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ORIGINAL RESEARCH

Evaluating Perceived Fatigue within an Adult Spinal Muscular Atrophy Population

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ABSTRACT

Introduction: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by progressive muscle weakness and atrophy. While chronic fatigue is a common manifestation of SMA, the field lacks comprehensive data to assess the extent of its impact. Cure SMA, an SMA patient advocacy organization, conducted an online survey of its adults with SMA community members to measure the impact of fatigue.

Methods: All survey respondents were asked to complete questions on demographics, use of SMA treatment, and quality of life, but respondents were randomized to receive three of the following fatigue instruments: the Modified Fatigue Impact Scale (MFIS), Multidimensional Fatigue Inventory (MFI), Fatigue Severity Scale (FSS), PedsQL™ Multidimensional Fatigue (PedsQL MF) Scale, and Spinal Muscular Atrophy Health Index (SMA-HI) fatigue modules. Scales were evaluated for reliability and overall fatigue scores were evaluated by multivariate regression models to determine which variables were related to the final scores of each instrument.

Results: A total of 253 adults completed the online survey. When measured against the general population, statistically significant differences were found among adults with SMA for certain variables within each measurement instrument. However, there did not appear to be differences in fatigue levels among key subgroups within the SMA population.

Conclusions: This was the first use of more than two fatigue questionnaires simultaneously in SMA. The lack of a consistent relationship between SMA severity and fatigue levels was surprising. This may be related to the lack of specificity of the instruments for this population. An SMA-specific scale is needed to evaluate differences in fatigue impact across the SMA population.

Keywords: Spinal muscular atrophy; Fatigue; Community survey; Patient-reported outcomes

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Key Summary Points

Why carry out this study?

Adults with spinal muscular atrophy (SMA) experience significant fatigue.

The objective of this study was to measure fatigue in an adult SMA population using a variety of instruments.

What was learned from the study?

The instruments used to measure perceived fatigue did not find a consistent relationship between SMA severity and fatigue.

An SMA-specific scale is needed to evaluate differences in fatigue impact across the SMA population.

INTRODUCTION

SMA is an autosomal recessive neuromuscular disease characterized by progressive muscle weakness and atrophy [1–3]. SMA is caused by the loss or mutation of the survivor of motor neuron (*SMN*) 1 gene. There is a wide range of clinical severity in SMA, and the key determinant of disease phenotype is the copy number of *SMN2*, a nonfunctional variant of the *SMN1* gene [4]. SMA has been historically classified into four types based on severity and age of symptom onset [3, 5–10]. The most severe and common type (accounting for approximately 60% of SMA births), type I, presents within the first six months of life. According to historical type classifications that predate approved disease-modifying therapies, babies with type I never achieve the ability to sit and usually require both ventilatory and feeding support, with the eventual use of permanent ventilation or death prior to the age of two years [11]. SMA type II, which accounts for about 30% of SMA cases, presents symptoms between 6 and 18 months of age, and while children may achieve the ability to sit independently, they will not be able to walk independently without treatment. About 10% of SMA cases are classified as SMA type III, in which symptoms appear after 18 months of age. Those with SMA type III may stand and walk independently, but lose these abilities over time [1, 12]. Lastly, those with SMA type IV, the rarest and least severe type of SMA, typically have onset of weakness in the second or third decade of life and experience mild motor impairment [13].

While SMA is often associated with pediatric patients—including infants and very young children—more than one-third of the global SMA population is estimated to be 18 or older [14]. This proportion is likely to increase over time as novel disease-modifying therapies improve outcomes and extend life spans.

There are currently three U.S. Food and Drug Administration (FDA) approved treatments for SMA. These include the antisense oligonucleotide nusinersen, approved in December 2016 for pediatric and adult SMA patients [15]; the gene therapy onasemnogene abeparvovecxioi, approved in May 2019 for children under the age of 2 [15, 16]; and the small-molecule drug risdiplam, approved in August 2020 for patients 2 months of age and older and now approved for all ages [17]. Clinical trial data for all of these drugs have demonstrated improved survival and motor function [18].

Despite these advances, adults with SMA continue to experience significant mental and psychosocial impacts associated with their disease. While these impacts remain less well studied or understood [19] than those for pediatric patients, one oft-cited challenge is fatigue [20–23]. With fatigue, it is helpful to distinguish between the physical construct of fatigability—which is defined as "magnitude or rate of change in a performance criterion relative to a reference value over a given time of task performance or measure of mechanical output"—and perceived fatigue [24]. Perceived fatigue can be characterized by an overwhelming sense of tiredness, increasing sense of effort, lack of energy and motivation, and a feeling of exhaustion [25–28]. Previous studies have reported significant levels of perceived fatigue in adults with SMA. In one study, 81% of SMA

patients complained of disabling fatigue and had higher severity scores than normal controls [29] and another study found that more than half of SMA patients had abnormal or severe levels of perceived fatigue [22].

There are many instruments available for measuring perceived fatigue, but only one developed specifically for use in SMA [30, 31]. The objectives of this study were to measure perceived fatigue in adults with SMA using five different fatigue instruments, evaluate the reliability of these instruments, and describe whether differences in fatigue levels were predicted by demographics, SMA type, *SMN2* copy number, and treatment experience. Quantifying fatigue in an adult SMA population using a variety of instruments can provide a more complete perspective on its effects as well as baseline measures for future studies that assess perceived fatigue.

METHODS

The survey was developed by Cure SMA and the Cure SMA Industry Collaboration (SMA-IC). Cure SMA is an SMA patient advocacy organization based in the United States that provides support and funding for the care and treatment of SMA and hosts the largest self-reported SMA membership database worldwide [32]. The SMA-IC was established in 2016 to leverage the experience, expertise, and resources of pharmaceutical and biotechnology companies, as well as other nonprofit organizations involved in the development of SMA therapeutics to address a range of issues. At the time of the study, the SMA-IC included Novartis Gene Therapies, Biogen, Genentech/Roche Pharmaceuticals, Scholar Rock, and SMA Europe.

All people with SMA who were in the Cure SMA membership database and over the age of 18 in December 2020 were invited to participate in the survey via email. The online survey was hosted on Alchemer, a cloud-based integrated feedback platform. Demographics, self-reported SMA type and *SMN2* copy number, use of SMA treatments, and fatigue and quality of life measures were captured. Institutional review board (IRB) approval was obtained from Western IRB on November 24, 2020 (IRB ID: 20203852). Survey participants were informed of the intention to publish the anonymized results before they began the survey. All survey respondents provided informed consent to participate in the study on the survey landing page prior to being able to start the survey. The study procedures were in accordance with the 1964 Declaration of Helsinki and its later amendments. Data were de-identified before analysis.

In order to prevent survey fatigue, a randomization feature on Alchemer was utilized so that each respondent randomly received three of the following instruments: the Modified Fatigue Impact Scale (MFIS), Multidimensional Fatigue Inventory (MFI), Fatigue Severity Scale (FSS), PedsQL™ Multidimensional Fatigue (PedsQL MF) scale, and Spinal Muscular Atrophy Health Index (SMA-HI) fatigue and sleep modules [33–36]. The instruments were selected based on previous use in SMA and/or availability in the public domain. Table 1 describes each instrument.

Statistical analyses

Cronbach's alpha and inter-item correlations were computed to evaluate the reliability of each instrument except the SMA-HI. These values were not calculated for the SMA-HI due to missing SMA-HI short-form questions (see below). However, the SMA-HI was designed for use specifically in SMA and has been validated previously.

Mean scores and standard deviations (SD) were calculated for all scales and subscales. Since the SMA-HI short form was not implemented in this study, the SMA-HI sleep and fatigue subscales were each missing one item that would typically be included in the calculation of subscale scores. Using a predetermined statistical plan for missing data, we utilized the average response from the completed items to estimate the response for the missing items in each subscale prior to calculating subscale scores.

Multivariable regression models were used to evaluate the relationship between the fatigue

Table 1 Fatigue instruments included in the study

Instrument	About	Domain	# Items	General population scores, mean (SD)	Interpretation	Previously validated in SMA
MFIS [37]	Originally developed to assess the effects of fatigue on quality of life in patients with chronic diseases, specifically MS. The MFIS asks patients to rate the extent to which fatigue has affected their life in the past 4 weeks on a questionnaire consisting of "physical", "cognitive" and "social" items	Total score (scores range from 0 to 84)	21	15.30 (0.47)	Higher scores indicate a greater impact of fatigue	No
		Physical (scores range from 0 to 36)	9	6.72 (0.23)		
		Cognitive (scores range from 0 to 40)	10	7.27 (0.24)		
		Psychological (scores range from 0 to 8)	2	1.33 (0.06)		
FSS	Designed to differentiate fatigue from clinical depression. Measures how fatigue affects motivation, exercise, physical functioning, carrying out duties, interfering with work, family, or social life. Originally developed for multiple sclerosis and systemic lupus erythematosus but later used for chronic fatigue syndrome; largely independent of self-reported depressive symptoms	Total score (scores range from 1 to 7)	9	2.30 (0.70)	Higher scores indicate greater fatigue levels	Yes [36, 38]

Table 1 continued

Instrument	About	Domain	# Items	General population scores, mean (SD)	Interpretation	Previously validated in SMA
MFI [34]	A self-report instrument containing 20 items which are categorized into five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. The MFI measures how a patient has felt "lately" on a five-point Likert-type scale	General (scores range from 4 to 20)	4	8.42 (3.59)	Higher scores indicate greater fatigue levels	Yes [30]
		Physical (scores range from 4 to 20)	4	7.77 (3.36)		
		Reduced activity (scores range from 4 to 20)	4	7.23 (3.07)		
		Reduced motivation (scores range from 4 to 20)	4	6.82 (2.91)		
		Mental fatigue (scores range from 4 to 20)	4	6.76 (2.67)		
PedsQL MF [39]	This scale was designed as a generic symptom-specific instrument to measure fatigue in patients with acute and chronic health conditions as well as healthy school and community populations	Total score (scores range from 0 to 100)	18	67.18 (13.92)	Higher scores indicate fewer fatigue symptoms	No
		General fatigue (scores range from 0 to 100)	6	70.92 (16.94)		
		Sleep/rest (scores range from 0 to 100)	6	59.76 (17.10)		
		Cognitive fatigue (scores range from 0 to 100)	6	70.88 (18.15)		

Table 1 continued

Instrument	About	Domain	# Items	General population scores, mean (SD)	Interpretation	Previously validated in SMA
SMA-HI	The SMA-HI is a disease-specific, patient-reported outcome measure questionnaire, designed to estimate the patients' perception of disease burden	Fatigue (scores range from 0 to 100)	6	n/a	Higher scores indicate more burden	Yes [40]
		Sleep (scores range from 0 to 100)	4	n/a		

scores and demographics, SMA type, *SMN2* copy number, and SMA treatment status. SMA type was categorized into types I, II, and III, and unknown/other. Unknown/other SMA type included those with distal SMA, type IV SMA, and unknown SMA type. *SMN2* copy number was categorized into ≤ 2 copies, 3 copies, 4 or more copies, and unknown. Treatment status was categorized as ever treated with an SMA disease-modifying therapy (DMT) and never treated with an SMA DMT. Type of DMT used was not captured in the survey.

RESULTS

A total of 253 adults completed the online survey (5.93% with type I, 44.66% with type II, 44.27% with type III, and 5.14% other/unknown) (Table 2). The mean (SD) age at SMA diagnosis within the total sample was 8.13 years (12.86), with many having lived with SMA for years. The majority of participants (75.49%) reported having used an SMA DMT. The respondent subgroups for each scale or subscale were relatively similar according to the demographic and disease-related characteristics assessed.

Reliability statistics and mean (SD) fatigue scores for each scale or subscale are presented in Table 3. Cronbach's alpha was greater than 0.90—which is the minimum accepted value for scales used for measurement on individuals—for the full MFIS, MFI, FSS, and PedsQL MF scales. However, the MFIS was the only scale with alpha values of 0.90 or above for all subscales with at least three items. Inter-item correlations varied widely (ranging from 0.29 to 0.74 for the scales and subscales). The relatively high number of IICs close to or exceeding 0.50 suggests that the items on several of the scales and their subscales may be too closely related and somewhat redundant.

Mean fatigue scores for respondents were higher than general population scores for all instruments for which comparators were available (see Table 3 vs. Table 1). Table 4 summarizes the factors associated with fatigue by instrument. Bold values indicate significant associations ($p < 0.05$) between fatigue and the independent variables. Higher income was associated with lower fatigue for the MFIS total score, the MFI general score, and all three subscores of the PedsQL MF. Gender was not significantly associated with fatigue scores for any of the five instruments. Among SMA-specific outcomes, less severe SMA type was associated with lower fatigue levels in the cognitive MFIS score, but higher fatigue levels in the FSS and the general PedsQL MF. Treatment with an SMA DMT was associated with lower fatigue levels in the physical, cognitive, and total MFIS scores; the physical MFI score; the general PedsQL MF score; and the fatigue SMA-HI score.

DISCUSSION

The scales evaluated in this research demonstrated reasonable levels of reliability for use in

Table 2 Characteristics of survey respondents

	Total sample	MFIS	MFI	FSS	PedsQL MF	SMA-HI
Total,, n	253	158	162	146	150	142
Gender, n (%)						
Female	164 (64.82)	102 (64.56)	113 (69.75)	95 (65.07)	90 (60.00)	91 (64.08)
Age, in years						
Mean (SD)	38.21 (13.62)	37.89 (12.56)	37.96 (14.14)	38.65 (13.36)	37.53 (13.80)	39.09 (14.25)
Range	18–79	18–78	18–79	18–79	18–78	18–79
Race, n (%)						
White	209 (82.61)	134 (84.81)	133 (82.10)	120 (82.19)	121 (80.67)	118 (83.10)
Income, n (%)						
≤ $40,000	76 (30.04)	51 (32.28)	46 (28.40)	41 (28.08)	44 (29.33)	46 (32.39)
$41,000-$100,000	92 (36.36)	55 (34.81)	57 (35.19)	58 (39.73)	60 (40.00)	45 (31.69)
≥ $101,000	39 (15.42)	22 (13.92)	28 (17.28)	22 (15.07)	22 (14.67)	23 (16.20)
Unknown	46 (18.18)	30 (18.99)	31 (19.14)	25 (17.12)	24 (16.00)	28 (19.72)
Education, n (%)						
Associate degree or less	95 (37.55)	56 (35.44)	61 (37.65)	50 (34.25)	64 (42.67)	54 (38.03)
Bachelor's degree	81 (32.02)	51 (32.28)	53 (32.72)	53 (36.30)	43 (28.67)	43 (30.28)
Master's degree or higher	75 (29.64)	50 (31.65)	46 (28.40)	42 (28.77)	42 (28.00)	44 (30.99)
Unknown	2 (0.79)	1 (0.63)	2 (1.23)	1 (0.68)	1 (0.67)	1 (0.70)
Age at diagnosis, in years, n	246	154	158	141	143	141
Mean (SD)	8.13 (12.86)	7.60 (12.47)	8.48 (13.75)	8.09 (12.85)	8.49 (12.94)	8.04 (12.28)
Range	0–77	0–71	0–77	0–77	0–71	0–77
SMA type, n (%)						
Type I	15 (5.93)	9 (5.70)	13 (8.02)	7 (4.79)	9 (6.00)	7 (4.93)
Type II	113 (44.66)	73 (46.20)	69 (42.59)	66 (45.21)	73 (48.67)	58 (40.85)
Type III	112 (44.27)	66 (41.77)	72 (44.44)	68 (46.58)	61 (40.67)	68 (47.89)
Other/unknown[a]	13 (5.14)	10 (6.33)	8 (4.94)	5 (3.42)	7 (4.67)	9 (6.34)
SMN2 copies, n (%)						
≤ 2 copies	36 (14.23)	23 (14.56)	23 (14.20)	20 (13.70)	21 (14.00)	20 (14.08)
3 copies	81 (32.02)	53 (33.54)	52 (32.10)	47 (32.19)	49 (32.67)	42 (29.58)
4 or more copies	36 (14.23)	16 (10.13)	38 (17.28)	24 (16.44)	18 (12.00)	22 (15.49)
Unknown	100 (39.53)	66 (41.77)	59 (36.42)	55 (37.67)	62 (41.33)	58 (40.85)

Table 2 continued

	Total sample	MFIS	MFI	FSS	PedsQL MF	SMA-HI
Ever treated with an SMA-DMT[b], n (%)						
Yes	191 (75.49)	116 (73.42)	122 (75.31)	112 (76.71)	114 (76.00)	108 (76.06)
No	62 (24.51)	42 (26.58)	40 (24.69)	34 (23.29)	36 (24.00)	34 (23.94)

[a]Other/unknown SMA type included those with a non-5q SMA
[b]Treatment includes any SMA DMT received through a clinical trial and/or commercially available therapy

SMA, although performance varied, and adaptations for the community may yield better performance. High inter-item correlations within certain scales and subscales suggest that their items may be repetitive, and scale modification could be appropriate for the SMA community. Future research may be useful in further confirming the validity and reliability of the scales, by more carefully and systematically examining the four dimensions of validity as well as test–retest reliability and inter-rater reliability. Ultimately, research to develop new or refined instruments that are tailored to the SMA community may yield the best understanding of fatigue within this population.

Examining predictors of perceived fatigue yielded a mixture of expected and surprising results. Given the impact of DMTs, it was not surprising that patients who had been treated with an SMA therapy had significantly lower fatigue scores than those who had never received treatment in the physical, cognitive, and total MFIS scores, as well as in the physical MFI score. However, given the significant variation in disease severity based on *SMN2* copy number and SMA type, it was surprising that not all scales demonstrated differences in fatigue by SMA severity. One possible explanation is that the instruments used may be more likely to pick up on sociodemographic differences (e.g., age, education, quality of life) rather than SMA-specific distinctions [41].

Several aspects of our results have similarities to previous studies. For example, the physical MFI results correspond with those from a previous study by Binz et al. in which 75% of participants were abnormally fatigued, with the highest scores in the physical dimensions, followed by general fatigue and reduced activity [41]. Additionally, the FSS results correspond with those from a previous study by Dunaway et al. in which all type II and type III SMA patients reported perceived fatigue [38].

Overall, however, the inability to tease out major distinctions among subgroups suggests several potential conclusions. It is possible that there are no differences in perceived fatigue among various subgroups within the adult SMA population despite the varying impact that SMA has on individuals' ability to pursue activities of daily living and enjoy a full life. Another conclusion is that motor function—and moreover differences in motor function by SMA type and copy number—is not related to perceived fatigue. This was also suggested by Dunaway Young et al. [22] when evaluating perceived fatigue in ambulatory SMA patients and reporting that they did not find differences in perceived fatigue between SMA type II and type III patients. On the other hand, however, given the heterogeneity among this population, it seems more likely that the lack of statistically significant differences identified in this study is due to insufficient specificity relating to fatigue within the available measurement instruments for this patient population.

Study Limitations

One significant limitation of this study is that current motor function was not collected in our survey. As a result, we could not evaluate perceived fatigue levels based on motor function—only based on SMA type. Future studies should

Table 3 Scale reliability and scores

Scale	# items	*n*	Cronbach's α[a]	Average inter-item correlation (IIC)[b]	Mean score (SD)
MFIS					
Total score	21	158	0.94	0.41	33.89 (14.31)
Physical	9	158	0.90	0.51	19.34 (7.35)
Cognitive	10	158	0.93	0.57	10.65 (7.43)
Psychological	2	158	Too few items	Too few items	3.90 (2.17)
MFI					
Total score	20	161	0.90	0.31	58.9 (14.00)
General fatigue	4	160	0.72	0.39	14.1 (3.35)
Physical fatigue	4	161	0.72	0.39	14.5 (3.60)
Reduced activity	4	161	0.82	0.53	11.34 (4.08)
Reduced motivation	4	161	0.62	0.29	9.94 (3.42)
Mental fatigue	4	161	0.85	0.58	8.89 (3.90)
FSS					
Total score	9	145	0.92	0.57	4.8 (1.4)
PedsQL MF					
Total score	18	150	0.91	0.37	60.31 (16.41)
General fatigue	6	150	0.87	0.53	48.91 (19.57)
Sleep/rest	6	149	0.77	0.36	59.48 (18.99)
Cognitive fatigue	6	150	0.94	0.74	72.81 (21.64)
SMA-HI					
Fatigue	6	142	*Values not calculated due to missing subscale items*		56.95 (24.72)
Sleep	4	142			29.75 (26.42)

[a]Threshold of acceptability for Cronbach's $\alpha > 0.7$
[b]Range of acceptability for IIC: 0.15–0.50

evaluate current motor function by perceived fatigue levels, as variation and loss in motor functions exist across SMA types in all ages including adults. An additional limitation of this study pertains to the cohort of survey respondents. When considering how representative the sample is of the overall SMA adult population, it appears that this specific group of survey respondents (which includes a significant number of type I patients) may be healthier, older, and experiencing longer life with SMA and therefore potentially less significant perceived fatigue than the general adult SMA population. Natural history data indicate that survival among SMA type I is generally less than 2 years [11].

CONCLUSION

Fatigue is a significant factor in the lives of people living with SMA. Understanding the impact of fatigue upon patients' ability to live their lives to the fullest is important to help

Table 4 Factors associated with subscale fatigue score by instrument

	Reference category	Outcomes: coefficients and *p*-values																	
		Predictors of MFIS Score								Predictors of MFI Score									
		Physical		Cognitive		Psychosocial		Total		General		Physical		Reduced Activity		Reduced Motivation		Mental	
		Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|
Gender																			
Female	Male	1.37	0.29	0.87	0.50	− 0.34	0.38	1.90	0.45	0.53	0.39	− 0.96	0.11	− 1.20	0.11	− 0.33	0.59	− 0.54	0.46
Age at Time of Survey																			
Age (Continuous)		0.08	0.12	0.02	0.73	0.02	0.14	0.12	0.22	0.005	0.82	**0.05**	**0.02**	0.02	0.41	0.01	0.53	− 0.04	0.16
Race																			
Non-White	White	− 0.16	0.92	1.58	0.35	0.16	0.74	1.58	0.62	− 0.80	0.28	0.12	0.86	0.28	0.75	**2.00**	**0.01**	0.62	0.48
Income																			
$41,000-$100,000	≤ $40,000	− 2.66	0.09	− 2.52	0.10	− 0.82	0.07	**− 5.99**	**0.04**	− 1.23	0.09	− 0.32	0.65	− 0.99	0.24	− 0.41	0.56	− 1.60	0.06
≥ $101,000	≤ $40,000	− 2.55	0.21	− 0.93	0.66	− 0.50	0.41	− 3.99	0.31	**− 1.71**	**0.05**	− 0.86	0.30	− 0.73	0.47	− 0.68	0.43	− 0.66	0.52
Unknown	≤ $40,000	− 2.05	0.26	− 3.10	0.09	− 0.50	0.36	− 5.65	0.11	− 1.46	0.10	− 0.84	0.32	− 0.68	0.51	− 1.22	0.16	− 0.89	0.39
Education																			
Bachelor's	Associate's or less	− 0.78	0.60	0.57	0.71	− 0.42	0.36	− 0.63	0.83	− 0.27	0.68	− 0.92	0.16	**− 2.13**	**0.01**	**− 1.49**	**0.03**	− 0.20	0.80
Master's or higher	Associate's or less	− 0.71	0.65	0.53	0.74	0.12	0.80	− 0.06	0.98	− 1.05	0.16	− 1.07	0.14	**− 2.78**	**0.002**	− 0.97	0.19	− 0.38	0.67
Unknown	Associate's or less	1.12	0.88	6.78	0.37	− 1.43	0.52	6.48	0.65	0.69	0.79	− 0.43	0.86	− 0.36	0.90	0.003	0.81	4.26	0.16
SMA Type																			
Type II	Type I	− 0.70	0.80	**− 6.33**	**0.03**	− 0.04	0.97	− 7.06	0.19	1.24	0.25	0.49	0.64	0.58	0.65	0.640	0.55	− 0.11	0.93
Type III	Type I	0.26	0.93	**− 6.73**	**0.03**	0.15	0.87	− 6.33	0.27	1.56	0.17	0.22	0.84	0.46	0.73	1.000	0.37	− 0.33	0.81
Other/ Unknown	Type I	− 0.25	0.95	− 4.16	0.28	0.45	0.69	− 3.97	0.59	2.26	0.17	0.86	0.59	− 0.51	0.79	0.003	1.00	0.92	0.64

Table 4 continued

	Reference category	Outcomes: coefficients and *p*-values																	
		Predictors of MFIS Score								Predictors of MFI Score									
		Physical		Cognitive		Psychosocial		Total		General		Physical		Reduced Activity		Reduced Motivation		Mental	
		Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|
SMN2 Copy Number																			
3 copies	≤ 2 copies	2.39	0.20	**5.32**	**0.01**	0.27	0.63	**7.98**	**0.03**	1.20	0.17	1.06	0.22	1.43	0.18	1.570	0.08	1.10	0.30
4 or more copies	≤ 2 copies	− 1.36	0.59	4.54	0.08	0.02	0.97	3.20	0.51	− 0.23	0.82	− 0.42	0.66	1.34	0.25	0.120	0.90	0.81	0.49
Unknown	≤ 2 copies	1.43	0.44	**4.52**	**0.02**	0.69	0.22	6.64	0.07	1.06	0.23	0.35	0.67	1.50	0.15	1.580	0.07	1.29	0.21
Treated with SMA DMT																			
Treated	Untreated	**− 3.88**	**0.01**	**− 3.42**	**0.03**	− 0.60	0.20	**− 7.91**	**0.01**	− 0.36	0.61	**− 1.59**	**0.02**	− 1.09	0.20	− 0.54	0.45	− 0.32	0.71

	Reference category	Outcomes: coefficients and p-values											
		Predictors of FSS Score		Predictors of PedsQL Score								Predictors of SMAHI Score			
		Total		Total		General		Sleep/Rest		Cognitive		Fatigue		Sleep	
		Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	P >|z|
Gender															
Female	Male	− 0.04	0.88	2.52	0.38	4.25	0.22	2.63	0.44	0.81	0.83	− 4.01	0.34	2.68	0.52
Age at Time of Survey															
Age (Continuous)		0.010	0.52	0.06	0.60	− 0.03	0.79	**0.29**	**0.03**	− 0.08	0.61	0.160	0.27	− 0.05	0.73
Race															
Non-White	White	− 0.04	0.90	− 1.35	0.70	− 2.80	0.50	− 2.72	0.51	1.28	0.78	− 1.11	0.83	− 3.30	0.53
Income															
$41,000-$100,000	≤ $40,000	− 0.39	0.19	11.65	**0.001**	**10.78**	**0.01**	**9.43**	**0.02**	**14.13**	**0.002**	1.37	0.77	− 5.53	0.24
≥ $101,000	≤ $40,000	− 0.96	0.31	12.76	**0.004**	**10.24**	**0.05**	**13.02**	**0.01**	**14.43**	**0.01**	3.93	0.56	− 5.87	0.31
Unknown	≤ $40,000	− 0.70	0.06	11.95	**0.01**	8.04	0.13	**18.33**	**0.001**	8.77	0.14	− 4.53	0.45	− 6.55	0.28

Table 4 continued

	Reference category	Outcomes: coefficients and p-values													
		Predictors of FSS Score		Predictors of PedsQL Score								Predictors of SMAHI Score			
		Total		Total		General		Sleep/Rest		Cognitive		Fatigue		Sleep	
		Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	*P* >|*z*|	Coef	P >|z|
Education															
Bachelor's	Associate's or less	− 0.08	0.79	2.38	0.47	4.80	0.22	− 0.07	0.99	1.91	0.67	− 2.83	0.56	− 6.73	0.16
Master's or higher	Associate's or less	− 0.47	0.15	3.25	0.34	5.79	0.16	4.65	0.26	− 0.82	0.86	− 6.19	0.22	− 7.53	0.13
Unknown	Associate's or less	1.62	0.26	− 24.53	0.14	− 36.49	0.06	0.38	0.98	− 37.08	0.09	− 12.82	0.57	− 2.25	0.92
SMA Type															
Type II	Type I	**1.24**	**0.03**	− 1.88	0.75	− 12.32	0.08	2.35	0.73	4.29	0.58	2.63	0.78	5.49	0.55
Type III	Type I	**1.44**	**0.02**	− 9.15	0.14	**− 20.09**	**0.01**	− 4.79	0.52	− 2.32	0.78	6.83	0.47	5.30	0.56
Other/Unknown	Type I	1.06	0.23	− 3.89	0.65	− 11.10	0.28	7.74	0.45	− 8.91	0.44	6.06	0.62	4.47	0.71
SMN2 Copy Number															
3 copies	≤ 2 copies	0.61	0.11	4.11	0.33	4.15	0.41	5.16	0.30	2.70	0.63	10.24	0.09	2.37	0.69
4 or more copies	≤ 2 copies	0.12	0.80	2.67	0.63	7.69	0.25	1.89	0.77	− 1.95	0.79	− 0.14	0.98	− 2.23	0.74
Unknown	≤ 2 copies	0.14	0.73	6.79	0.11	9.36	0.07	4.38	0.39	6.55	0.25	1.65	0.78	− 1.43	0.81
Treated with SMA DMT															
Treated	Untreated	− 0.50	0.12	6.55	0.06	**8.07**	**0.05**	3.50	0.39	7.46	0.10	**− 10.17**	**0.05**	− 7.26	0.15

focus efforts by the SMA community to reduce the burden of this disease. This effort by Cure SMA marks a step in the direction of developing this evidence base and defining a roadmap for progress. That said, to develop a more definitive understanding of how adult SMA patients perceive fatigue, it would be useful to develop a detailed, SMA-specific fatigue scale that could effectively tease out differences across subgroups within the SMA patient population as well as treatment effects. Of the five instruments used in this survey, only one was specific to the SMA population. Further, even that one instrument was not a complete tool focused on fatigue but rather the two modules from a broader survey aimed at assessing a variety of aspects of living with SMA. Further analysis of the data from this study is being contemplated to better understand the similarities and differences of specific tools and which items best represent perceived fatigue in the SMA population. These efforts are especially important to advance improved quality of life as more patients' lives are extended well into adulthood with the development and approval of effective disease-modifying therapies.

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Data Availability. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Jill Jarecki is currently an employee of BioMarin Pharmaceuticals and was an employee of Cure SMA at the time of this study. Lisa Belter and Ilse Peterson declare that they have no competing interests.

Ethical Approval. Institutional review board (IRB) approval was obtained from Western IRB on November 24, 2020 (IRB ID: 20203852). Consent was assumed from a respondent's survey participation. The study was performed in accordance with the Helsinki Declaration of 1964.

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