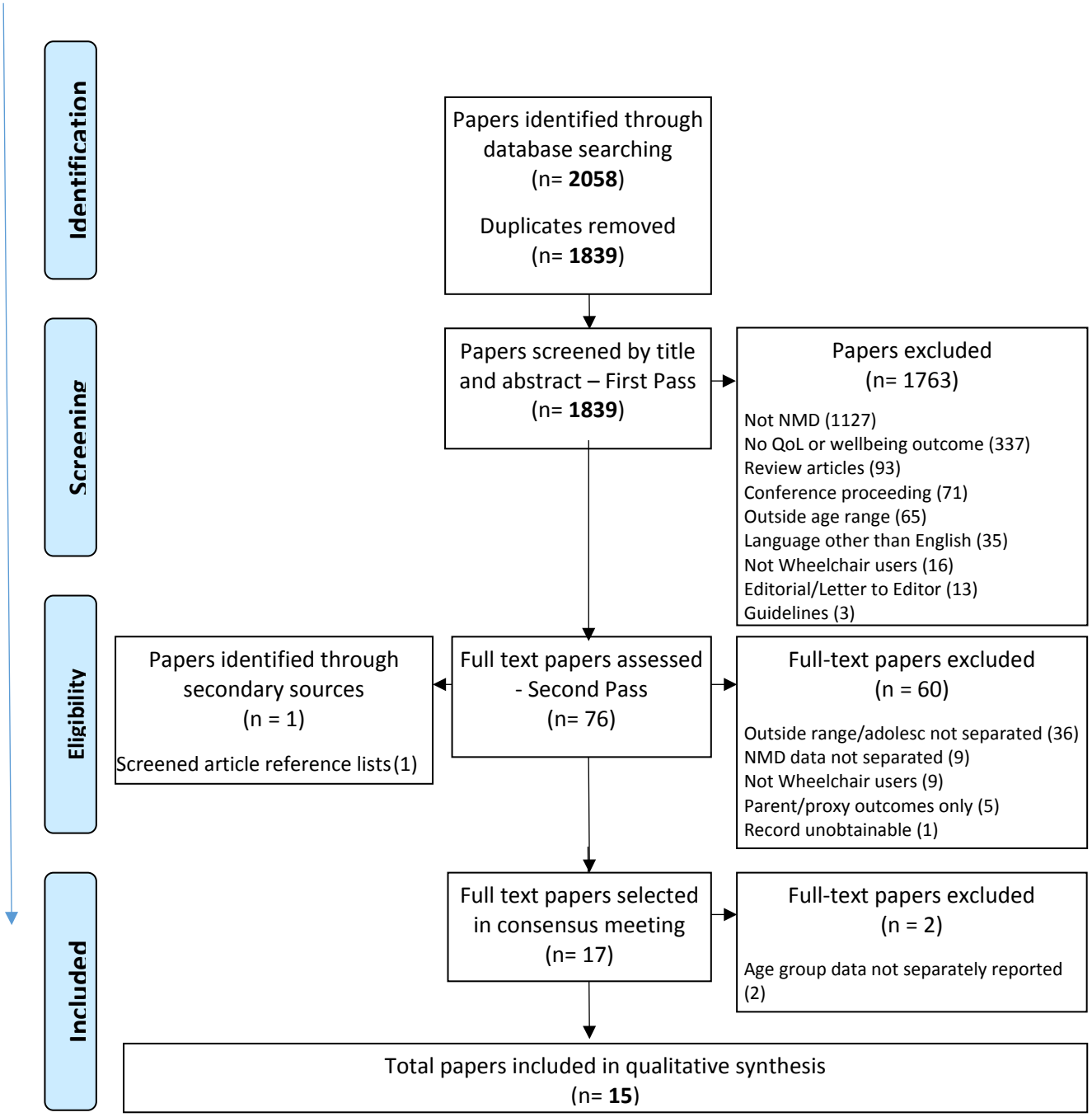

Figure 1 PRISMA flow diagram of study selection

Table 1 Quality and Risk of Bias Assessment Criteria* of selected studies

	Criterion	LOW risk of bias. (+)	UNCLEAR risk of bias. (?)	HIGH risk of bias (-)
External validity/ generalisability	**1. Representative sample/ selection bias** Was the study based on a representative sample from a relevant population?	Clearly described sampling strategy, source and demographic details (age, sex, level of functional ability) of the participants with NMD and comparison groups.	Incompletely described sampling strategy, source and demographic details of participants with NMD and/or groups of comparison.	Not reported.
	2. Response bias Was the participant group comparable to non-responders?	Total potential participant population identified. Responders and non-responders compared to each other.	Total participant population numbers unclear. Responders and non-responders not compared.	Not reported
Internal Validity	**3. Valid & reliable outcome measure(s)** Were study instrument(s) that measured the parameter of interest shown to have validity and reliability?	Validated outcome measure used.	Outcome measure was not validated for age used.	Not reported
	4. Interpretation bias Was an appropriate statistical analysis used? Was qualitative data analysis credible, trustworthy and rigorous?	Reported outcome measure data as means and SDs, or medians and interquartile range, for each group and utilised an appropriate statistical test for comparison. Qualitative studies clearly described all relevant steps taken to ensure rigour and trustworthiness.	Only means and SDs reported. Qualitative studies omitted some steps in data analysis (for example, opportunity for member checking/ independent coding).	Statistical test inappropriate Or Unable to determine appropriateness of data analysis to type of data.

* Adapted from the STROBE quality appraisal checklist [37], Shields *et al* [79] risk of bias assessment specific to observational studies and Hoy *et al* [39] risk of bias assessment specific to prevalence studies.

Table 2 a Quantitative studies' QoL outcomes by measure used: PedsQL™

Quality of Life Measure	**PedsQL™** (international generic - Higher scores indicate better QoL, highest score in each domain 100)			
Author, Year, Study Design	**Bray et al (2010)[41]** *Cross-sectional Survey*	**Davis et al (2010)[44]** *Cross-sectional Survey & Feasibility study*	**Uzark et al (2012)[46]** *Cross-sectional Survey & Feasibility study*	**Young et al (2007)[43]** *Retrospective Survey*
Country	*Australia*	*USA*	*USA*	*Australia*
N*	35 (Male)	43 (Male)	39 (Male)	4 (Gender NR)
Age Range (Mean ± SD†)	9-17yo (12.5 ±2.8)	8-18yo (12.85 ±3.05)	13-18yo	13-16yo
Disorder	DMD	DMD	DMD	MyoD‡ 13yo (1) CMD 13yo (1) DMD 14yo (1) & 16yo (1)
Recruitment	Via multiple sources across three Eastern Australian states. Opt-in mail out questionnaire.	Via single source: tertiary children's hospital specialist clinic.	Via multiple sources: tertiary hospital clinic and national patient organisation.	Via single source: tertiary children's hospital specialist clinic. NIV users only.
Steroid Users(ST), NIV Users (NIV), Spinal Fusion (SpF) if reported	ST n=22	ST n=21, NIV n=3	NR	NIV n=4
Findings	Mean (SD)	Mean (SD) **Group of comparison**	Mean (SD)	Mean (SD) **Individual Scores**

PedsQL™ 4.0 generic core scales			Mean (SD) Healthy Controls n=275 boys (age 13.1±2.0)			13 yo MyoD	13yo CMD	14yo DMD	16yo DMD
Physical Functioning	34.0 (19.9)	44.1 (21.8)	90.1 (11.6)	33.1 (18.9)	26.5 (27.6)	44	56	0	6
Emotional Functioning	60.1 (23.3)	70.3 (15.9)	84.7 (15.9)	68.2 (17.6)	56.0 (18.8)	70	75	40	40
Social Functioning	64.1 (17.3)	73.0 (16.0)	89.6 (14.2)	67.6 (13.4)	70.0 (26.1)	4	95	90	50
School Functioning	59.0 (15.3)	64.0 (15.2)	80.1 (16.1)	65.8 (14.2)	60.0 (18.5)	35	90	55	NR
Findings **PedsQL™ 3.0 NMD Module** (NMD specific		Mean (SD)			**Group of comparison** Children with SMA Mean (SD)	13yo MyoD **Individual Scores**	13yo CMD	14yo DMD	16yo DMD
Total Score		73.8 (13.2)			61.4±19.8	59.7	96.6	48.9	43.3
About my NMD		72.9 (13.2)			-	-	-	-	-
Communication		75.6 (23.7)			-	-	-	-	-
Family Resources		76.5 (19.1)			-	-	-	-	-
Assessment of potential for bias	Included 16 boys still ambulant.	Research assistants interviewed and scribed if child "unable to read or write as consequence of physical or cognitive impairment". Not formally assessed. Included 5 boys still ambulant.		Recruitment process unclear: "convenience sample". Patients completed questionnaires with a research coordinator "as needed".					

*N - Number, †SD – Standard Deviation, ‡MyoD – Myotonic Dystrophy

Table 2 b Quantitative studies' QoL outcomes by measure used: SF-36

Quality of Life Measure	**SF-36 - 36-item Short Form Health Survey** (international generic - Higher scores indicate better QoL, highest score in each domain 100)					
Author, Year, Study Design	**Kohler et al (2005)[49]** *Cross-sectional Survey*		**Read et al (2010)[50]** *Retrospective Survey*		**Suk et al (2015)[52]** *Prospective Cross-sectional Survey*	
Country	*Switzerland*		*United Kingdom (UK)*		*Korea*	
N*	21 (Male)		10 (Male)		58 (40 Male, 18 Female)	
Age Range (Mean ± SD)	Range NR (16.2±5.0)		12-25yo (19.7yo±4.6)		13-21yo (15.0±4.1 at surgery)	
Disorder (n)	DMD		DMD (6), UCMD (1), M+veCMD† (1), SMA‡ II (1),EDMD§ (1)		DMD (27), SMA (15), progressive MD (16)	
Recruitment	Via single source: specialist DMD facility, only non-NIV users.		Via single source: tertiary hospital respiratory clinic.		Via single source: specialist orthopaedic clinic.	
ST, NIV, SpF if reported	NIV n=0		NIV n=10		NIV n=29, SpF n=58	
Findings *Mean (SD)*		**Group of comparison** DMD NIV users n=14 (age 23.3±5yo)		**Group of comparison** UK general population n=1792.		**Group of Comparison** Korean general population
Physical function (fx)	1 (0)	0 (0)	1.9 (3.2)	95.5 (12.1)	53.0 (27.1)	86.5 (21.7)
Physical role fx	68 (29)	71 (29)	63.8 (39.7)	90.7 (24.5)	70.4 (23.3)	89.2 (20.3)
Pain	85 (20)	79 (22)	58.5 (28.6)	86.0 (22.6)	71.2 (13.5)	84.2 (22.3)
General health	70 (20)	67 (13)	31.0 (18.3)	78.6 (17.7)	59.6 (4.5)	66.3 (20.0)
Vitality	70 (20)	67 (14)	58.5 (19.1)	68.3 (19)	61.0 (7.0)	67.5 (20.1)
Social function	80 (25)	90 (15)	62.5 (33.3)	91.5 (17.2)	43.5 (10.1)	89.0 (17.9)
Emotional role fx	94 (23)	98 (9)	66.6 (47.1)	91.1 (24.6)	82.1 (21.4)	89.7 (19.3)
Mental health	73 (17)	78 (10)	70.8 (23)	79.6 (15.2)	69.0 (6.1)	76.9 (17.4)
Assessment of potential for bias	Prospective enrolment of all residents and daytime patients who require "support that cannot be provided at home".		Opt-in mail out questionnaire to 20 eligible families. NIV users only.		All consecutive patients undergoing spinal fusion. SF-36 developed for >17yo used with <17yo.	

†M+veCMD – Merosin positive Congenital Muscular Dystrophy; ‡SMA II – Spinal Muscular Atrophy Type II; § EDMD – Emery-Dreifuss Muscular Dystrophy

Table 2 c Quantitative studies' QoL outcomes by measure used: Other QoL measures

Other Quality of Life Measures									
Author, Year, Study Design	**Grootenhuis et al (2007)[54]**			**Simon et al (2011)[51]**			**Vuillerot et al (2010)[53]**		
Country	*Cross-sectional Survey*			*Cross-sectional Survey*			*Cross-sectional Survey*		
N*	*Netherlands*			*Brazil*			*France*		
Age Range	22 (2 Female?)			44 (Male)			43 (32 Male, 11 Female)		
Disorder (n)	12-17yo			11-17yo			10-17yo		
	DMD			DMD			DMD (19), SMA (9), CMD (6), CMT‖ (5), LGMD¶ (3), FSHD# (1)		
Recruitment	Via multiple sources: hospital specialist clinics and rehabilitation centres.			Via single source: tertiary hospital specialist NMD clinic.			Via multiple sources: three French specialist outpatient clinics.		
ST, NIV, SpF if reported	NR			ST n=44			NIV n=11		
Quality of Life Measure	**TAC-QoL for 12-15yo** (n=14) **TAA-QoL for >16yo** (n=7) (Dutch generic - Higher scores indicate better QoL)			**Life Satisfaction Index for Adolescents (LSI-A)** (DMD specific - Higher scores indicate better QoL)			**VSP-A "Vécu Santé Perçu par l'Adolescent"** (self-perceived health state in adolescents) (French generic - highest possible score 100)		
Findings *Mean (SD)*		**Group of Comparison** Healthy Controls *n=1249 (age 12-15*			*11-13yo n=28*	*13-17yo n=16*		All n=42	low MFM n=14	high MFM n=14
	Physical Symptoms	26.8 (4.4)	23.7 (5.4)	General Wellbeing	28.1(2.7)	29.6(3.3)	Leisure activities	43.8(22.6)	33.5(21.5)	50.7(24.3)
	Motor Functioning	23.2 (4.4)	29.8 (3.3)	Interpersonal Relationships	34.3(3.6)	35.9(3.6)	Relationship with parents	59.5(23.2)	64.9(20.8)	51.8(24.4)
	Cognitive Functioning	28.1 (4.7)	27.6 (4.1)	Personal Development	35.3(3.9)	36.1(4.5)	Body image	70.3(26.7)	83.0(11.6)	59.8(24.1)
	Positive Emotions	12.9 (2.3)	13.0 (2.8)	Personal Satisfaction	32.9(3.2)	33.5(2.6)	Relationship with teachers	67.0(25.1)	69.6(31.4)	59.5(22.8)
	Negative Emotions	12.4 (2.3)	11.6 (2.6)	Leisure and Recreation	33.3(3.5)	34.6(3.0)	Psychological wellbeing	73.4(19.3)	74.6(16.7)	65.0(20.9)
							School performance	67.8(27.7)	67.3(22.6)	54.5(33.1)

Assessment of potential for bias	Recruitment approach unclear. 40 of 43 children & adolescents consented. Social functioning and autonomy scores excluded from TAC-QoL analysis due to unsatisfactory scale structure and reliability in 12-15yo.	Steroid users only. Excluded those with intellectual impairment –number NR. Questionable validity of outcome measure tested in single study with n=15 adolescents.	Opt-in at clinic visit. Total possible number NR, "only two refused to participate". Excluded those with intellectual impairment, undergoing surgery within 3 months and those with expected health status change within 6 months. MFM – Motor Function Measure: Lower score indicates lower physical functional ability. Low MFM group included 11/14 NIV users. High MFM group included 9/14 "partially ambulant".

||CMT – Charcot Marie Tooth Disease; ¶LGMD – Limb Girdle Muscular Dystrophy; #FSHD – FascioScapuloHumeral Muscular Dystrophy

Table 3 Quantitative Studies' Mental Health & Social Participation Outcomes

Mental Health and Social Participation Outcome Measures			
Author, Year, Study Design ***Country***	**Elsenbruch et al (2013)[47]** *Cross-sectional Survey* *Germany*	**Read et al (2010)[50]** *Retrospective Survey* *United Kingdom*	**Janssen et al (2014)[40]** *Cross-sectional. Survey* *International*
N*	45	10 (Male)	24
Age Range (Mean ± SD†)	n=11 13-16yo n=34 17-23yo	12-25yo (19.7yo±4.6)	8.4-19.5yo (Early non-ambulatory stage) (13.5 ±NR)
Disorder (n)	DMD	DMD (6), UCMD (1), M+veCMD† (1), SMA‡ II (1),EDMD§ (1)	DMD
Recruitment	Via single source: tertiary children's hospital specialist clinic.	Via single source: tertiary hospital respiratory clinic. NIV users only.	Via multiple sources: internationally through Duchenne patient organisations. Opt-in online questionnaire.
Steroid Users (ST), NIV Users (NIV), Spinal Fusion (SpF) if reported	ST‡ n=24, NIV§ n=13	NIV n=10	ST n=21, NIV n=3, SpF n= NR (n=10 scoliosis)
Outcome	**Mental Health**	**Mental Health**	**Social Participation**
Measure	13-16yo **Depression Inventory for Children and Adolescents (DIKJ)** (sum scores ≥18 indicates clinically significant depression)	**Hospital Anxiety and Depression Scale** (HADS) "Patients did not have an excess risk for anxiety or depression on the HADS."	Open ended and scaled de-novo questions
Findings	DIKJ Mean ±SD (range) 3.7 ± 0.8 (0-7) >17yo **Beck Depression Inventory (BDI)** (sum scores 11-17 indicates mild-mod depressive symptoms) BDI Mean ±SD (range) 4.1±4.2 (0-14) BDI sum score 11-17 n=3/34 Previous psychological counselling n=6/45 Contact with school psychologist n=3/45	Psychological problems in the past n=6/10 Sought help for psychological problems n=4/10	At school 83% Working 66% Playing Sport 89% Have a hobby 92%

	Psychotherapy n=1/45		
Assessment of potential for bias	Opt-in at clinic visit. 61 consecutive patients approached. 11 declined to participate. Excluded 24hour NIV users and those with "known or obvious mental disabilities". Included nocturnal NIV users and those with psychiatric conditions. Younger adolescent group only 1/3 of the older adolescent group.	HADS compared to British normative sample mean age 41.5 years (SD = 15.9, range = 18–91) [80]	Reported in four groups by functional ability – early and late ambulatory, early and late non-ambulatory stage. Large age range in each functional group.

†M+veCMD – Merosin positive Congenital Muscular Dystrophy; ‡SMA II – Spinal Muscular Atrophy Type II; § EDMD – Emery-Dreifuss Muscular Dystrophy.

Table 4 Qualitative Findings

Author, Year	**Hamdani et al (2015)** [48]	**Parkyn & Coveney (2013)**[42]	**Pehler et al (2009)**[45]
Country	*Canada*	*Australia*	*USA*
N*	7 (Male)	7 (Male)	9 (Male)
Age Range	16-21yo	14-17yo	12-17yo
Disorder (n)	DMD	Any MD – "majority DMD"	DMD
Recruitment	Single source: tertiary children's hospital	Single source: disease specific social group	Not described
Method	*Critical social science perspective* Individual semi-structured interviews	*Not described* Focus groups	*Phenomenology* Individual semi-structured interviews
Themes	**Psychosocial Wellbeing:** Approximating normal adult roles and milestones, but avoiding discourses of normal development **Social Participation:** Delaying becoming as independent as possible	**Psychosocial Wellbeing:** *Enablers:* sense of identity and self-confidence born from belonging to a specific peer group **Social Participation:** Opportunities MD-Mafia role: a 'safe haven' or 'social challenge' *Barriers:* assisted toileting	**Psychosocial Wellbeing:** Longing to be seen as a person Connecting with self and beyond self Connecting with others **Social Participation:** Longing for missed activities Longing for relationship
Assessment of potential for bias	Nil independent coding nor member checking reported.	All 12 participants of social group invited; reasons for non-participation not reported.	Method of recruitment not reported.

Table 5 Quality and risk of bias assessment of selected studies

	External validity/ Generalisability		*Internal validity*	
	1. Representative sample	**2. Response bias**	**3. Valid & reliable outcome measure**	**4. Interpretation bias**
Quantitative Studies				
Bray et al (2010)[41]	?	?	+	+
Davis et al (2010)[44]	?	-	+	+
Elsenbruch et al (2013)[47]	+	?	+	-
Grootenhuis et al (2007)[54]	?	-	?	?
Janssen et al (2014)[40]	+	-	?	?
Kohler et al (2005)[49]	?	?	+	?
Simon et al (2011)[51]	?	-	?	?
Suk et al (2015)[52]	+	?	?	?
Uzark et al (2012)[46]	?	-	+	+
Vuillerot et al (2010)[53]	+	-	+	+
Young et al (2007)[43]	+	?	+	?
Mixed Quantitative & Qualitative Study				
Read et al (2010)[50]	+	?	+	?
Qualitative Studies				
Hamdani et al (2015)[50]	?	-	N/A	?
Parkyn & Coveney (2013)[42]	+	-	N/A	+
Pehler & Craft-Rosenberg (2009)[45]	?	-	N/A	+

Supplemental Appendix 1 MEDLINE search terms (MeSH and Key Words) within PICO Categories

Population – (age) Youth, Adolescence
adolescen*.mp. OR exp adolescence/ or teen*.mp. OR juvenile.mp. OR youth*.mp.
Population – (diagnosis) Neuromuscular Disorders
Neuromuscular Dis*.mp. OR exp muscular dystrophy/ OR (dystroph* adj5 (becker or myotonic or duchenne)).mp. OR motor neuron disease/ or exp spinal muscular atrophy/ or acute motor axonal neuropathy/ or exp amyotrophic lateral sclerosis/ or primary lateral sclerosis/ or progressive muscular atrophy/ OR spinal muscular atrophy.mp. OR exp myopathy/ OR exp spinocerebellar degeneration/ OR exp hereditary motor sensory neuropathy/ OR ((rare dis* and muscle*) adj5 (weakness or atrophy or dystroph*)).mp.
Outcome – Wellbeing
exp wellbeing/ OR (wellbeing or well-being or well being).mp. OR exp "quality of life"/ OR mental health.mp. or exp mental health/ OR mental disorder.mp. OR adjustment disorder/ OR anxiety.mp. or anxiety/ or anxiety disorder/ OR exp cognitive defect/ OR exp mood disorder/ OR behavior disorder/ or behavioural disorder.mp. OR psychological impact.mp. or depression/ OR ((education* or social or recreation*) adj3 participation).mp.

[PICO – Population, Intervention, Comparison/Context, Outcome, .mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Supplemental Appendix 2 Number of participants by diagnosis and gender

	Diagnosis				Gender	
	DMD	**SMA**	**CMD**	**Other NMD**	**Male**	**Female**
Bray et al (2010)[41]	35				35	
Davis et al (2010)[44]	43				43	
Uzark et al (2012)[46]	39				39	
Young et al (2007)[43]	2		1	1	NS	NS
Kohler et al (2005)[49]	21				21	
Read et al (2010)[50]	6	1	1	2	10	
Suk et al (2015)[52]	27	15		16	40	18
Grootenhuis et al (2007)[54]	18?			4? age NS*	20 + ?	2? (age NS)
Simon et al (2011)[51]	44				44	
Vuillerot et al (2010)[53]	19	9	6	9	32	11
Elsenbruch et al (2013)[47]	45				45	
Janssen et al (2014)[40]	24				24	
Hamdani et al (2015) [48]	7				7	
Parkyn & Coveney (2013)[42]				7NS "majority DMD"	7	
Pehler et al (2009)[45]	9				9	
SUBTOTAL (%)	**339? (82)**	**25 (6)**	**8 (2)**	**39 (10)**	**376 (91)**	**29 (7)**
TOTAL			**411**		**405 (+6NS)**	

? at least. May be more, as diagnoses and gender within age group NS.
*NS Not Specified