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Review article

# Quality of life of patients with spinal muscular atrophy: A systematic review

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ABSTRACT

*Objectives:* To systematically review the literature of quality of life (QoL) of patients with spinal muscular atrophy (SMA), a rare, autosomal-recessive neuromuscular disease associated with extensive morbidity and elevated mortality.
*Methods:* We searched Embase, Web of Science, and PubMed for full-text, English-language articles (published between January 1, 2000 and July 31, 2018) reporting results from studies of QoL of patients with SMA. We excluded review and editorial articles, studies reporting results for samples comprising <5 patients (to allow for meaningful inference), and case reports/qualitative assessments.
*Results:* Of 824 identified articles, 15 met study criteria. Included publications contained data derived from samples from a total of 11 countries and three continents (Europe, North America, and South America). Estimates of the latent trait, primarily derived using the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and the PedsQL 3.0 Neuromuscular Module, indicated impairment in patient QoL, in particular physical functioning. However, both patient self- and caregiver proxy-assessments varied markedly across studies and subgroups. Among adult individuals, the mean self-assessed EuroQol-5D-3L utility has been estimated at 0.16 for a pooled sample of patients with SMA type I, II, and III, and −0.01 for SMA type II. Little is known of the impact of available treatments, including nusinersen, on patient QoL.
*Conclusions:* Our review show that QoL is impaired in SMA, mainly due to compromised physical health, but also reveal that little is known of the impact of the disease across different phenotypes and clinical interventions.

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## Contents



## 1. Introduction

Spinal muscular atrophy (SMA) is a rare, autosomal-recessive neuromuscular disease caused by a homozygous deletion in the survival motor neuron 1 gene on chromosome 5q13 resulting in muscle atrophy and proximal muscle weakness.[1] SMA is categorized into clinical subtypes based on age at onset and severity of symptoms. Children with SMA type I, the most common and also the most severe subtype of the disease, experience onset before 6 months of age, never learn to sit independently, and seldom survive beyond the first two years of life without respiratory support. In contrast, patients with SMA type II have an onset of disease between 6 and 18 months of age, achieve independent sitting but not ambulation, and usually live into adulthood. Finally, patients with SMA type III, the least severe phenotype, experience onset after 18 months of age and acquire independent ambulation, but may subsequently lose this ability due to the progressive nature of the disease.[2]

In recent years, an extensive body of literature has been accumulated with respect to the quality of life (QoL) of patients with rare, disabling neuromuscular conditions, including SMA. These data are important to help understand the clinical implications of a disease and inform optimum medical management, as well as to facilitate economic evaluations of new health technologies. Although tools employed to measure QoL in patients with SMA have been systematically reviewed,[3] to the best of our knowledge, no study has examined and synthesized published estimates with respect to QoL in this indication. The aim of this study was therefore to review the literature of QoL of patients with SMA. Specifically, this systematic literature review sought to answer the following questions:

(i) In which geographical settings have QoL of patients with SMA been studied?
(ii) For which types of SMA have patient QoL been measured?
(iii) What instruments have been used to measure QoL of patients with SMA?
(iv) What is known about QoL of patients with SMA?
(v) How is QoL of patients with SMA modified by available treatments?

## 2. Materials and methods

This systematic literature review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[4]

### 2.1. *Search strategy*

We searched Embase, Web of Science, and PubMed for full-text articles reporting results from studies of QoL of patients with SMA. The search string contained a combination of the following Medical Subject Heading terms, title/abstract, and topic field tags: “Muscular Atrophy, Spinal”, “spinal muscular atrophy”, “Werdnig-Hoffmann Disease”, “Kugelberg Welander Syndrome”, “quality of life”, “health-related quality of life”, “utility”, “well-being”, and “Clinical Trial” (full search strings available as supplemental material online). For the purpose of this review, we excluded (i) articles published before the year 2000 (to ensure that estimates of QoL reflect current standard of care practices), (ii) review and editorial articles, (iii) articles written in a language other than English, and (iv) studies reporting results for samples comprising <5 patients (to allow for meaningful inference). For studies of patients with

different indications, we also required that results were reported separately for patients with SMA. Moreover, given the objective to review studies of QoL, we did not include publications only reporting data concerning specific disease complications, manifestations, or domains of psychological or physical health (e.g. depression, pain, or fatigue), or case reports/qualitative assessments. Lastly, we did not consider studies only reporting correlations between QoL and other outcomes/instruments.

### 2.2. *Screening, data extraction, and synthesis of results*

The searches were performed July 31, 2018. Two independent investigators (EL and JE) initially screened article titles and abstracts for eligibility, and subsequently reviewed full-text versions of selected records. For all articles included in the review, the following data were extracted: Author, year of publication, setting, sample, methods for measuring QoL (including employed instruments), and main results. The reasons for article exclusion were recorded and potential disagreements were specified to be resolved by consensus or, if necessary, the involvement of a third investigator (JK). Result data from each article was synthesized and reported with respect to the five review questions (as stated in the Introduction).

## 3. Results

The systematic literature review resulted in the identification of 824 publications (Fig. 1). Of these, 253 were duplicates, 536 records were excluded following title and abstract screening, and 35 articles were selected for full-text review. Finally, 15 articles[5–19] were considered for data synthesis. Table 1 presents summary data of the included publications.

### 3.1. *In which geographical settings have QoL of patients with SMA been studied?*

Estimates of QoL of patients with SMA were found for samples from a total of 11 countries and three continents (Europe, North America, and South America) (Table 1). Of the 15 included publications, 60% (9 of 15) represented research of samples of patients from the US.[5,9,10,11,12,14,15,17,19]

### 3.2. *For which types of SMA have patient QoL been measured?*

In total, approximately 20% (3 of 15) of the identified articles reported results based on samples of patients with one type of SMA: 7% (1 of 15) with SMA type I[17] and 13% (2 of 15) with SMA

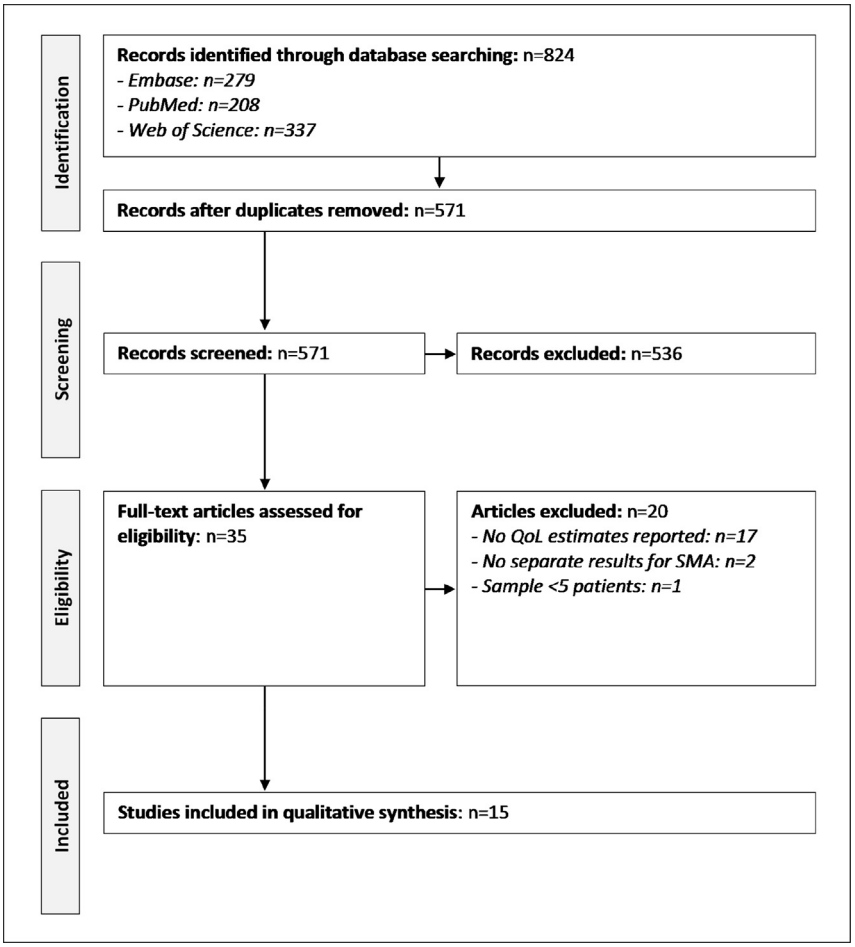


**Fig. 1 – PRISMA diagram of the selection process of the included publications. Note: Quality of life (QoL). Spinal muscular atrophy (SMA).**

**Table 1 – Summary data of included publications.**

| Authors (year) | Patient sample | Instrument(s) (type of assessment) | Main finding(s) |
|---|---|---|---|
| Abresch et al. (2002)[5] | 97 US patients (distribution of sex and age not reported); 70% with SMA type II and 30% with SMA type III. | SF-36 (patient self-assessment) | The mean SF-36 "Bodily Pain" (BP) score was not significantly different from US general population reference data. BP was associated with gender, constipation or incontinence, sleep disturbance, and coping with stress. |
| Bach et al. (2003)[17] | 46 US patients (distribution of sex and age not reported) with SMA type I. | Single-item question (Likert-scale) of patient QoL (caregiver and clinician proxy-assessment) | Children with SMA type 1 do not have poor QoL as rated by their caregivers (the estimated mean score was 7.8 on a 0–10 Likert scale, where 0 = minimum QoL and 10 = maximum QoL). In contrast, clinicians rated patient QoL at 2.9. |
| Iannaccone and Hynan (2003)[12] | 33 US patients (distribution of sex not reported; mean age not reported, age range: 2–17 years); SMA type not reported. | PedsQL NMM (patient self- and caregiver proxy-assessment) | Patients had impaired QoL across all instrument domains. |
| Iannaccone et al. (2009)[9] | 125 US patients (distribution of sex and age not reported); SMA type not reported. | PedsQL NMM and PedsQL GCS (patient self- and caregiver proxy-assessment) | Patients had impaired QoL across all instrument domains. Agreement between patient self-assessments and caregiver proxy-assessments was moderate to poor. |
| Swoboda et al. (2010)[14] | 61 US patients (54% male; mean age: 4 years, range: 2–9 years) with SMA type II or III. | PedsQL GCS (patient self- and caregiver proxy-assessment) | Patients had impaired QoL across all instrument domains. L-Carnitine and valproic acid had no benefit on patient QoL. |
| de Oliveira and Araújo (2011)[13] | 33 Brazilian patients (52% male; mean age: 10 years, range not reported); 42% with SMA type II and 58% with SMA type III. | The Autoquestionnnaire Qualité de Vie Enfant Imagé (AUQEI) (patient self-assessment) | The mean AUQEI score (ranging 0–78, where a higher score denotes higher QoL) was estimated at 56 and 53 for patients with SMA type II and III, respectively. |
| Kissel et al. (2011)[15] | 33 US patients (67% male; median age: 7 years, range: 3–16 years) with SMA type III. | PedsQL GCS (patient self- and caregiver proxy-assessment) | Patients had impaired QoL across all instrument domains. L-Carnitine and valproic acid had no benefit on patient QoL. |
| Kaufmann et al. (2012)[10] | 57 US patients (distribution of sex and age not reported) with SMA type II or III. | PedsQL GCS (patient self- and caregiver proxy-assessment) | Patients had impaired QoL across all instrument domains. Instrument scores were markedly different across SMA type. |
| Kocova et al. (2014)[8] | 35 Czech patients (60% male; mean age not reported, range: 3–18 years); 11% with SMA type I, 66% with SMA type II, and 23% with SMA type III. | PedsQL NMM (patient self- and caregiver proxy-assessment) | Patients had impaired QoL across all instrument domains, and lower scores compared with US reference data. |
| Montes et al. (2014)[a 11] | 14 US patients (79% male; mean age: 27 years, range: 10–48 years); 21% with SMA type IIIa and 79% with SMA type IIIb. | SF-36 (patient self-assessment) and PedsQL GCS (patient self- and caregiver proxy-assessment) | For adult patients, the mean SF-36 PCS and MCS scores were estimated at 38 and 54, respectively. |
| Chiriboga et al. (2016)[19] | 28 US patients (39% male; mean age: 6 years, range: 2–14 years); 54% with SMA type II and 46% with SMA type III. | PedsQL NMM and PedsQL GCS (patient self- and caregiver proxy-assessment) | No statistically significant changes in PedsQL NMM and PedsQL GCS scores were observed for patients treated with nusinersen. |
| Klug et al. (2016)[7] | 189 German patients (59% male; median age: 19 years, range: 0–73 years); 6% with SMA type I, 39% with SMA type II, and 55% with SMA type III. | PedsQL NMM (patient self- and caregiver proxy-assessment) | Patient QoL was impaired across all instrument domains and inversely associated with SMA type. |

| | | | |
|---|---|---|---|
| Kruitwagen-Van Reenen et al. (2016)[6] | 62 Dutch patients (42% male; mean age: 42 years, range not reported); 6% with SMA type I, 34% with SMA type II, 21% with SMA type IIIa, 32% with SMA type IIIb, and 6% with SMA type IV. | SF-36 (patient self-assessment) | The mean SF-36 PCS and MCS scores were estimated at 30 and 60, respectively. Scores for "Physical Functioning" (PF) were lower than Dutch general population reference data for all SMA types. |
| Bertini et al. (2017)[18] | 160 patients from Belgium, France, Germany, Italy, Netherlands, Poland, and the UK (50% male; mean age 10 years, range: 3–27 years); 71% with SMA type II and 29% with SMA type III. | PedsQL NMM (patient self- and caregiver proxy-assessment) | No statistically significant differences in mean PedsQL NMM global and subscale scores were observed for patients treated with olesoxime compared with placebo. |
| López-Bastida et al. (2017)[16] | 81 Spanish patients (42% male; mean age: 7 years, range not reported); 10% with SMA type I, 74% with SMA type II, and 16% with type SMA III. | EQ-5D-3L and a VAS (caregiver proxy-assessment) | The authors estimated the mean EQ-5D-3L utility at 0.158 (SMA type I, II, and III) and −0.012 (SMA type II) (using the UK value set by Dolan[20]). Corresponding VAS scores were 54 and 53, respectively. |

Note: Point estimates from the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL GCS) and the Pediatric Quality of Life Inventory 3.0 Neuromuscular Module (PedsQL NMM) are reported in Figs. 2–5 (or in the text). Spinal muscular atrophy (SMA). Quality of life (QoL). The 36-Item Short Form Survey (SF-36). Physical Component Summary (PCS). Mental Component Summary (MCS). EuroQol EQ-5D (EQ-5D). Visual Analog Scale (VAS).

[a] Result were not considered for strata with <5 patients.

type III.[11,15] In addition, 67% (10 of 15) measured QoL in samples with different types of SMA: 40% (6 of 15) with SMA type II and III,[5,10,13,14,18,19] 20% (3 of 15) with SMA type I, II, and III,[7,8,16] and 7% (1 of 15) with SMA type I, II, III, and IV.[6] Two studies[9,12] did not explicitly disclose SMA type.

### 3.3. *What instruments have been used to measure QoL of patients with SMA?*

In 40% (6 of 15) of the identified publications, QoL was measured using the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales (PedsQL GCS),[9,10,11,14,15,19] in 40% (6 of 15) using the PedsQL 3.0 Neuromuscular Module (PedsQL NMM),[7,8,9,12,18,19] in 20% (3 of 15) using the 36-Item Short Form Survey (SF-36),[5,6,11] and in 7% (1 of 15) using the EuroQol EQ-5D (EQ-5D),[16] a Visual Analog Scale (VAS),[16] a single-item question (Likert-scale),[17] and/or the Autoquestionnnaire Qualité de Vie Enfant Imagé,[13] respectively. As shown in Table 1, 67% (10 of 15) of the included records encompassed both patient self- and proxy-assessments of patient QoL,[7,8,9,10,11,12,14,15,18,19] 20% (3 of 15) only patient self-assessments,[5,6,13] and 13% (2 of 15) only proxy-assessments.[16,17] Of the proxy-assessments, all comprised parents or other relatives, with the exception of Bach et al.,[17] which also included nurses and clinicians.

### 3.4. *What is known about QoL of patients with SMA?*

Mean PedsQL NMM scores (ranging from 0 to 100, where a higher score represents higher QoL) are presented in Fig. 2 (patient self-assessments) and Fig. 3 (caregiver proxy-assessments). Across studies and subgroups, the mean self-assessed "About my neuromuscular disease" score ranged between 57 and 73, "Communication" score between 61 and 74, "About our family resources" score between 57 and 79, and total instrument score between 58 and 72. Corresponding ranges for caregiver proxy-assessed scores were 49 and 70, 56 and 68, 41 and 73, and 34 and 70, respectively. In addition, one study[7] also reported mean PedsQL NMM scores derived from a mix of patient self- and caregiver proxy-assessments stratified by SMA type. Across the three instrument domains and the total score, estimates were 39, 4, 30, and 34 for SMA type I, 54, 78, 49, and 56 for SMA type II, and 68, 82, 69, and 69 for SMA type III, respectively. Two studies[18,19] only reported changes in PedsQL NMM scores.

Estimates of patient QoL from the PedsQL GCS (ranging from 0 to 100, where higher score represents higher QoL) are presented in Fig. 4 (patient self-assessments) and Fig. 5 (caregiver proxy-assessments). Across studies and subgroups, the mean self-assessed "Physical Health" score ranged between 35 and 52, "Psychosocial Health" score between 63 and 70, "Emotional Functioning" score between 63 and 70, "Social Functioning" score between 62 and 67, "School Functioning" score between 65 and 70, and total instrument score between 55 and 65. Corresponding ranges for caregiver proxy-assessed scores were 20 and 45, 62 and 75, 64 and 72, 54 and 61, 61 and 67, and 47 and 65, respectively. Kissel et al.[15] reported median instrument scores for patients with SMA type III at 61 for "Physical Health", 70 for "Psychosocial Health", 70 for "Social Functioning", 80 for "School Functioning", and 67 for

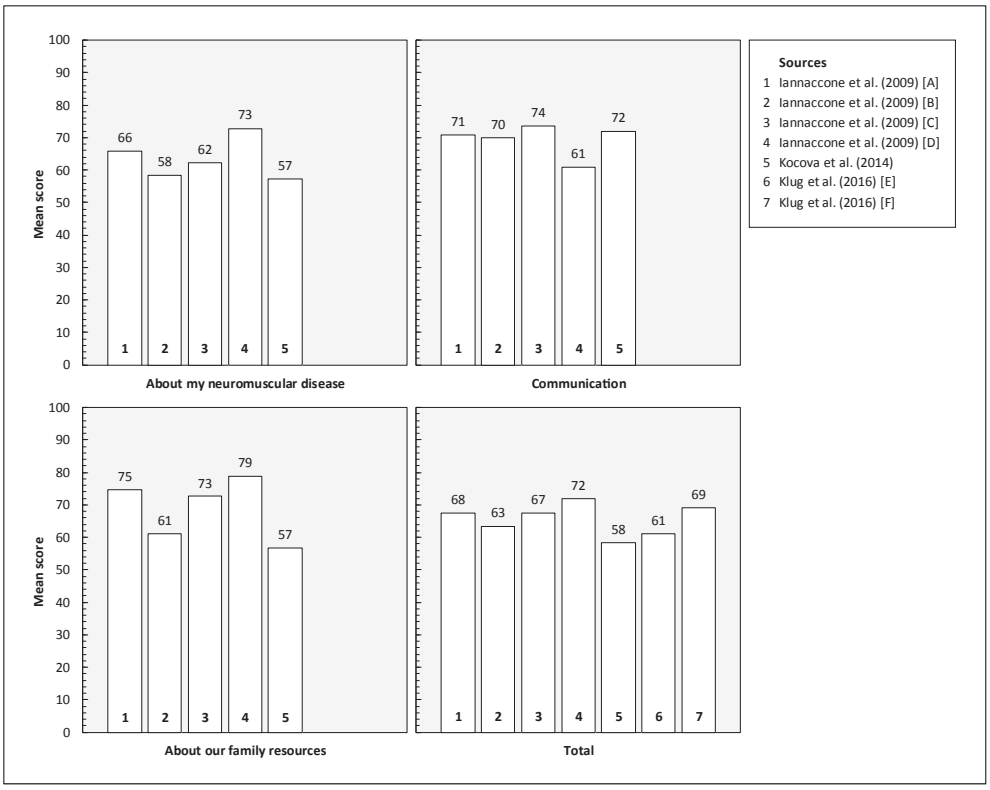


**Fig. 2 – Self-assessed QoL of patients with SMA as measured using the PedsQL NMM. Note: For references, see Table 1. The Pediatric Quality of Life Inventory 3.0 Neuromuscular Module (PedsQL NMM). PedsQL NMM scores range from 0 to 100, where a higher score represents higher QoL. Subgroups from Iannaccone et al.[9]: [A] All patients, [B] Non-sitter, [C] Sitter, and [D] Walker. Subgroups from Klug et al.[7]: [E] SMA type II, and [F] SMA type III.**

the total instrument score (only baseline scores reported due to non-significant/minor differences across follow-up). One study[19] only reported changes in PedsQL GCS scores.

Concerning patient self-assessed QoL as measured using the SF-36 instrument (comprising eight subscales, as well as two summary measures, each scored between 0 and 100, where higher score represents higher QoL), Abresch et al.[5] estimated the mean "Bodily Pain" (BP) score at 72 for SMA type II and 77 for SMA type III, and Kruitwagen-Van Reenen et al.[6] at 81 for SMA type II, 76 for SMA type IIIa, and 61 for SMA type IIIb. Kruitwagen-Van Reenen et al.[6] also reported results for all SF-36 subscales for patients with SMA type II, type IIIa, and type IIIb, respectively (data for SMA type I and type IV were not considered due to insufficient sample sizes). Specifically, across SMA types, mean "Physical Functioning" (PF) scores ranged between 5 and 18, "Role Physical" (RP) between 53 and 64, "General Health" (GH) between 51 and 64, "Vitality" (VT) between 48 and 72, "Social Functioning" (SF) between 63 and 77, "Role Emotional" (RE) between 89 and 92, and "Mental Health" (MH) between 80 and 83. Moreover, Montes et al.[11] estimated the Physical Component Summary (PCS) at 38 and the Mental Component Summary (MCS) at 54 for patients with SMA type III. Corresponding estimates for the pooled sample from Kruitwagen-Van Reenen et al.[6] were 30 and 60, respectively. None of the included publications reported results from proxy-assessments of QoL using the SF-36, or utilities derived from the SF-36 through the SF-6D algorithm.

Of the 15 included publications, only one study, López-Bastida et al.,[16] estimated QoL of patients with SMA in terms of utilities. Specifically, using the UK value set by Dolan,[20] the authors estimated the mean EQ-5D-3L utility (ranging between −1 and 1, where ≤0 equals dead and 1 equals perfect health) at 0.16 (SMA type I, II, and III) and −0.01 (SMA type II). Corresponding VAS scores were 54 and 53, respectively.

Finally, Bach et al.[17] proxy-assessed QoL using a single-item Likert scale (ranging between 0 = minimum QoL and 10 = maximum QoL) and estimated the overall score at 7.8 for caregivers, ranging between 6.5 and 8.4 across respondent type (i.e. mother, farther, grandparent, and nurse), and 2.9 for clinicians.

### 3.5. *How is QoL of patients with SMA modified by available treatments?*

We identified four articles[14,15,18,19] reporting results in terms of patient QoL from RCTs of treatments of SMA. The first investigated the impact of olesoxime on patient self- and caregiver proxy-assessed QoL measured using the PedsQL NMM in a multi-national cohort comprising 160 patients followed for 24 months. No statistically significant changes in instrument scores were observed for patients treated with olesoxime compared with placebo.[18] In the second article, Chiriboga et al.[19] studied patient self- and caregiver proxy-assessed QoL (measured using the PedsQL NMM and the PedsQL GCS) as an

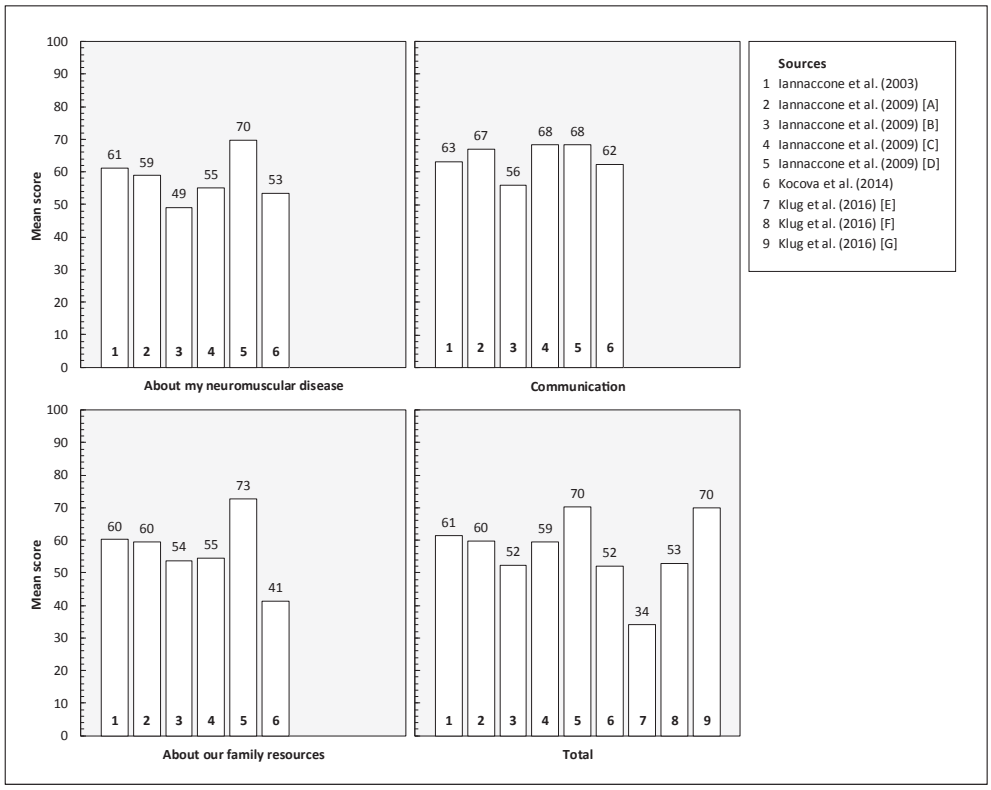


**Fig. 3 – Proxy-assessed QoL of patients with SMA as measured using the PedsQL NMM. Note: For references, see Table 1. The Pediatric Quality of Life Inventory 3.0 Neuromuscular Module (PedsQL NMM). PedsQL NMM scores range from 0 to 100, where a higher score represents higher QoL. Subgroups from Iannaccone et al.[9]: [A] All patients, [B] Non-sitter, [C] Sitter, and [D] Walker. Subgroups from Klug et al.[7]: [E] SMA type I, [F] SMA type II, and [G] SMA type III.**

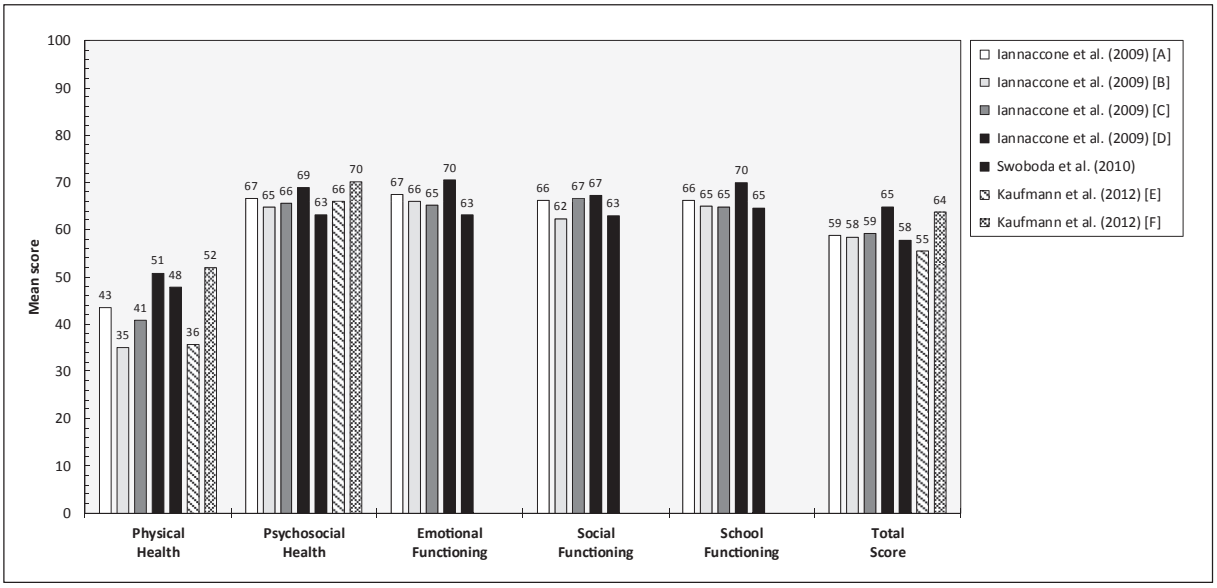


**Fig. 4 – Self-assessed QoL of patients with SMA as measured using the PedsQL GCS. Note: For references, see Table 1. The Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL GCS). PedsQL GCS scores range from 0 to 100, where a higher score represents higher QoL. Subgroups from Iannaccone et al.[9]: [A] All patients, [B] Non-sitter, [C] Sitter, and [D] Walker. Subgroups from Kaufmann et al.[10]: [E] SMA type II, and [F] SMA type III.**

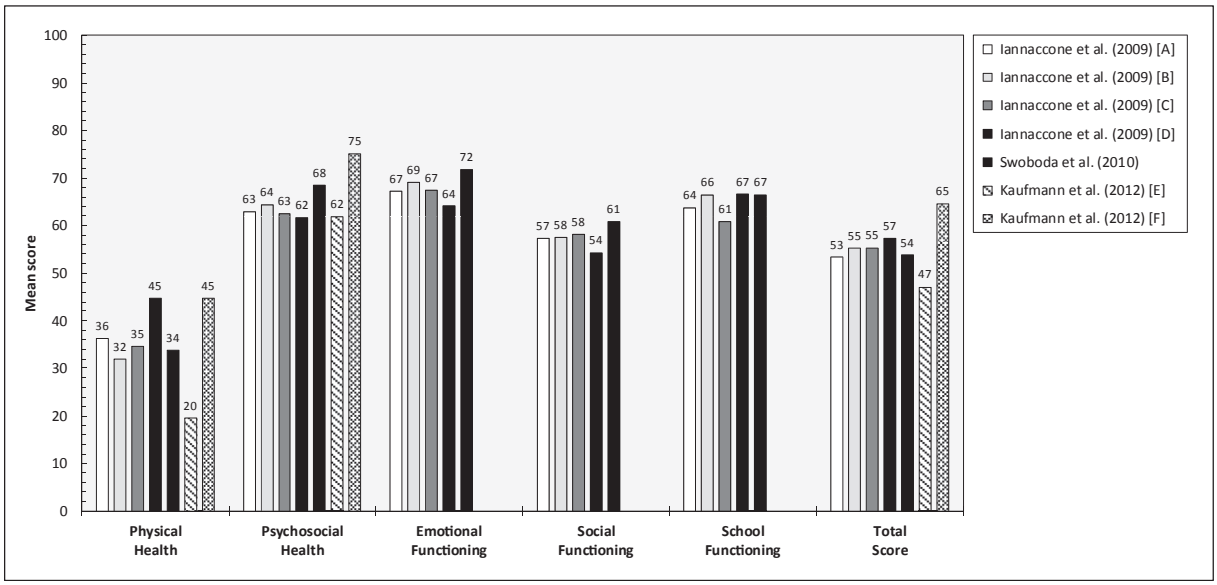


**Fig. 5 – Proxy-assessed QoL of patients with SMA as measured using the PedsQL GCS. Note: For references, see Table 1. The Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL GCS). PedsQL GCS scores range from 0 to 100, where a higher score represents higher QoL. Subgroups from Iannaccone et al.[9]: [A] All patients, [B] Non-sitter, [C] Sitter, and [D] Walker. Subgroups from Kaufmann et al.[10]: [E] SMA type II, and [F] SMA type III.**

exploratory endpoint in 28 US patients with SMA treated with different doses of nusinersen. The authors found that changes in instrument scores from baseline to day 85 were not statistically significant in any dose group, although numerically higher for patients treated with 9 mg. Finally, the third trial[14,15] studied the efficacy of L-Carnitine and valproic acid versus placebo in a sample of US patients with SMA type II and III. No benefit on patient QoL was identified.

## 4. Discussion

The outcomes of this systematic literature review show that QoL of patients with SMA has been studied in several geographical settings and populations primarily through the PedsQL NMM and PedsQL GCS, but that little is known of the impact of the disease as measured using other scales across different types of SMA. In particular, our synthesis of estimates of QoL as measured using the PedsQL NMM and PedsQL GCS revealed non-trivial heterogeneity across instrument domains for both self- and proxy-assessments (Figs. 2–5). Compared with PedsQL GCS reference data for healthy individuals, which range between 80 and 90 across most subscales and the total score,[21] patient self-assessments indicated that SMA in particular has an impact on physical health, although all subscales were impaired to some degree. Moreover, concerning proxy-assessments, caregivers indicated that "Social Functioning" (as recorded through the PedsQL GCS) also was a domain of life markedly influenced by the disease. Yet, given that not all studies stratified their results by, for example, SMA type, functional ability, and/or other measures of disease severity/stage/progression, and because of non-trivial differences across study samples concerning the distribution of demographic characteristics (e.g. sex and age), as well as possible differences in general QoL across countries, it is not possible to draw any definite conclusions concerning the determinants of the observed differences. Nevertheless, some data suggests that the impact on physical health is inversely associated with SMA type.

It is worth noting that previous psychometric research[22] of the PedsQL NMM has indicated that the rating-scale may not be fit for purpose to measure QoL of patients with Duchenne muscular dystrophy (DMD) (a serious, and ultimately fatal neuromuscular disease also associated with muscle degeneration), as a consequence of the ordinal, Likert scale scoring algorithm. For example, although it is clear that a higher PedsQL score implies higher QoL, it is not clear what a specific score means in terms of QoL, or how changes in scores should be interpreted. In addition, in the context of DMD, there is also evidence of other issues with the PedsQL NMM concerning, for example, item dependency (i.e. that a reply to one item predicts the reply to another item), disordered thresholds (i.e. that respondents have difficulty discriminating between response categories given their level of QoL), and multidimensionality (i.e. that the measurement describes more than one attribute of the object measured). For this reason, until a full psychometric analysis of these tools has been performed in populations with SMA, we recommend that outcomes from PedsQL scales should be interpreted with some caution.

Similarly to identified outcomes from the PedsQL scales, results from the SF-36 instrument also indicated that SMA mainly affects physical, as opposed to mental health, where estimated mean PCS scores were nearly half of that of MCS scores (i.e. 38 vs. 54,[11] and 30 vs. 60[6]). These findings warrant further investigation, in particular considering the recognized notion that without mental health there can be no true physical health.[23]

Surprisingly, despite being available through the SF-6D algorithm, none of the included studies measuring QoL using the SF-36 reported outcomes in terms of utilities. Still, one study estimated QoL using a different preference-based instrument (i.e. a scale linked to utilities), namely the EQ-5D-3L. Specifically, López-Bastida et al.[16] estimated the mean patient utility at 0.16 (SMA type I, II, and III) and −0.01 (SMA type II), which may be compared with previously published estimates for patients with, for example, asthma (0.72), multiple sclerosis (0.50), blindness and vision defects (0.78), and acute myocardial infarction (0.61)[24] derived through the same multi-attribute health status classification system.[20] In other words, the utility data reported by López-Bastida et al.[16] indicates that members of the general population attribute very low preference, or utility, to the health states generated by SMA – in fact, for SMA type II, healthy individuals rated this state as being worse than dead. That being said, to help inform health technology assessments (HTAs) of medicines targeting the disease, and to provide a richer description and understanding of the health burden associated with the SMA, we believe that it would be of interest to further measure QoL using preference-based tools that are relatively more granular than the EQ-5D, for example the Health Utilities Index.[25]

Our review show that data is limited with respect to the impact of available treatments on patient QoL in SMA. Indeed, we only found four relevant publications from RCTs in SMA: a phase 1 trial of nusinersen, a phase 2 trial of olesoxime, and a phase 2 trial of L-Carnitine and valproic acid. Neither study reported any significant changes in QoL, which may not come as a surprise given the variability in measurements found in this review, the size of studied sample populations, and considering the psychometric issues of some QoL instruments mentioned above. Additionally, in the RCT of olesoxime, the lack of significant changes in QoL may also be a function of the relatively modest drug effect size, and for nusinersen the relatively short trial duration (85 days). Hence, it cannot be concluded that nusinersen would not have a significant effect on QoL in longer trials comprising larger patient populations. Accordingly, further investigations of QoL in exposed populations are thus needed to help assess efficacy and effectiveness, as well as to further inform treatment algorithms and HTA processes in SMA.

In contrast to research of adult patients, measuring QoL in pediatric populations is associated with additional challenges and considerations.[26,27] For example, toddlers, children, adolescents, and adults have varying cognitive abilities and have also been shown to have different reference systems and perceptions of QoL and its determinants. Indeed, although there is no consensus regarding at which age children are capable of providing reliable self-assessments of their QoL, it is not until adolescence that cognitive skills become more complex, allowing the individual to formulate ideas, contemplate their future more systematically, and engage in deductive reasoning.[26] For this reason, for childhood diseases, it is common practice to use age-specific formats of pediatric QoL tools and also proxy-record data on patient QoL, usually from caregivers. That being said, for patients equal to or older than 8 years of age, it would be of interest to further study self-perceived QoL in SMA using a tool other than the PedsQL, for example KIDSCREEN,[28] as well as the relationship between cognitive ability and self-perceived QoL across different types of SMA. For studies involving proxy-assessments of patient QoL, it may also be relevant to explore estimates by patient age.

As expected given the rarity of SMA, many estimates of QoL identified in our review were derived from relatively small samples. Indeed, 40% (6 of 15) of studies were based on ≤35 patients (Table 1). Accordingly, the establishment of global, regional, and/or local disease registry networks and data collection platforms, such as TREAT-NMD[29] and SMArtCARE,[30] constitute important initiatives to facilitate the identification and recruitment of patients to research in SMA to help improve precision and minimize potential bias.

In conclusion, our review show that patient QoL is impaired in SMA, mainly due to compromised physical health, but also reveal that little is known of the impact of the disease across different phenotypes and clinical interventions.

## Conflicts of interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.03.004.

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