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Remaining Burden of Spinal Muscular Atrophy Among Treated Patients: A Survey of Patients and Caregivers

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ABSTRACT

Objective: Spinal muscular atrophy (SMA) significantly impacts motor function. This study aimed to assess the persistent burden and unmet needs among currently treated patients with SMA and their caregivers.

Methods: Two complementary web-based surveys were distributed in August 2024 among patients with SMA and their caregivers. Non-ambulant patients with SMA currently receiving risdiplam or nusinersen, and/or their primary, informal caregivers were eligible to participate. Survey modules captured clinical, humanistic, productivity, and caregiver-related burden of disease. The PROMIS Fatigue and EQ-5D-5L were used to assess fatigue and quality of life.

Results: 40 pediatric (mean age 8.3 years; represented by caregiver proxies) and 68 adult patients (mean age 37.5 years) were included, of which the majority were on SMN-targeted treatment for ≥2 years (82.5% and 94.1%, respectively), and nearly half were on treatment for ≥4 years. Despite continued treatment, muscle weakness was reported in 95% of pediatric and 100% of adult patients, with 63% of pediatric and 68% of adult patients reporting "severe" or "very severe" muscle weakness that substantially impacted motor function and performance of activities of daily living. Increased fatigue and muscle weakness were associated with worse overall health. Findings also demonstrated impacts of SMA on patient quality of life and well-being. Most participants reported mobility limitations and muscle weakness as being least improved by current treatment.

Interpretation: Despite the use of current treatments, there remains a significant burden of SMA on patients and their caregivers. Muscle weakness and mobility limitations remain key areas of unmet need.

1 | Introduction

Spinal muscular atrophy (SMA) is a genetic condition characterized by the degeneration of motor neurons, progressive weakness, and skeletal muscle atrophy with an incidence of approximately 1 in every 10,000–15,000 live births [1–4]. Traditionally, SMA has been classified into types based on age of onset, motor milestones, and the number of survival motor neuron 2 (*SMN2*) gene copies. However, in the era of widespread use of SMN-targeted treatments, SMA classification has moved toward characterization by functional status, with patients categorized as non-sitters, sitters, or walkers [5].

SMA imposes a substantial clinical burden; typical patients present with hypotonia and muscle weakness, which significantly impact mobility, motor function, and fatigue levels [6]. The overall burden of disease is greatly attributed to its debilitating impact on patients' functional abilities and limitations

when performing activities of daily living [6, 7]. Outside of the newborn period, SMA typically impacts lower limbs first and advances to upper limbs, progressively limiting the patient's overall mobility and function [6]. As children with SMA reach and exceed the age of expected mobility milestones, this translates into increased use of assistive devices, caregiving needs, and limited personal autonomy [8, 9].

In addition to physical impacts, SMA imposes a considerable psychological burden on patients, with fear of physical decline and premature death being reasons for significant emotional challenges [9, 10]. Further, physical limitations from SMA and the need for frequent medical care may limit the ability of individuals with SMA to maintain regular attendance at school or work [11]. This can result in lost productivity and absenteeism—when an individual has to take time off from work or school—for both pediatric and adult patients and their caregivers [12–14]. Among adult patients, SMA may also result in presenteeism—when an individual is at work but cannot complete their work responsibilities—limited employment opportunities, or the inability to work at all.

Onasemnogene abeparvovec (OA), nusinersen, and risdiplam are three treatments currently available for individuals with SMA [15]. OA is a one-time gene therapy approved for the treatment of pediatric patients less than 2 years of age. Nusinersen and risdiplam are currently available for patients from newborn through adulthood. These treatments have been shown to slow the natural progression of the disease and improve motor function [16, 17]. However, the benefits of these treatments may potentially reach a ceiling or lessen over time, and the long-term impact of these treatments remains uncertain [16–18]. Further, the relationship between improved functional abilities and amelioration of SMA-related muscle weakness and fatigue is not well established, making it difficult to understand the remaining burden of disease in patients undergoing treatment [19–21]. To gain a better understanding of these relationships, we conducted a survey of patients with SMA in the US currently being treated with SMN-targeted treatments and their caregivers. Our objective was to assess the remaining clinical, humanistic, and productivity burden for these patients and to identify areas of unmet need.

2 | Methods

2.1 | Study Design and Population

To quantify and describe the remaining burden in SMA among patients currently receiving SMN-targeted treatments and primary informal caregivers of these patients, we conducted an online cross-sectional survey from July 31, 2024, to August 27, 2024, using two distinct but complementary survey instruments. One survey was designed for self-reporting in patients with SMA. The other was designed for caregivers, who served as proxy respondents for the patient while also reporting on the burden of SMA they experience themselves. Recruitment was facilitated by a patient advocacy organization (Cure SMA). Potential participants were identified within Cure SMA's network of patients and caregivers through an email outreach to their constituents containing a brief overview of the survey and a link to the survey screener. Recruitment and data collection were conducted in a double-blind manner, such that the identities of the respondents were not revealed to the study sponsor or research team, and the identity of the study sponsor was not revealed to respondents until after the survey was completed.

Patients were eligible to participate if they self-reported an SMA diagnosis, were non-ambulant, were currently receiving risdiplam or nusinersen, were never enrolled in an anti-myostatin or neuromuscular junction specific treatment clinical trial, were at least 12 years of age, and were English-speaking US residents. Participants were asked to report any previous treatment history with OA. Informal (unpaid, untrained) caregivers were eligible to participate if they reported currently being the primary caregiver of a patient diagnosed with SMA, who met the same baseline eligibility criteria of patient participants, regardless of patient age. Additionally, caregivers were required to report providing over 10 h of help per week on average to the patient with SMA and be US residents at least 18 years of age. Patient and caregiver members of the same household were considered a dyad. Members of a dyad completed their respective surveys and were flagged for analytical purposes.

Eligible adult patients and caregiver participants were required to provide informed consent electronically prior to completing the survey. Patients below the age of majority (i.e., <18 years, or <19 years in Nebraska and Alabama or <21 years in Mississippi) were required to have a parent provide informed consent and to provide assent to participate. Patients and caregivers who did not meet the specified inclusion criteria or did not provide consent were excluded from the study. All study documents were processed through a complete ethics review by an independent Institutional Review Board organization (Advarra) and approval was granted prior to recruitment initiation. Survey programming and online hosting were facilitated through a third-party research vendor (Sago) which tracked recruitment progress and managed data collection.

2.2 | Survey Instrument

The patient survey instrument included an eligibility screener and five modules to capture aspects related to clinical, productivity, and humanistic burden, unmet needs, and respondent background clinical and demographic characteristics. The caregiver survey included the same modules with adapted language for proxy completion and an additional module to assess caregiver-specific burden. Outcomes related to fatigue and quality of life were assessed for both patients and caregivers using validated instruments.

2.2.1 | PROMIS Fatigue

To characterize perceived fatigue among patients living with SMA, the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form (SF) instrument was used [22, 23]. Adult patients (≥ 18 years) completed the self-report Fatigue—SF 10a, while adolescent patients (12–17 years) completed the self-report Pediatric Fatigue—SF 10a. Caregivers of patients aged 5–17 years completed the Parent

Proxy Fatigue—SF 10a (v2). The Parent Proxy Fatigue—SF 10a has only been validated for parents of children aged 5–17 years; thus, caregivers of children < 5 or > 17 in the study sample did not complete this measure. The instruments include a series of 10 questions using a 5-point Likert scale to assess a range of symptoms, including feelings of tiredness and its impact on completing tasks and participating in activities over the past 7 days. Raw scores were converted to standardized T-scores according to PROMIS Fatigue scoring guidelines [24]. Higher scores indicate worse health, with cutoff definitions for each level of fatigue varying based on the version of the form: adult patients (< 55 within normal limits, 55–60 mild, 60–70 moderate, > 70 severe); proxy form used by parents (< 50 within normal limits, 50–55 mild, 55–65 moderate, > 65 severe).

2.2.2 | EQ-5D-5L

To assess quality of life, the EuroQoL Five Dimension Five Level Scale (EQ-5D-5L) was used [25]. The EQ-5D-5L is a widely used general measure of health consisting of two parts. The first part includes a short five-item questionnaire that assesses health across five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) using five levels of responses (1) no problems; (2) slight problems; (3) moderate problems; (4) severe problems; (5) unable to/extreme problems. Assessed together, the scores across all five dimensions create a health state that can then be converted into a summary index score based on a country-specific (United States) reference value set [26]. Higher index scores indicate higher quality of life and can range from less than 0 (where 0 is the value of a health state equivalent to dead; negative values represent an experience worse than death) to 1 (the value of full health). The second part includes a visual analogue scale (VAS) where the respondent rates their perceived overall health on a scale from 0 (the worst imaginable health) to 100 (the best imaginable health). Patients and caregivers self-completed the EQ-5D-5L to assess their own quality of life and overall health. Additionally, caregivers completed the proxy version of the EQ-5D-5L to assess the quality of life of the patient they care for.

2.3 | Statistical Analysis

Descriptive analyses were conducted on all variables collected in the surveys. Continuous variables were summarized using measures of central tendency (i.e., means, medians, standard deviation, ranges) and categorical or dichotomous variables were summarized using frequencies and percentages. Survey data cleaning, management, and analysis were conducted using SAS 9.4. Patient self-report and caregiver proxy data were analyzed independently, and results are reported separately for pediatric (< 18 years old) and adult patients (≥ 18 years old).

Differences in overall health (EQ-VAS/EQ-VAS proxy scores) were assessed by patients' levels of fatigue (PROMIS/PROMIS proxy T-scores) and reported severity of muscle weakness using Student's *t*-tests. *P*-values were reported, with statistical significance defined as $p < 0.05$. Overall health was compared between patients with mild or less fatigue, defined by standardized PROMIS Fatigue cut points as a T-score < 55 for pediatric patients or a T-score < 60 for adult patients, and those with moderate-to-severe fatigue, defined as a T-score > 55 for pediatric patients or a T-score > 60 for adult patients [24]. Muscle weakness severity was self- or proxy-reported on a scale from "not at all severe" to "very severe". Overall health was compared across patients with "moderate" or "less" muscle weakness (i.e., "not at all severe", "mild", or "moderate") and those with "severe" or "very severe" muscle weakness. In addition, dyad respondent data was assessed to qualitatively describe any differences observed in patient and caregiver proxy responses.

3 | Results

3.1 | Respondent Characteristics

Following the distribution of the study survey, a total of 183 patients and 192 caregivers responded. Of these respective patients and caregivers, 72 and 61 did not meet the eligibility criteria, preventing them from moving forward with the survey, while 40 patients and 81 caregivers failed to complete the survey. A total of 71 eligible patients ($n = 3$ pediatric, $n = 68$ adults) and 50 eligible caregivers ($n = 40$ caregivers of pediatric patients, $n = 10$ caregivers of adult patients) completed the survey, 10 of which were dyad pairs. To avoid double-counting and mixing caregiver proxy and patient self-reported data, patient-related results focus on the 40 pediatric patients, represented by caregiver proxies (mean age = 8.3 years) and 68 self-reporting adult patients (mean age = 37.5) (Table 1). Table S1 includes a brief overview of the patient-related background and clinical characteristics for the $n = 3$ pediatric self-reporting patients and $n = 10$ adult patients represented by caregiver proxies.

All patients were reportedly receiving SMN-targeted treatments and 27.5% of pediatric patients had reportedly previously received gene therapy in addition (Table 2). Among pediatric patients, 37.5% and 62.5% were reportedly taking nusinersen and risdiplam, respectively, as compared to 51.5% and 48.5% of adult patients. Most pediatric and adult patients received SMN-targeted treatment for ≥ 2 years (82.5% and 94.1%, respectively), and nearly half received treatment for ≥ 4 years (45.0% and 48.5%, respectively). Table S2 includes additional patient characteristics.

Caregiver burden-related results include the $n = 40$ caregivers of pediatric patients and $n = 10$ caregivers of adults.

3.2 | Muscle Weakness

The majority of caregivers of pediatric patients (62.5%) and adult patients (67.7%) described muscle weakness as "severe" or "very severe" (Figure 1). On a scale of 1–10, where 10 is "completely because of muscle weakness", caregivers of pediatric patients and adult patients strongly attributed the patients' difficulties in performing daily activities to muscle weakness (mean = 7.7 and 7.7, respectively) (Table 3). Similarly, limitations experienced in motor function were highly attributed to muscle weakness (mean = 7.8 and 8.3, respectively). On average, muscle strength was described as generally stable throughout the day (Table S3). At least one-third of respondents reported that muscle weakness

TABLE 1 | Patient background and clinical characteristics.

	Pediatric patients (<18 years old; caregiver proxy)	Adult patients (≥18 years old; self-reported)
	***n* = 40**	***n* = 68**
Age, mean (SD)	8.3 (4.9)	37.5 (12.1)
Range	[<1–17]	[19–68]
Sex, *n* (%)		
Male	17 (42.5)	23 (33.8)
Female	23 (57.5)	45 (66.2)
Type of SMA, *n* (%)		
Type I	23 (57.5)	2 (2.9)
Type II	16 (40.0)	42 (61.8)
Type III	1 (2.5)	24 (35.3)
Age at SMA diagnosis, *n* (%)		
Less than 6 months	21 (52.5)	0 (0.0)
6–11 months	7 (17.5)	4 (5.9)
1–5 years	9 (22.5)	51 (75.0)
6–10 years	1 (2.5)	5 (7.4)
Older than 10 years	2 (5.0)	8 (11.8)
Ever received genetic testing for SMA, *n* (%)		
Yes	38 (95.0)	59 (86.8)
No	1 (2.5)	4 (5.9)
Don't know/not sure	1 (2.5)	5 (7.4)
Number of *SMN2* copies, *n* (%)[a]	*n = 38*	*n = 59*
1	3 (7.9)	2 (3.4)
2	20 (52.6)	8 (13.6)
3	12 (31.6)	25 (42.4)
4	0 (0.0)	9 (15.3)
5 or more	0 (0.0)	1 (1.7)
Don't know/not sure	3 (7.9)	14 (23.7)

Note: All patients were reportedly non-ambulant (cannot walk without using any help or aids).
[a]Only asked to those who previously selected yes to having received genetic testing.

impacts the patient's ability to hold their head upright, eat, communicate, breathe, and participate in daily activities (Figure S1).

3.3 | Fatigue

The adjusted mean T-score for pediatric patients was 59.9, indicating moderate levels of fatigue (defined as 55–65, PROMIS Fatigue parent proxy). Adult patients on average scored within the limits of mild fatigue (defined as 55–60, PROMIS Fatigue adult self-report) with an average T-score of 56.5 (Table 3). On average, respondents moderately attributed the limitations experienced in daily activities and motor function to the patient feeling fatigued. Caregivers also indicated that pediatric patients experience increasingly higher levels of fatigue as the day progresses, while self-reported fatigue levels among adult patients did not vary greatly throughout the day (Table S3). In addition, for at least 20% of patients, fatigue was reported to impact the patient's ability to hold their head upright, eat, communicate, breathe, and participate in daily activities (Figure S2).

3.4 | Association Between Muscle Weakness and Fatigue and Overall Health

Among pediatric patients, overall health was reportedly lower among those indicating "severe" or "very severe" muscle weakness (mean EQ-VAS = 67.6) compared to those with "moderate"

TABLE 2 | Patient SMA treatment history.

	Pediatric patients (<18 years old; caregiver proxy)	Adult patients (≥18 years old; self-reported)
	n **= 40**	***n*** **= 68**
Treatment history, *n* (%)		
Risdiplam (Evrysdi)		
Never taken	13 (32.5)	27 (39.7)
Taken in the past, but not currently	2 (5.0)	8 (11.8)
Currently taking	25 (62.5)	33 (48.5)
Nusinersen (Spinraza)		
Never taken	9 (22.5)	13 (19.1)
Taken in the past, but not currently	16 (40.0)	20 (29.4)
Currently taking	15 (37.5)	35 (51.5)
Length of time taking risdiplam (Evrysdi), *n* (%)[a]	*n = 25*	*n = 33*
Less than 6 months	2 (8.0)	0 (0.0)
6 months to less than 1 year	3 (12.0)	0 (0.0)
1 year to less than 2 years	0 (0.0)	1 (3.0)
2 years to less than 3 years	7 (28.0)	6 (18.2)F
3 years to less than 4 years	7 (28.0)	22 (66.7)
4 years or more	6 (24.0)	4 (12.1)
Length of time taking nusinersen (Spinraza), *n* (%)[a]	*n = 15*	*n = 35*
Less than 6 months	2 (13.3)	1 (2.9)
6 months to less than 1 year	0 (0.0)	1 (2.9)
1 year to less than 2 years	0 (0.0)	1 (2.9)
2 years to less than 3 years	1 (6.7)	1 (2.9)
3 years to less than 4 years	0 (0.0)	2 (5.7)
4 years or more	12 (80.0)	29 (82.9)
History of gene therapy (onasemnogene abeparvovec/ Zolgensma), *n* (%)		
Yes	11 (27.5)	0 (0.0)
No	29 (72.5)	68 (100.0)
Age received onasemnogene abeparvovec (Zolgensma), *n* (%)[b]	*n = 11*	*n = 0*
Less than 6 months	3 (27.3)	N/A
6–12 months	4 (36.4)	N/A
13–18 months	2 (18.2)	N/A
19–24 months	1 (9.1)	N/A
Other	1 (9.1)	N/A

[a]Only asked to those who previously selected currently taking risdiplam or nusinersen respectively.
[b]Only asked to those who previously selected having received onasemnogene abeparvovec.

or less muscle weakness (mean EQ-VAS = 76.6), this difference was not statistically significant ($p = 0.127$, Table S4). Among adult patients, those who indicated current "severe" or "very severe" muscle weakness reported significantly worse overall health than those with "moderate" or less muscle weakness (mean EQ-VAS = 59.1 and 76.3, respectively; $p = 0.001$). Pediatric and adult patients with moderate-to-severe fatigue according to the PROMIS Fatigue scale had significantly worse overall health compared to those with mild or less fatigue ($p = 0.049$ and $p < 0.001$, respectively).

3.5 | Activities of Daily Living

Overall, pediatric and adult patients most valued being able to complete activities requiring fine motor skills independently, including using their hands (77.5% and 82.4%, respectively), using their fingers (72.5%, 82.4%), using everyday tools with push buttons (85.0%, 76.5%), and holding a cup and drinking from it (50.0%, 58.8%) (Figure 2). Nearly half of caregivers (45.0%) indicated the ability to sit on the floor independently with no back support as highly valued by pediatric patients. Adult patients more frequently reported valuing the ability to independently perform activities related to personal hygiene, including brushing their teeth (57.4%), getting dressed (39.7%), and cleaning themself after going to the bathroom (35.3%). For both pediatric and adult patients, independent performance of mobility-related activities was generally regarded as least important. Moreover, while some pediatric and adult patients reportedly were able to perform select activities of daily living on their own or easily with help, other activities were generally reported as being more difficult or impossible to do, even with help, particularly activities like getting dressed and mobility-related activities such as getting in and out of bed (Figures S3 and S4).

3.6 | Humanistic Burden

The EQ-5D-5L was used to measure the patient's quality of life and overall health (Table 3). Pain or discomfort was reported in

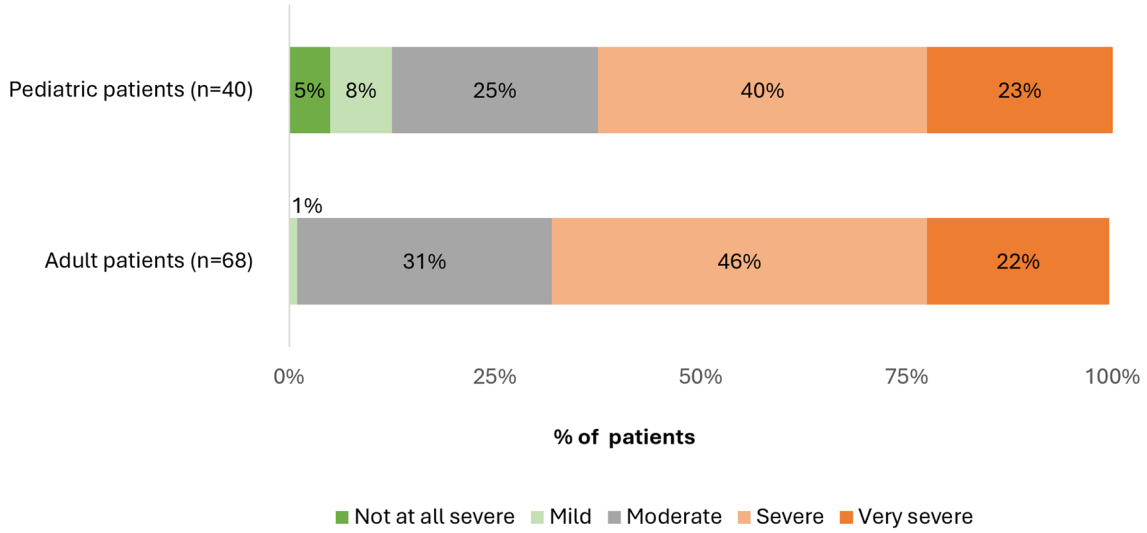

FIGURE 1 | Severity of muscle weakness experienced by pediatric ($n = 40$) and adult patients ($n = 68$). Pediatric patient data was reported by caregiver proxies. Adult patient data was self-reported.

most pediatric and adult patients (67.5% and 83.8% respectively). The majority of pediatric patients were described as having "no problems" with anxiety or depression (60.0%), whereas the majority of adult patients reported at least some level (72.1%). The average health index score, derived from the scores across all five health dimensions, for pediatric and adult patients was 0.19 and 0.20, respectively (range: less than 0–1, where 1 is the value of full health). According to the EQ-VAS, caregivers of pediatric patients on average rated the patient's overall health as 71.0 on a scale of 0–100 (where 100 is the best health imaginable), while adult patients on average rated their health as 64.7.

Respondents were also asked to indicate the most burdensome impacts of living with SMA. The top three most frequently reported for both pediatric and adult patients included difficulties performing daily activities independently (85.0% and 91.2%, respectively), followed by limited physical functioning (75.0%, 64.7%), and limited ability to participate in social activities (72.5%, 63.2%) (Figure 3). Patients and caregivers were also asked to briefly imagine and describe a scenario where these most burdensome impacts disappeared. Respondents repeatedly cited how this disappearance would result in greater quality of life, improved independence, improved social life and acceptance, an enhanced ability to navigate the world, and less stress, anxiety, and depression. Additionally, it was frequently reported that both pediatric and adult patients lower their expectations or goals, accomplish less than they would like, and experience feelings of being overwhelmed due to SMA (Table S3).

3.7 | Productivity Burden

School and work-related impacts of SMA were assessed among patients currently enrolled in school or who were currently employed (Table 4). Pediatric patients currently enrolled in school ($n = 34$) were reported to have missed an average of 9.6 days (SD = 10.2) of school in the past 90 days due to SMA-related health issues, whereas adult patients enrolled in school ($n = 9$) described missing an average of 1.0 day (SD = 2.4). Over half of adult patients were employed either full-time (36.8%) or part-time (22.1%). Employed adult patients ($n = 40$) reported missing, on average, 2.0 days (SD 3.4) of work in the last 90 days due to SMA. Among most patients who reported being enrolled in school or currently employed, SMA-related health problems were associated with at least some impact on school or work performance. However, most still rated their overall ability to perform as "good" or "very good".

3.8 | Unmet Need

Among both pediatric and adult patients, mobility limitations (75.0% and 69.1%, respectively) and muscle weakness (52.5%, 55.9%) were the most common aspects of SMA cited as being least improved by the patient's current treatment (Figure 4). Additionally, among pediatric patients, nutritional challenges (42.5%), fatigue (40.0%), and pain/discomfort (30.0%) were frequently reported as being least improved. Among adult patients, fatigue (45.6%), pain/discomfort (39.7%), and psychological/mental and emotional impacts (36.8%) were frequently reported as being least improved. For each of these least improved items, respondents were asked to rate how much that aspect impacted the patient's quality of life (Figure S5). Muscle weakness was reported to have "very much" of an impact on the patient's quality of life by 57.1% of caregivers of pediatric patients and 42.1% of adult patients. Similarly, 56.7% of caregivers of pediatric patients and 42.2% of adults noted mobility limitations had "very much" of an impact on the patient's quality of life.

3.9 | Caregiver Burden

Caregiver-related characteristics are reported in Table 5. In addition to serving as patient proxies, caregivers were asked to self-report on the burden of caregiving, including their quality of life and impacts on their employment.

TABLE 3 | Patient clinical burden and quality of life.

	Pediatric patients (<18 years old; caregiver proxy)	Adult patients (≥18 years old; self-reported)
	n **= 40**	***n*** **= 68**
PROMIS Fatigue score, mean (SD)[a]	59.9 (9.6) [*n* = 32]	56.5 (6.5)
Limitations in daily activities attributed to fatigue (scale 1–10), mean (SD)[b]	4.8 (2.4)	4.8 (2.3)
Limitations in motor function attributed to fatigue (scale 1–10), mean (SD)[b]	4.8 (2.6)	4.0 (2.6)
Limitations in daily activities attributed to muscle weakness (scale 1–10), mean (SD)[c]	7.7 (2.4)	7.7 (2.5)
Limitations in motor function attributed to muscle weakness (scale 1–10), mean (SD)[c]	7.8 (2.4)	8.3 (2.4)
EQ-5D health state index score, mean (SD)	0.19 (0.19)	0.20 (0.21)
EQ-5D, *n* (%)		
Mobility		
No problems walking	0 (0.0)	0 (0.0)
Slight problems walking	0 (0.0)	0 (0.0)
Moderate problems walking	0 (0.0)	1 (1.5)
Severe problems walking	3 (7.5)	2 (2.9)
Unable to walk	37 (92.5)	65 (95.6)
Self-care		
No problems washing/dressing	0 (0.0)	3 (4.4)
Slight problems washing/dressing	2 (5.0)	5 (7.4)
Moderate problems washing/dressing	3 (7.5)	7 (10.3)
Severe problems washing/dressing	7 (17.5)	7 (10.3)
Unable to wash/dress myself	28 (70.0)	46 (67.7)
Usual activities		
No problems doing usual activities	3 (7.5)	13 (19.1)
Slight problems doing usual activities	8 (20.0)	22 (32.4)
Moderate problems doing usual activities	9 (22.5)	24 (35.3)
Severe problems doing usual activities	10 (25.0)	6 (8.8)
Unable to do usual activities	10 (25.0)	3 (4.4)
Pain/discomfort		
No pain/discomfort	13 (32.5)	11 (16.2)
Slight pain/discomfort	18 (45.0)	29 (42.7)
Moderate pain/discomfort	9 (22.5)	21 (30.9)
Severe pain/discomfort	0 (0.0)	6 (8.8)
Extreme pain/discomfort	0 (0.0)	1 (1.5)
Anxiety/depression		
Not anxious/depressed	24 (60.0)	19 (27.9)

(Continues)

TABLE 3 | (Continued)

	Pediatric patients (<18 years old; caregiver proxy)	Adult patients (≥18 years old; self-reported)
	n **= 40**	***n*** **= 68**
Slightly anxious/depressed	9 (22.5)	25 (36.8)
Moderately anxious/depressed	5 (12.5)	16 (23.5)
Severely anxious/depressed	2 (5.0)	7 (10.3)
Extremely anxious/depressed	0 (0.0)	1 (1.5)
EQ VAS, mean (SD)[d]	71.0 (20.3)	64.7 (20.9)

[a]The PROMIS Proxy Fatigue measure for caregivers was only administered to participants who cared for an individual aged 5–17 years ($n = 32/40$). Raw scores were rescaled to standardized T-scores. Lower scores indicate better health, and higher scores indicate worse health. PROMIS T-Score cut points for adult patients: < 55 within normal limits; 55–60 mild; 60–70 moderate; > 70 severe. Standardized PROMIS T-Score cut points for parent proxy v2.0: < 50 within normal limits; 50–55 mild; 55–65 moderate; > 65 severe.
[b]Scale from 1 to 10, where 1 = not at all because of feeling fatigued and 10 = completely because of feeling fatigued.
[c]Scale from 1 to 10, where 1 = not at all because of muscle weakness and 10 = completely because of muscle weakness.
[d]The EQ VAS is a 0–100 scale where participants are asked to indicate their overall health on the day of questionnaire completion: 0 = worst health imaginable, 100 = best health imaginable.

Caregivers completed the EQ-5D-5L to measure their own quality of life and overall health (Table 5). Most caregivers of pediatric and adult patients indicated having at least some level of anxiety/depression (70.0% and 90.0%, respectively). Mean health index scores among caregivers of pediatric and adult patients were 0.81 and 0.75, respectively (where 1 is the value of full health) and mean EQ-VAS scores were 80.9 and 68.3, respectively (where 100 is the best health imaginable).

Caregivers of pediatric patients frequently noted that caring for a patient with SMA resulted in needing to reduce work hours (50%) or that they stopped working all together (37.5%) (Table 6). Those who reduced their work hours did so by nearly half, on average (42.3 to 24.3 h per week). Among caregivers of adult patients, 60.0% reported needing to stop working and 20.0% had to reduce their work hours. Moreover, most caregivers reported spending "less" or "a lot less" time on volunteer activities and chores since becoming a caregiver for a patient with SMA (Table S6). Among caregivers who were currently employed, the majority cited SMA-related health problems as having at least some impact on their ability to perform at work, however, most still rated their ability to perform at work as "good" or "very good".

3.10 | Comparison of Patient and Caregiver Dyad Responses

Data from patient and caregiver dyads ($n = 10$ pairs) were collected to provide insight into the level of convergence and divergence in reported perceptions and experiences of patients living with SMA. Two of the dyads involved patients < 18 years old, while the remaining 8 dyads involved adult patients. Divergence between patient and caregiver dyads was analyzed. Among dyads, patients more frequently reported fatigue as having a higher impact on daily activities and motor function, whereas caregiver proxies cited muscle weakness as having a higher impact. Patients more frequently reported valuing getting dressed and cleaning themselves after going to the bathroom independently compared to caregiver proxies. Caregivers more frequently indicated holding and drinking from a cup, brushing teeth, and washing hands as valuable to the patient. Patients also rated their overall health (EQ-VAS) as better than it was rated by caregivers.

4 | Discussion

Our findings revealed that despite current treatment with SMN-targeted treatment, there remains a significant residual burden and unmet need among patients with SMA, particularly related to muscle weakness impacting patients' motor function, ability to perform daily activities, and overall health. Notably, muscle weakness and mobility limitations were reported as least improved by the current treatments. The most burdensome symptoms cited among patients, along with the activities they most valued being able to perform independently, were closely linked to issues of muscle weakness. This underscores the critical need to focus on improving muscle strength as a key component of SMA treatment and management. Moreover, our findings demonstrated the impacts of SMA on patient quality of life and activities of daily living, further emphasizing the ongoing challenges faced by these patients and the need to manage muscle weakness and fatigue more effectively.

Interestingly, while most patients indicated having significant muscle weakness, fatigue levels were lower than expected. According to the PROMIS Fatigue standardized scaling for the proxy and adult versions [24], mean PROMIS scores fell within the moderate range (55–65) among pediatric patients (mean score: 59.9) and within the mild range (55–60) among adult patients (mean score: 56.5). Adult scores were only slightly higher than what is considered the normal limit range (< 55). Similarly, in Cure SMA's 2019 survey, PROMIS Fatigue scores ranged from 55 to 59 depending on SMA type and functional milestones [10]. Observation of lower than expected levels of fatigue may be due to the fact that the PROMIS Fatigue scale is a generic instrument that is not specifically designed for use in SMA and thus may not be suited to detect the nuances of fatigue within the context of SMA, potentially resulting in an under-representation of fatigue [27]. Their experience of fatigue may also be reduced by intentional limiting of their activities.

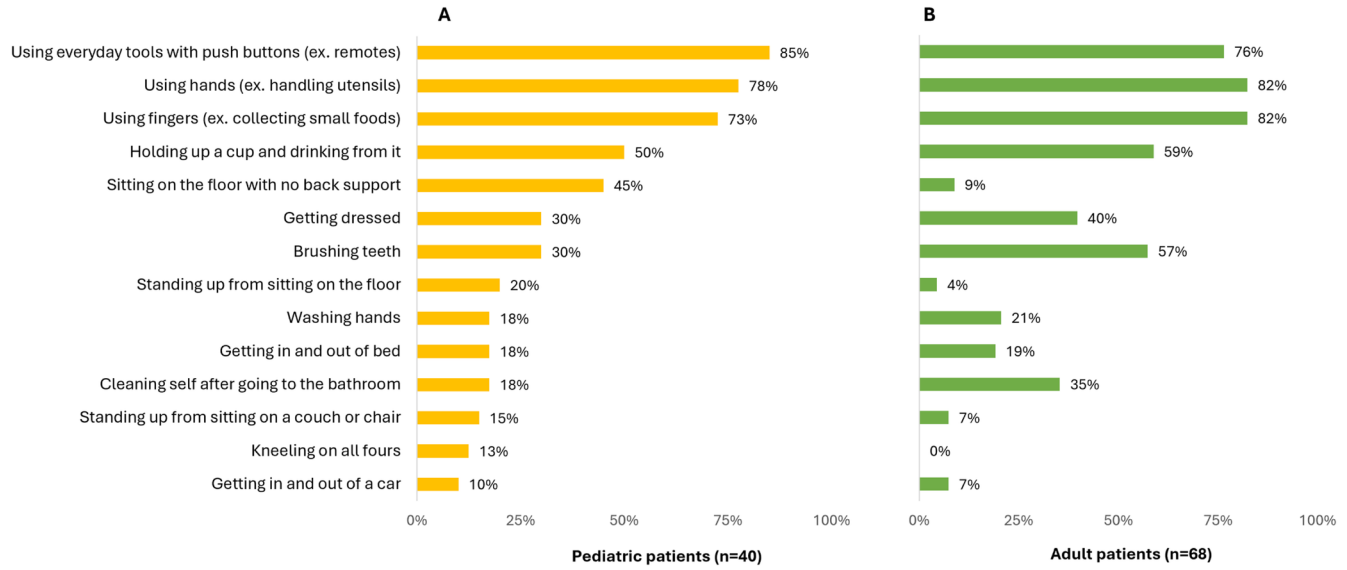

FIGURE 2 | Activities patients value most in terms of being able to do independently: (A) Pediatric patients ($n = 40$), (B) Adult patients ($n = 68$). Pediatric patient data was reported by caregiver proxies. Adult patient data was self-reported. Participants were asked to select the top 5 activities the patient valued/caregivers thought the patient with SMA valued the most.

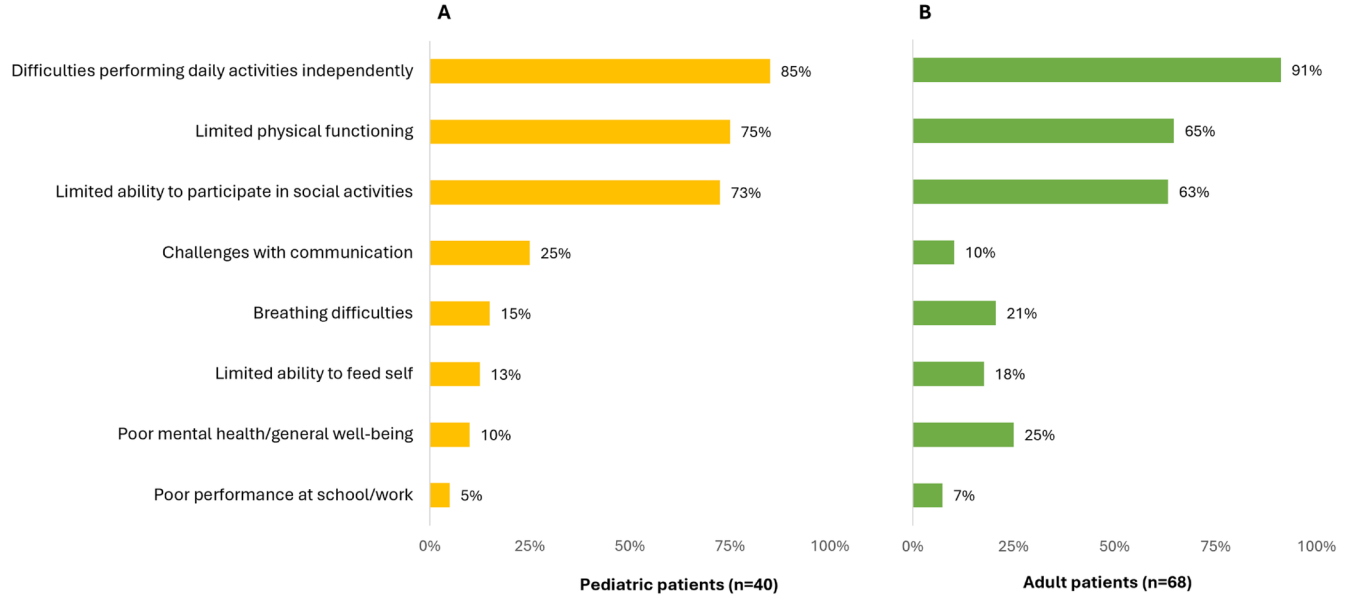

FIGURE 3 | Most burdensome impacts of SMA: (A) Pediatric patients ($n = 40$), (B) Adult patients ($n = 68$). Pediatric patient data was reported by caregiver proxies. Adult patient data was self-reported. Participants were asked to select the three impacts the patient considered/caregivers thought the patient with SMA considered to be the most burdensome.

The EQ-5D-5L and the respective proxy version, was used to assess quality of life, overall health, and utility. Most adult patients reported some level of anxiety or depression, highlighting the significant burden that SMA has on mental health. We observed similar health utility scores for pediatric patients (mean index score = 0.19) and adult patients (mean index score = 0.20), while overall health was slightly higher on average among pediatric patients (mean EQ-VAS = 71.0) compared to adults (mean EQ-VAS = 64.7). Additionally, results from our study reflected variation in reported overall health by muscle weakness and fatigue. Specifically, higher severity of muscle weakness and fatigue was associated with poorer reported levels of overall health, further highlighting the importance of addressing these key symptoms of SMA.

Utility and overall health estimates were generally in line with previous studies in SMA [28–35]. While several previous studies have reported EQ-5D utility and EQ-VAS estimates for patients with SMA, evidence for pediatric patients and patients in the US is limited, underscoring the importance of the findings from this current study. In this study, utility and overall health among both pediatric and adult patients with SMA were lower than the normative US population (mean index score = 0.85; mean EQ-VAS = 80.4), highlighting the significant impacts of SMA despite

TABLE 4 | Patient productivity burden.

	Pediatric patients (<18 years old; caregiver proxy)	Adult patients (≥18 years old; self-reported)
	n **= 40**	***n*** **= 68**
School enrollment, *n* (%)		
Public or private school	30 (75.0)	9 (13.2)
Home school	4 (10.0)	0 (0.0)
Not currently enrolled in any type of schooling	6 (15.0)	59 (86.8)
Number of days of school/class missed due to SMA-related health problems in the past 90 days, mean (SD)[a]	9.6 (10.2) [*n* = 34]	1.0 (2.4) [*n* = 9]
How much SMA-related health problems affected school performance in the past 90 days, *n* (%)[a]	*n = 34*	*n = 9*
Not at all	8 (23.5)	3 (33.3)
A little bit	10 (29.4)	5 (55.6)
Somewhat	6 (17.7)	1 (11.1)
Quite a bit	8 (23.5)	0 (0.0)
Very much	2 (5.9)	0 (0.0)
Ability to perform at school in the past 90 days on days went to school/had class, *n* (%)[a]	*n = 34*	*n = 9*
Very poor	2 (5.9)	0 (0.0)
Poor	4 (11.8)	0 (0.0)
Acceptable	9 (26.5)	2 (22.2)
Good	9 (26.5)	4 (44.4)
Very good	10 (29.4)	3 (33.3)
Employment status, *n* (%)		
Employed full-time	0 (0.0)	25 (36.8)
Employed part-time	1 (2.5)	15 (22.1)
Not employed but seeking full-time employment	0 (0.0)	4 (5.9)
Not employed but seeking part-time employment	2 (5.0)	8 (11.8)
Not employed and not seeking employment	37 (92.5)	16 (23.5)
Reason employed part-time, *n* (%)[b]	*n = 1*	*n = 15*
Work part-time by choice	1 (100.0)	3 (20.0)
Work part-time, but seek full-time employment	0 (0.0)	1 (6.7)
Work part-time due to SMA health-related complications	0 (0.0)	7 (46.7)
Work part-time to stay below income threshold to qualify for/retain healthcare and other public services	0 (0.0)	4 (26.7)
Number of days of work missed due to SMA-related health problems in the past 90 days, mean (SD)[c]	2.0 (0.0) [*n* = 1]	2.0 (3.4) [*n* = 40]
How much SMA-related health problems affected work performance in the past 90 days, *n* (%)[c]	*n = 1*	*n = 40*
Not at all	1 (100.0)	7 (17.5)
A little bit	0 (0.0)	13 (32.5)

(Continues)

TABLE 4 | (Continued)

	Pediatric patients (<18 years old; caregiver proxy)	Adult patients (≥18 years old; self-reported)
	***n* = 40**	***n* = 68**
Somewhat	0 (0.0)	11 (27.5)
Quite a bit	0 (0.0)	6 (15.0)
Very much	0 (0.0)	3 (7.5)
Ability to perform at work in the past 90 days on days went to work, *n* (%)[c]	*n = 1*	*n = 40*
Very poor	0 (0.0)	0 (0.0)
Poor	0 (0.0)	2 (5.0)
Acceptable	0 (0.0)	13 (32.5)
Good	1 (100.0)	13 (32.5)
Very good	0 (0.0)	12 (30.0)

[a]Only asked to those who selected currently enrolled in school.
[b]Only asked of those who selected being employed part-time.
[c]Only asked to those who selected currently employed.

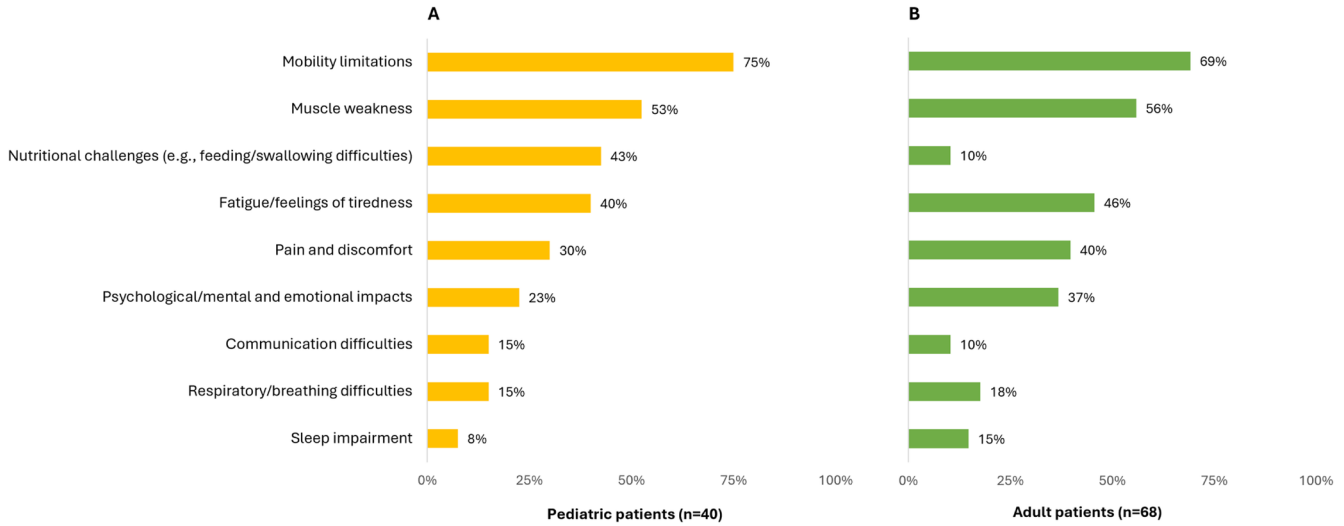

FIGURE 4 | SMA symptoms least improved with current SMN-targeted treatment: (A) Pediatric patients ($n = 40$), (B) Adult patients ($n = 68$). Pediatric patient data was reported by caregiver proxies. Adult patient data was self-reported. Participants were asked to select the three impacts the patient considered/caregivers thought the patient with SMA considered to be least improved or helped by the patient's current treatment.

currently available therapies. Compared to other similar conditions, utility estimates among our sample were slightly lower than previously reported ranges among Duchenne muscular dystrophy (DMD) patients (0.24–0.44) while EQ-VAS scores fell within DMD score ranges (50.5–78) [36].

Although the majority of findings were similar across pediatric and adult patients, there were some interesting differences. One notable difference was that being able to sit on the floor with no back support independently was frequently reported as being highly valued among pediatric patients, whereas adult patients frequently valued performing activities related to personal hygiene independently. This finding may be because sitting independently is a key milestone for children, while privacy becomes more important to patients as they age. Furthermore, results related to psychological and emotional impacts were more prominent among adult patients. Adults more frequently cited poor mental health as one of the most burdensome impacts of SMA and more frequently indicated psychological and emotional impacts as one of the SMA symptoms least improved or helped by current treatment. This highlights the importance of addressing psychological impacts of SMA, particularly among adults.

It is important to note that while differences observed between pediatric and adult patients may be attributed to age-related factors and aspects associated with different life stages, the differences may also be attributed to reporting source bias for caregiver proxy-reported data. Findings from the 10 dyad pairs suggest that there may be differences between caregivers'

TABLE 5 | Caregiver background characteristics and quality of life.

	Caregivers of pediatric patients	Caregivers of adult patients
	***n* = 40**	***n* = 10**
Caregiver age, mean (SD)	38.5 (6.3)	58.6 (15.9)
Caregiver sex, *n* (%)		
Male	8 (20.0)	3 (30.0)
Female	32 (80.0)	7 (70.0)
Caregiver role, *n* (%)		
I am the primary caregiver	29 (72.5)	7 (70.0)
I share primary caregiving responsibilities	11 (27.5)	3 (30.0)
Relationship to individual with SMA, *n* (%)		
Parent	40 (100.0)	6 (60.0)
Other[a]	0 (0.0)	4 (40.0)
EQ-5D health state index score, mean (SD)	0.81 (0.19)	0.75 (0.21)
EQ-5D [caregiver self-complete], *n* (%)		
Mobility		
No problems walking	32 (80.0)	8 (80.0)
Slight problems walking	4 (10.0)	1 (10.0)
Moderate problems walking	1 (2.5)	1 (10.0)
Severe problems walking	0 (0.0)	0 (0.0)
Unable to walk	3 (7.5)	0 (0.0)
Self-care		
No problems washing/dressing myself	38 (95.0)	9 (90.0)
Slight problems washing/dressing myself	2 (5.0)	1 (10.0)
Moderate problems washing/dressing myself	0 (0.0)	0 (0.0)
Severe problems washing/dressing myself	0 (0.0)	0 (0.0)
Unable to wash or dress myself	0 (0.0)	0 (0.0)
Usual activities		
No problems doing my usual activities	30 (75.0)	6 (60.0)
Slight problems doing my usual activities	8 (20.0)	3 (30.0)
Moderate problems doing my usual activities	1 (2.5)	1 (10.0)
Severe problems doing my usual activities	1 (2.5)	0 (0.0)
Unable to do my usual activities	0 (0.0)	0 (0.0)
Pain/discomfort		
No pain/discomfort	19 (47.5)	3 (30.0)
Slight pain/discomfort	11 (27.5)	2 (20.0)
Moderate pain/discomfort	9 (22.5)	3 (30.0)
Severe pain/discomfort	1 (2.5)	1 (10.0)
Extreme pain/discomfort	0 (0.0)	1 (10.0)

(Continues)

TABLE 5 | (Continued)

	Caregivers of pediatric patients	Caregivers of adult patients
	***n* = 40**	***n* = 10**
Anxiety/depression		
Not anxious/depressed	12 (30.0)	1 (10.0)
Slightly anxious/depressed	13 (32.5)	8 (80.0)
Moderately anxious/depressed	12 (30.0)	0 (0.0)
Severely anxious/depressed	3 (7.5)	1 (10.0)
Extremely anxious/depressed	0 (0.0)	0 (0.0)
EQ VAS [caregiver self-complete], mean (SD)[b]	80.9 (14.2)	68.3 (21.7)

[a]Other responses included: sister, boyfriend, and spouse.
[b]The EQ VAS is a 0 to 100 scale where participants are asked to indicate their overall health on the day of questionnaire completion: 0 = worst health imaginable, 100 = best health imaginable.

TABLE 6 | Impact on caregiver employment.

	Caregivers of pediatric patients	Caregivers of adult patients
	***n* = 40**	***n* = 10**
Caregiver employment status, *n* (%)		
Employed full-time	19 (47.5)	1 (10.0)
Employed part-time	9 (22.5)	2 (20.0)
Not employed but seeking full-time employment	1 (2.5)	0 (0.0)
Not employed but seeking part-time employment	2 (5.0)	1 (10.0)
Not employed and not seeking employment	9 (22.5)	6 (60.0)
Reason employed part-time, *n* (%)[b]	*n* = 9	*n* = 2
Work part-time by choice	1 (11.1)	0 (0.0)
Work part-time, but seek full-time employment	1 (11.1)	0 (0.0)
Work part-time due to providing care for the individual with SMA	7 (77.8)	2 (100.0)
Work part-time to stay below income threshold to qualify for/ retain healthcare and other public services	0 (0.0)	0 (0.0)
Impact of caring for an individual with SMA on caregiver employment, *n* (%)[a]		
Lost a job	7 (17.5)	0 (0.0)
Stopped working	15 (37.5)	6 (60.0)
Changed jobs/professions	9 (22.5)	3 (30.0)
Reduced work hours	20 (50.0)	2 (20.0)
Took leave of absence or unpaid time off	6 (15.0)	2 (20.0)
Changed job responsibilities	4 (10.0)	1 (10.0)
Have not sought a promotion, or been granted a promotion	6 (15.0)	1 (10.0)
Other[c]	11 (27.5)	1 (10.0)

(Continues)

TABLE 6 | (Continued)

	Caregivers of pediatric patients	Caregivers of adult patients
	***n* = 40**	***n* = 10**
Average number of hours working for pay per week prior to caregiver role versus currently, mean (SD)[d]	*n = 20*	*n = 2*
Prior to caregiver role	42.3 (5.5)	40.0 (0.0)
Currently	24.3 (13.2)	26.0 (8.5)

[a]Participants could select more than one answer option.
[b]Only asked to those who selected being employed part-time.
[c]Other responses included: working from home, no time to get a job, requested flexibility, got fired while child was in hospital due to SMA, working extra in evenings to make up for work time lost, worked more while spouse took a leave of absence while child had surgery, cannot find a job (stay home with kid), never had a chance to apply to work, hard to keep a consistent schedule, has not changed work, retired, delaying work deadlines.
[d]Only asked to those who selected reduced work hours.

perceptions of SMA and patients' experiences. However, these results are anecdotal, based on the small sample size. Future research should further explore areas of divergence.

Finally, findings from this study also echo existing literature regarding the burden SMA poses to caregivers, including impacts to caregivers' employment and quality of life. Previous evidence has shown caregiver burden is closely related to patient burden and is impacted by the patient's disease severity, level of disability, and level of required support to perform activities, as well as the patient's quality of life [13, 29]. This highlights the importance of effectively addressing challenges patients continue to face to support the well-being of caregivers.

5 | Limitations of Study

As with all survey studies, the information collected is self-reported and, as such, may be prone to reporting or recall bias. Use of caregiver proxy responses to represent patients may not be reflective of patients' subjective perceptions and experiences. Additionally, as SMA is a life-long chronic condition, patients may adapt to life with the condition and thus perceive their quality of life and impacts as being less severe. Convenience sampling methods were used for recruitment through a patient advocacy organization. As such, study results may not reflect all patient and caregiver experiences. Furthermore, while it is not uncommon to see smaller sample sizes in studies being conducted in rare disease spaces such as SMA [37–40], the sampling methods and eligibility criteria may have confounded the study sample size, leading to a reduced overall participation. Individuals who are engaged with advocacy groups may differ from the broader patient and caregiver populations in terms of disease awareness, access to resources, and level of involvement in disease management. Because the survey was conducted online, the respondent sample is reflective of those with adequate access to and ability to use technology and may not reflect individuals with no access to or limited understanding of internet-based surveys. Given that study participants volunteered to participate, self-selection bias may be present. The patients and caregivers participating in this study may be more enthusiastic about the study subject or face more challenges than those who chose not to participate. Because the survey was designed to be relevant for a heterogenous patient population who were currently treated with an SMN-targeted treatment, information on whether patients were diagnosed with SMA via newborn screening and the timing of SMA symptom manifestation, relative to SMN-targeted treatment initiation, were not collected. Although these two attributes are known to impact treatment outcomes [41, 42], and would be valuable considerations for future research, the SMA population comes to treatment from a variety of diagnosis and access backgrounds, which we wanted to capture in this research. Lastly, it is important to note that this study was limited to the experiences of non-ambulant patients. Future research is needed to explore the burden and unmet need among the broader population of patients with SMA to identify areas of similarities and differences.

6 | Conclusion

Despite the use of current SMN-targeted treatments, there remains a significant clinical, humanistic, and productivity-related burden of SMA on pediatric and adult patients and their caregivers. In addition, muscle weakness and mobility limitations remain key areas of unmet need, underscoring the importance of future treatments in addressing these critical aspects of SMA, which impact patients' health and quality of life.

Author Contributions

N.L., C. Cagle, A.J., and M.C.M. developed initial drafts of all study documents, including the study protocol and survey instruments, oversaw data collection, and wrote the first draft of the manuscript. J.A.P., T.B., H.S., C. Cherubino, and M.G. reviewed and provided feedback on all study documents and reviewed and edited the manuscript. N.L. and M.C.M. oversaw data analysis and had unrestricted access to all data. All authors agreed to submit the manuscript, read and approved the final draft, and take responsibility for its content, including the accuracy of the data and analysis.

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Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki. All study documents were processed through a complete ethics review by an independent Institutional Review Board organization (Advarra) and approval was granted in July 2024 prior to recruitment initiation (Pro00079148).

Conflicts of Interest

N.L., M.C.M., C. Cagle, and A.J. are employees of Precision AQ, a research consultancy that provides health economics and outcomes research services to life sciences companies, which received funding from the sponsor to conduct this study. M.C.M. owns equity interest in Precision AQ's parent company, Precision Medicine Group. T.B., C. Cherubino, and M.G. are employees of Scholar Rock Inc. J.A.P. has received funds for clinical trials fromBiogen, Novartis, Scholar Rock, Biohaven, Genentech, and PTC Therapeutics. J.A.P. has been an advisor for Biogen, Novartis, Scholar Rock Inc., Genentech, Ultragenex, and Dyne. H.S. has been an advisor for Scholar Rock Inc.

Data Availability Statement

Requests for further information should be directed to Natalie Land (natalie.land@precisionaq.com). Data for this study is available from the lead contact upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.