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Exploring sleep quality, depressive symptoms, and quality of life in adults with spinal muscular atrophy

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ABSTRACT

Spinal Muscular Atrophy (SMA) is a genetic neuromuscular disorder caused by the mutation of the survival motor neuron 1 (SMN1) gene. Sleep disturbances and their impact on mental health and quality of life in patients with SMA are being understudied, and most of the evidence comes from pediatric SMA patients. We conducted a cross-sectional survey of adult patients with SMA. The participants underwent questionnaires exploring sleep quality with the Pittsburgh Sleep Quality Index (PSQI), depressive symptoms with the Patient Health Questionnaire-9 (PHQ-9), and quality of life with the Short-Form Health Survey 36 (SF-36). Fifty patients with SMA were enrolled in the study: 66 % were females with a median age of 41 years. Of them, 60 % had poor sleep quality, and 72 % had depressive symptoms. SMA 2 patients showed higher PSQI and PHQ-9 scores than SMA 3 patients (8 ± 3 vs 6 ± 1, $p < 0.001$ and 13 ± 5 vs 7 ± 5, $p < 0.001$). PSQI total score correlated with the PHQ-9 ($r = 0.32$, $p = 0.02$), which was higher in patients with respiratory symptoms. Poor sleep is associated with depressive symptoms and respiratory dysfunction in adult SMA patients. Clinicians should consider sleep quality in SMA patients for optimal care; future studies are needed to understand this aspect better.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by the mutation or deletion of the survival motor neuron 1 (SMN1) gene located on chromosome 5q13.2, and it is characterized by muscle weakness, leading to functional decline [1]. SMA has an estimated incidence of 1 in 6000 to 1 in 10,000 live births.

The severity of the disease is variable and, based on the clinical picture and the age of the onset, typically classified into types 0–4, with types 2 and 3 accounting for almost 50 % of affected individuals [2]. Type 0 is the most severe form of SMA, resulting in fetal or neonatal death; type 1 manifests at age 0–6 months with patients unable to sit or walk; type 2 is generally diagnosed at age 7–18 months with patients who can sit but typically not walk and type 3 manifests after the age of 18 months with patients that are generally ambulatory, although the loss of ambulation is common if untreated [3–5]. A milder disease phenotype is associated with higher SMN2 copy numbers [6].

Recent advancements in medical research have led to the development of promising treatments. Specifically, in late 2016, the FDA approved using Nusinersen, the first disease-modifying therapy for SMA, with an intrathecal administration [7]. In addition, Risdiplam is the first oral available drug approved by the FDA in 2020 for SMA type 1, 2, or 3 [8]. These interventions have shown considerable efficacy in stabilizing or improving motor functions [9]. Interestingly, with the introduction of therapeutic drugs for the SMA population, this five-phenotype model is changing as the clinical course.

Moreover, the impact of new therapies is changing the attitude of families and physicians toward a more proactive approach. In fact, the impact of living with SMA extends to various other aspects that have received insufficient attention in research and warrant greater scrutiny. Indeed, many symptoms contribute to the disease burden experienced by adults affected by SMA. A comprehensive understanding of the symptomatic burden associated with SMA is crucial for clinicians as they endeavor to enhance the monitoring and treatment of adult SMA patients.

Sleep disturbance in chronic diseases is an increasing subject of

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research because of its potential impact on quality of life, and mental illness partly mediates this association [10]. Exploring sleep quality and depressive symptoms in patients with SMA is crucial due to their strong association and profound influence on patients' already compromised quality of life [11]. Sleep quality in SMA patients may be particularly vulnerable due to several factors associated with the condition. Muscle weakness can lead to physical discomfort and difficulty finding a comfortable sleeping position, while respiratory issues may cause sleep-disordered breathing or frequent awakenings. Additionally, progressive muscle weakness can result in reduced mobility, contributing to poor sleep quality. These factors combine to create a heightened risk of sleep disturbances in individuals with SMA, potentially exacerbating other health issues and impacting overall well-being.

However, sleep disturbances in patients with SMA are strikingly understudied, and most evidence comes from pediatric patients [12]. At the same time, there is a growing need to study adult patients with SMA, as their experiences and challenges can differ significantly from those of children. Adults with SMA may face unique issues related to long-term disease progression, changing healthcare needs, and different psychological and social impacts. Nonetheless, symptoms of impaired sleep are prevalent in adults with SMA, which is in line with evidence of other types of neuromuscular disease [13]. Respiratory dysfunction associated with neuromuscular disorders impacts sleep quality in relation to orthopnea and sleep-disordered breathing, manifesting most commonly as sleep fragmentation and morning headaches [14]. Treatment with non-invasive ventilation (NIV) during sleep may improve sleep quality and quality of life.

In addition, given the diverse SMA phenotypes characterized by varying symptoms and levels of severity, it is pertinent to explore differences between patients with different types of SMA. Understanding these differences could provide valuable insights into tailoring interventions and support strategies to effectively address each subgroup's unique needs.

Thus, the primary objectives of this study were to assess self-reported sleep quality in adult patients with SMA and to evaluate the difference between patients with SMA 2 and 3. This objective is driven by the need to understand how varying disease severities and progression patterns affect patient outcomes, particularly in areas such as sleep quality and depressive symptoms. SMA type 2 and type 3 patients experience distinct challenges due to the differences in disease onset and progression, which can influence their overall health and quality of life. Evaluating these differences is crucial for several reasons. First, it allows for a more nuanced understanding of how disease severity impacts patient health, including sleep and mental well-being. By comparing these two groups, we can identify specific needs and challenges associated with each type, which can inform the development of targeted interventions and care strategies. Additionally, this comparison helps to address gaps in the existing literature, which often aggregates data across different SMA types, potentially overlooking the unique experiences and requirements of individuals with SMA type 2 and type 3.

The secondary objectives were to evaluate the association between sleep disturbances, depressive symptoms, and quality of life and explore respiratory dysfunction's impact on sleep quality.

2. Methods

2.1. Study design and participants

We conducted a cross-sectional study design using an anonymous online self-report survey. Individuals diagnosed with SMA were recruited as study participants, facilitated by the Association of Italian SMA patients. Before full participation, potential respondents were asked to complete a pre-screening questionnaire that gathered key demographic and clinical information. This allowed us to confirm eligibility before proceeding to the main survey. Although the survey was anonymous, recruitment was not entirely open to the public. To maintain control over who participated, the invitations to participate in the study were distributed to potential participants through controlled and secure channels, such as email lists or social media groups run by trusted organizations. Only those who received these direct invitations could access the survey. Participants were assured of the anonymity of their responses. By maintaining confidentiality and not linking responses to individual identities, we aimed to reduce social desirability bias and encourage more honest and accurate reporting. Participants received clear instructions emphasizing the importance of honest and accurate responses. We explained that their truthful input was crucial for the reliability of the study results and a better understanding of their experiences and needs. This multi-layered approach to recruitment ensured that we reached and included the correct population while maintaining participant anonymity within the survey.

Participants had to meet the following inclusion criteria: i) a confirmed clinical diagnosis of SMA type 2 or 3; ii) age between 18 and 65 years iii) being able to read and sign an informed consent form. Exclusion criteria comprised: i) presence of severe psychiatric disorder (e.g., psychotic or bipolar disorder).

The study specifically included only patients diagnosed with SMA type 2 and type 3. This focus was intentional due to the distinct clinical characteristics and progression patterns associated with these SMA types. SMA type 2 and type 3 were selected to explore how different severities and trajectories of the disease impact outcomes such as sleep quality and depressive symptoms. The choice to exclude other types, such as SMA type 1 and type 4, was based on the differences in their clinical presentations and management needs. SMA type 1 is characterized by severe, early-onset symptoms that significantly impact survival into adulthood. In contrast, SMA type 4 presents with milder, late-onset symptoms and does not fully capture most patients' challenges with SMA type 2 and type 3. By focusing on SMA types 2 and 3, the study addresses a critical gap in understanding patients' experiences more likely to live into adulthood and face long-term management issues.

After obtaining written informed consent, eligible participants were consecutively enrolled in the study and completed all survey measures using Survey Monkey. This research was designed according to the STROBE statement and conducted following the Declaration of Helsinki. An independent University of Modena and Reggio Emilia, Italy's ethics committee, approved this study.

2.2. Data collection

The survey gathered sociodemographic and anthropometric characteristics of patients, including factors such as gender, age, weight, height, educational attainment, and employment status.

Patients' medical information was also collected. This information comprised the type of SMA, the number of SMN copies, the type of treatment received (supportive care only, Nusinersen or Risdiplam), and the presence of cardiovascular and endocrinal comorbidities. Concerning the respiratory situation, participants completed two ad hoc items assessing respiratory dysfunction in a typical month in the past year: i) the item "Do you experience difficult breathing in a supine position?" assesses orthopnea, which is related to diaphragmatic dysfunction [15]; ii) the item "Do you wake up in the morning with a headache?" assesses morning headache which is related to sleep hypoventilation [16]. Moreover, we investigated whether the patients underwent regular pneumological follow-up, regular nocturnal pulse oximetry, and used NIV during the night.

2.3. Self-reported sleep quality

The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire consisting of 19 items designed to evaluate an individual's sleep quality over the past month. It evaluates seven components of sleep, including quality, latency, duration, efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Scores on the questionnaire range

from 0 to 21, with higher scores indicating poorer sleep quality. A total score exceeding 5 suggests poor sleep quality. This study utilized the validated Italian version of the PSQI [17].

2.4. Depressive symptomatology

The Patient Health Questionnaire (PHQ-9) was used to evaluate the level of depressive symptomatology. The PHQ-9 consists of 9 items and is widely used in screening individuals on their level of depression [18]. It requires patients to assess, using a four-point scale from "not at all" to "nearly every day," the frequency of specific depression symptoms experienced over the preceding two weeks. Scores on the PHQ-9 range from 0 to 27. Scores between 5 and 9 indicate subthreshold depression, while a score of 10 serves as the optimal cutoff for identifying clinically significant depression, delineating three levels of severity based on the score [19].

2.5. Health-related quality of life

The Short Form Health Survey 36 (SF-36) was used to evaluate the health-related quality of life. The SF-36 assesses eight dimensions of health: emotional well-being, general health, energy and vitality, social functioning, physical functioning, role limitations due to emotional health problems, bodily pain, and mental health. Each dimension is converted to a scale of 0–100, assuming equal importance for each question. Lower scores indicate poorer health-related quality of life [20].

2.6. Statistical analysis

Descriptive statistics were used to summarize the demographic characteristics of the study participants, including mean values and standard deviations for continuous variables and frequencies and percentages for categorical variables.

Due to the skewed data distribution, the Mann-Whitney U test, a non-parametric statistical method, was employed to compare sociodemographic and clinical characteristics, sleep quality, quality of life, and depressive symptoms between the two groups. This test is suitable for comparing continuous variables between two independent groups when the assumptions of normality and homogeneity of variance are unmet.

Furthermore, associations between these variables and sociodemographic characteristics were assessed using correlation analysis. Spearman's rank correlation coefficient was utilized to evaluate the strength and direction of associations between continuous variables, while point-biserial correlation was used for associations between continuous and dichotomous variables.

The significance level was set at $p < 0.05$ for all statistical tests. Statistical analyses were performed using JASP.

3. Results

All participants ($n = 50$) were included in the analysis, and no data were missing. Table 1 presents the participants' characteristics. Most individuals were female (66 %), with a mean age of 40 and normal weight. Half of the participants had attained a high level of education, and the majority were employed. Most patients were undergoing pharmacological treatment, and 32 % took no medication. Regarding the respiratory situation, 66 % of patients had a regular pneumological follow-up, 80 % performed regular nocturnal pulse oximetry, 12 % complained about orthopnea, 36 % had morning headaches, and 16 % used nocturnal NIV. Type 2 was the most prevalent phenotype in our sample, followed by type 3 (58 % vs. 42 %, respectively), with no relevant differences between the two groups except for lower BMI in patients with SMA 2.

Table 2 presents the results of questionnaires exploring sleep quality, depressive symptoms, and quality of life. According to the PSQI, 60 % of patients had poor sleep, with a higher total score in SMA type 2 patients than in SMA type 3 patients. The mean PSQI score in our SMA cohort was 6, which is substantially higher than the general population mean of 4.5–5, indicating significantly poorer sleep quality. The PHQ-9 indicated that 72 % of patients had clinically significant depressive symptoms with a higher total score in SMA type 2 than type 3. Following this, no significant differences were observed between SMA type 2 and SMA type 3 patients regarding the global quality of life total at SF-36. However, SMA type 2 patients demonstrated significantly lower scores on the SF-36 subscales for emotional well-being and general health.

The correlation analysis revealed that the PSQI total score correlated with the PHQ-9 total score; poorer sleep quality is associated with more severe depressive symptoms. (Table 3).

As shown in Fig. 1, patients with respiratory symptoms (both orthopnea and morning headaches), as well as patients with nocturnal NIV use, had higher PSQI than patients without.

In Table 4, the comparisons between patients receiving and without treatment reveal no statistically significant differences in the evaluated measures. These findings suggest that treatment status, at least in this sample, is not associated with significant variations in sleep, depressive symptoms, or quality of life.

Table 5 shows a significant difference in PSQI scores between patients treated with Risdiplam and those treated with Nusinersen ($p = 0.04$). In contrast, no significant differences are found between these groups in depressive symptoms or quality of life. These results suggest that Nusinersen may have a more favorable effect on sleep quality than Risdiplam. At the same time, both treatments appear to have similar outcomes for depressive symptoms and quality of life.

Table 1
Sociodemographic and clinical characteristics.

	SMA Patients (N = 50)	SMA 2 Patients (N = 29)	SMA 3 Patients (N = 21)	*p value*
Sex, n (%)				
Females	33 (66)	20 (71)	13 (61)	0.49
Age, *Median (IQR)*	41 (18)	40 (15.25)	43 (23)	0.39
BMI, kg/m^{2,} *Median (IQR)*	18 (8.74)	16 (6.33)	22 (6.64)	**0.007**
Education, n (%)				
Primary school	1 (2)	1 (3)	0	0.65
Secondary school	24 (48)	12 (42)	12 (57)	
≥ High school	25 (50)	15 (53)	9 (42)	
Employed, n (%)				
Yes	31 (62)	16 (57)	14 (67)	0.50
No	19 (38)	12 (43)	7 (33)	
SMN copies, n (%)				
2	21 (43)	18 (64)	3 (14)	**<0.001**
3	27 (54)	10 (36)	17 (81)	
4	1 (2)	0	1 (5)	
Comorbidity, n (%)				
Cardiovascular diseases	7 (14)	4 (14)	3 (14)	0.73
Endocrinal diseases	5 (10)	2 (7)	1 (4)	
Respiratory symptoms				
Orthopnea, n (%)	6 (12)	3 (10)	2 (9)	0.89
Morning headaches, n (%)	18 (36)	12 (42)	6 (28)	0.31
Nocturnal NIV use, n (%)	8 (16)	8 (28)	0 (0)	**<0.001**
Drug theraphy for SMA, n (%)				
None	16 (32)	8 (28)	7 (33)	**0.04**
Risdiplam	25 (50)	19 (68)	6 (24)	
Nusinersen	9 (18)	1 (4)	8 (38)	

SMA: Spinal Muscular Atrophy, SMN: Survival Motor Neuron, IQR: Interquartile range, NIV: non-invasive ventilation, BMI: Body max index.

4. Discussion

The present study provides insights into individuals' characteristics

Table 2
Questionnaires exploring sleep quality, depressive symptoms, and quality of life.

	SMA Patients (N = 50)	SMA 2 Patients (N = 29)	SMA 3 Patients (N = 21)	*p value*
Pittsburgh Sleep Quality score >5 n (%)	30 (60)	18 (62)	12 (57)	0.93
Pittsburgh Sleep Quality Index, *Median (IQR)*	6 (3.12)	8.6 (5.25)	6.2 (2.43)	**<0.001**
Quality	2 (1.91)	3 (1)	1 (0.10)	**<0.001**
Latency	2 (1.20)	2 (2)	1 (1.32)	0.23
Duration	2 (1)	2 (1.25)	1 (1.12)	0.14
Efficiency	1 (0.22)	1 (1.32)	0 (1)	0.09
Disturbances	1 (1)	1.12 (1)	1 (0.23)	0.84
Medications	1 (1)	0.50 (1)	1 (1)	0.99
Daytime dysfunction	1 (0.22)	1 (0.25)	1 (0.30)	0.15
Patient Health Questionnaire-9 > 10 n (%)	36 (72)	21 (72)	15 (71)	0.96
Patient Health Questionnaire-9, *Median (IQR)*	7.50 (5.32)	12.25 (4.22)	7 (3.41)	**<0.001**
Short Form Health Survey-36, *Median (IQR)*	483 (174.20)	434 (157.37)	513.80 (132.20)	0.13
Emotional well-being	75 (37)	68 (32)	60 (24)	**0.01**
General health	55 (35)	50 (31)	60 (10)	**0.03**
Energy and vitality	66 (67)	66 (67)	66 (67)	0.34
Social functioning	75 (37)	62 (37)	75 (25)	0.89
Physical functioning	55 (20)	60 (20)	50 (25)	0.69
Role limitations due to emotional health problems	75 (37)	62 (37)	75 (25)	0.62
Bodily pain	80 (12)	80 (12)	87 (35)	0.27
Mental health	55 (35)	50 (31)	60 (10)	0.91

SMA: Spinal Muscular Atrophy, M(SD): IQR: Interquartile range.

Table 3
Correlations between PSQI, SF-36 and PHQ-9.

Variable		PSQI Total score	SF-36 Total score
PSQI Total score	Pearson's r	—	
	p-value	—	
SF-36 Total Score	Pearson's r	−0.16	—
	p-value	0.25	—
PHQ-9 Total Score	Pearson's r	0.32	−0.24
	p-value	**0.02**	0.08

PSQI: Pittsburgh Sleep Quality Index, SF-36: Short-Form Healthy Survey; PHQ-9: Patient Health Questionnaire 9.

and health outcomes with SMA. The findings of our research reveal a concerning pattern of poor sleep quality, clinically significant depressive symptoms, and poor quality of life among patients with SMA. The elevated PSQI scores observed in SMA patients reflect substantial sleep disturbances compared to the general population. Similarly, the lower SF-36 domain scores indicate compromised quality of life, aligning with the burden of SMA-related symptoms.

Our study specifically included patients with SMA types 2 and 3, associated with varying degrees of physical impairment that can significantly influence sleep quality. In contrast, Wennberg and colleagues did not differentiate between SMA types, which may have resulted in a more heterogeneous sample, potentially obscuring differences in PSQI scores [21].

Several factors can contribute to perceived poor sleep quality, high levels of depression, and reduced quality of life observed in patients with SMA. Firstly, chronic pain and discomfort experienced by SMA patients due to muscle weakness and joint contractures can disrupt sleep patterns. In addition, studies with other types of progressive neuromuscular diseases have shown that chronic respiratory problems are associated

Table 4
Differences in questionnaires between patients in and without treatment.

	In treatment (N = 34)	Without treatment (N = 16)	*p value*
Pittsburgh Sleep Quality Index, *Median (IQR)*	7 (1.5)	6 (4.5)	0.56
Patient Health Questionnaire-9, *Median (IQR)*	6 (5)	6.5 (3)	0.69
Short Form Health Survey-36, *Median (IQR)*	496 (144)	489 (169)	0.57

IQR: Interquartile range.

Table 5
Differences in questionnaires between patients in treatment with Risdiplam vs. Nusinersen.

	In theraphy with Risdiplam (N = 25)	In theraphy with Nusinersen (N = 9)	*p value*
Pittsburgh Sleep Quality Index, *Median (IQR)*	7 (6)	5.3 (1)	**0.04**
Patient Health Questionnaire-9, *Median (IQR)*	7 (3)	5.5 (3)	0.41
Short Form Health Survey-36, *Median (IQR)*	477 (181)	489 (124)	0.40

IQR: Interquartile range.

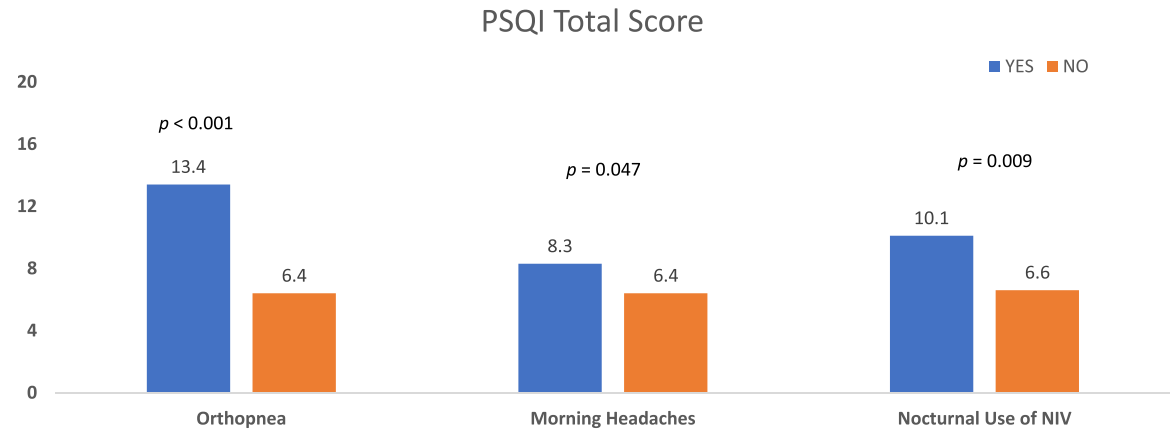

Fig. 1. Sleep quality and respiratory symptoms.

with sleep deprivation due to decreased sleep time and efficiency [22]. On the other side, the progressive nature of SMA and the associated physical limitations can lead to significant challenges in daily functioning, independence, and social participation, which may contribute to feelings of helplessness and isolation, ultimately contributing to depressive symptoms, which can, in turn, negatively impact sleep quality. The physical and emotional toll of SMA not only directly affects individuals but also places considerable stress on caregivers, potentially leading to increased caregiver burden and further exacerbating the psychosocial challenges faced by patients. Emerging evidence is expanding our understanding and encompassing patients' psychological aspects. For instance, a study involving 13 patients diagnosed with SMA type 2 and 3 revealed that 7 of them acknowledged experiencing mental health challenges, reporting feelings of stress, anxiety, or depression [23]. Furthermore, the constant need for medical interventions, frequent hospitalizations, and the uncertainty surrounding disease progression can negatively impact overall health-related quality of life.

Interestingly, our results showed an association between sleep quality alteration and depressive symptoms. There is growing evidence of a bidirectional association between sleep disorders and depression [24,25]. The psychological stress of managing a chronic and progressive condition like SMA can exacerbate both sleep disturbances and depressive symptoms. The emotional burden of adapting to physical changes, coping with the disease, and dealing with future uncertainties creates significant psychological stress, which disrupts sleep and increases the risk of depression. There may also be underlying biological mechanisms linking sleep disturbances and depression. Sleep disruptions can affect neurotransmitter systems and hormonal balances that are crucial for mood regulation, while depressive symptoms can influence sleep architecture and circadian rhythms, compounding sleep issues.

In particular, sleep disorders are considered to be a predictor of suicide risk in MDD, and the risk of relapse is significantly increased if sleep problems persist after other symptoms improve [26]. In addition, improving patients' sleep disturbances can alleviate disease-related clinical symptoms [27].

Respiratory involvement is a well-recognized feature of neuromuscular disorders, including SMA. While this study provides insights into the clinical aspects of respiratory dysfunction in SMA, it is important to contextualize these findings alongside objective clinical measures and technical studies used in other neuromuscular conditions. Unfortunately, this study did not include specific assessments such as forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP), nor technical evaluations such as polysomnography (PSG) or capnometry. Hypoventilation, particularly during sleep, is a major contributor to morbidity in many motoneuron disorders. Sleep-disordered breathing and associated consequences, including impaired sleep quality and daytime fatigue, have been well-documented in ALS and myotonic dystrophy [28,29]. These studies emphasize the need for comprehensive respiratory evaluations to understand the disease trajectory and guide clinical management strategies such as NIV. Research on spinal and bulbar muscular atrophy (SBMA) disorders has further highlighted the interplay between neuromuscular weakness and sleep disruption [30]. These findings underscore the critical role of early and accurate identification of respiratory impairment to prevent secondary complications and improve quality of life.

The findings of our study revealed compelling differences between patients with different phenotypes of SMA, with SMA type 2 exhibiting notably poorer sleep quality, emotional well-being, and health status, along with higher levels of depression. Progressive muscle weakness, altered respiratory function, sleep breathing disturbances such as sleep apnea and nocturnal hypoventilation, and difficulties finding a comfortable sleeping position may contribute to lower levels of sleep quality. Moreover, the heightened levels of depression observed in SMA type 2 patients likely reflect the profound impact of physical disability, functional limitations, and disease-related stressors on mental health. The diminished emotional well-being and health status in SMA type 2 patients further highlight the pervasive nature of the disease's impact on several domains of quality of life.

In this study, we hypothesized that motor symptoms in SMA (particularly differences between SMA type 2 and type 3) likely impact sleep quality. However, we acknowledge the absence of objective motor functional assessments, such as standardized motor scales, as a limitation in our study design. Quantitative evaluation using scales like the Hammersmith Functional Motor Scale (HFMS) or the Revised Upper Limb Module (RULM) would have allowed for robust correlations between motor impairment severity and sleep-related outcomes. Including such data is essential for substantiating hypotheses regarding the interplay between motor function and sleep disturbances in SMA. Previous studies in other neuromuscular disorders have established significant relationships between motor function and respiratory or sleep disturbances, reinforcing the importance of this approach. For example, studies in facioscapulohumeral dystrophy (FSHD) demonstrated a link between motor impairment and sleep-related breathing disorders, highlighting the need for functional assessments to guide respiratory management [31]. In myotonic dystrophy type 1 (MD1), motor weakness correlates with reduced respiratory muscle strength and disrupted sleep [32]. Similarly, in Charcot-Marie-Tooth disease (CMT) and Pompe disease, motor dysfunction has been associated with sleep-disordered breathing, emphasizing the clinical importance of motor functional scales in drawing meaningful conclusions [33,34].

One hypothesis for why SMA type 2 patients experience poorer outcomes relates to the earlier onset and more rapid progression of the disease. Type 2 SMA patients often exhibit more severe muscle weakness and reduced motor function at an earlier age. This early onset of severe symptoms can lead to more pronounced physical limitations, reduced mobility, and increased need for assistive devices and supportive care. The cumulative effect of these early impairments can result in greater challenges in achieving and maintaining functional milestones, which may contribute to poorer overall outcomes. Furthermore, early onset SMA type 2 may impact the development of compensatory strategies and adaptations that can be more readily achieved in the later-onset SMA type 3. The early loss of motor skills and muscle strength in type 2 patients can limit their ability to develop and use compensatory mechanisms effectively, which can further exacerbate functional impairments and negatively impact quality of life. Understanding these differences has important implications for clinical care. For SMA type 2 patients, early and intensive intervention may be crucial to address the severe symptoms and prevent or mitigate the impact of the disease. Tailoring therapeutic strategies to enhance motor function, improve mobility, and provide comprehensive supportive care from an early age can help optimize outcomes and quality of life. This might include early physical therapy, respiratory support, and assistive technologies to address specific needs associated with severe early onset. In contrast, for SMA type 3 patients, who may experience a more gradual progression, clinical care could be tailored to focus on monitoring and managing symptoms over time, with an emphasis on preserving function and adapting to gradual changes in motor abilities.

By recognizing and addressing the distinct needs of patients with different SMA types, clinicians can develop more targeted and effective treatment plans that improve functional outcomes and quality of life across the spectrum of SMA severity.

While our findings suggest a possible association between motor impairment and poorer sleep quality, it is important to consider additional factors that may contribute to these outcomes, particularly fatigue, which we did not explicitly address in our analysis. Fatigue is a well-documented symptom in motor neuron diseases and other neuromuscular disorders, including SMA. It is known to significantly impact both the quality of life and the severity of depressive symptoms [35]. Patients with neuromuscular diseases often report fatigue as one of the most debilitating symptoms, and it has been linked to both reduced physical function and impaired emotional well-being. As such, fatigue

could be a major contributing factor to the depressive symptoms and decreased quality of life observed in our study cohort. However, we did not specifically assess fatigue in our sample, which is a critical limitation of this study. The literature on fatigue in neuromuscular diseases supports the idea that fatigue may substantially influence sleep quality and emotional health. These findings suggest that fatigue may play a significant role in exacerbating sleep disturbances, as patients who experience excessive daytime sleepiness and poor-quality sleep may be compensating for the fatigue caused by their underlying disease [36].

In this study, we found no significant differences in sleep quality, depressive symptoms, or quality of life between patients receiving treatment and those not receiving treatment. These results suggest that treatment status may not strongly influence these outcomes. However, it is important to note that the need for significant differences might be influenced by the relatively small sample size, which may limit the statistical power to detect subtle effects. Additionally, the variability in individual responses, as indicated by the interquartile ranges, could mask potential differences.

Interestingly, when comparing patients treated with Risdiplam versus Nusinersen, we observed a significant difference in sleep quality, with patients on Nusinersen reporting better sleep. This finding aligns with the hypothesis that treatment regimens may have differential effects on sleep regulation, possibly due to distinct mechanisms of action or side effect profiles. However, no significant differences were observed in depressive symptoms or quality of life between these two treatment groups, suggesting that the overall impact on psychological well-being and daily functioning might be comparable. These findings provide valuable preliminary insights into the differential effects of treatments for spinal muscular atrophy on patient-reported outcomes. Nevertheless, the clinical relevance of the observed difference in sleep quality should be further investigated in larger, longitudinal studies to establish whether it translates into meaningful improvements in patients' overall health and well-being. Moreover, exploring the underlying mechanisms these treatments influence sleep could help tailor interventions to address patient-specific needs more effectively.

This study has potential limitations that should be acknowledged. Two key factors, self-report biases, and the small sample size, may limit the accuracy and generalizability of our findings. While valuable for capturing subjective experiences, self-report measures are inherently susceptible to biases. Participants may be influenced by social desirability, recall bias, or personal interpretation of questions, which can affect the accuracy of their responses. For instance, individuals might underreport symptoms or overstate positive outcomes due to the desire to present themselves favorably or difficulties recalling their experiences accurately. These biases can skew the data and impact the reliability of the findings. Future research should incorporate objective measures alongside self-reports to validate and complement participants' subjective accounts to mitigate this. A small sample size can limit the robustness and generalizability of the study results. With a limited number of participants, there is a higher risk of sampling bias, which may not accurately represent the broader population. This limitation can affect the statistical power of the analysis and the ability to detect significant differences or associations. Small sample sizes also restrict the generalization of findings to different subgroups within the population, such as varying severities of SMA or other demographic characteristics.

We recognize that the conclusions regarding the impact of motor symptoms on sleep remain hypothetical due to our study's lack of direct motor function assessments. Future research should incorporate at least one validated motor functional scale to provide quantitative data and establish clear correlations.

A further limitation of this study is the need to directly assess daytime sleepiness using validated tools such as the Epworth Sleepiness Scale or objective methods like actigraphy. Including such measures would help distinguish the impact of daytime sleepiness from depressive symptoms and provide a more nuanced understanding of their relationship with sleep disturbances.

We conducted a regression analysis to examine the effects of age, BMI, treatment type, and PSQI, PHQ-9, and SF-36 scores on SMA type classification. However, the results did not significantly alter the interpretation of our univariate findings. While variables such as BMI and treatment type achieved statistical significance, others, including PSQI and PHQ-9 scores, did not. Since these results did not substantially contribute to the central message of our study, we chose not to include them in the manuscript. We recognize that these associations deserve further exploration in larger studies focused on SMA subtype-related outcomes.

Finally, the relatively low proportion of SMA type 2 patients under NIV in our cohort, with only one-third receiving this intervention, appears lower than reported in previous studies. This discrepancy may reflect differences in patient selection, regional guidelines for initiating NIV, or access to specialized respiratory care variations. Moreover, the composition of our cohort, which primarily includes patients actively engaged in follow-up care, may only partially represent the broader SMA type 2 population. Future studies should explore these factors further and assess how they influence the utilization of NIV in this population.

5. Conclusion

The findings of this study highlight a significant association between poor sleep quality, depressive symptoms, and respiratory dysfunction in adult SMA patients. These results underscore the importance of addressing sleep disturbances in comprehensive care for individuals with SMA. Given the impact of sleep on both emotional well-being and respiratory health, clinicians should incorporate regular sleep assessments into routine evaluations of SMA patients. By identifying and addressing sleep issues early, healthcare providers may improve overall management and potentially enhance the quality of life by mitigating the impact of associated depressive symptoms and respiratory complications. However, as this study only demonstrates an association and does not include an intervention, further research is needed to confirm whether treating sleep issues directly improves quality of life and depressive symptoms.

Integrating sleep assessments and targeted interventions into standard care practices can lead to better outcomes and more personalized care for adult patients with SMA. In addition, these findings underline the importance of comprehensive multidisciplinary care approaches that address not only the physical symptoms but also the psychological and emotional needs of individuals with SMA, particularly those with more severe phenotypes.

Future research should further explore the underlying mechanism driving these observed differences and identify target interventions to address the specific needs of different SMA phenotypes.

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CRediT authorship contribution statement

Valentina Baldini: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giorgia Varallo:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Stefania Redolfi:** Writing – review & editing, Validation, Supervision, Investigation. **Rocco Liguori:** Writing – review & editing, Validation, Supervision. **Giuseppe Plazzi:** Writing – review & editing, Validation, Supervision, Project administration, Investigation.

Declaration of competing interest

Giuseppe Plazzi has received honoraria for advisory board and

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

Data are available from the corresponding author upon responsible request.

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