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Determinants of Fatigue and Perceived Fatigability in Spinal Muscular Atrophy: A Registry-Based Multivariable Analysis Identifies Associated Factors

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Introduction

Despite disease-modifying therapies, people with SMA (pwSMA) continue to face substantial unmet needs that meaningfully affect daily life. Fatigue and fatigability are among the most frequent and disabling patient-reported symptoms, and they often persist even in the context of widespread use of SMN-directed therapies.

Performance fatigability
Objective decline in the ability to sustain or repeat a task over time

Perceived fatigue
Subjective sense of exhaustion

Perceived fatigability
Subjective tendency to become exhausted during a defined activity

Methods

All data were derived from RegistrAME: the Spanish Registry of Spinal Muscular Atrophy. The dataset analyzed reflects the registry's data up to December 2025.

Assessment of Fatigue and Fatigability

Perceived fatigue and perceived fatigability were assessed using the multidimensional PROfuture questionnaire. PROfuture is a patient-centered, SMA-specific multidimensional patient-reported outcome measure administered via computerized adaptive testing.

This methodological distinction was addressed by fitting two separate multivariable regression models: the first focused on the general fatigue component (items 1–5), and the second on fatigability burden (items 6–19).

Results: key facts

338
pwSMA
Mean age 21.7 years

51.48%
younger than 18 years

52%
male

92.6%
receiving DMT

38%
using salbutamol or pyridostigmine for fatigability management

36.6%
perceived fatigue in at least one domain

Motor function status

24.56% non-sitters
59.17% sitters
16.27% walkers

SMN2 copy number

2 copies — **27.0%**
3 copies — **61.6%**
4 copies — **11.4%**

-Available for 315 participants-

Multivariable Model for the Aggregated Score of Fatigue Items (1–5)

Variables	Estimate	Std Error	Lower 95	Upper 95	*P*-value
(Intercept)	18.027	1.377	15.318	20.737	<0.001
SMN2 copies: 3	1.608	0.632	0.365	2.851	0.011
SMN2 copies: 4	0.976	1.066	-1.123	3.074	0.361
DMT	0.517	1.15	-1.747	2.78	0.654
Motor: sitter	0.75	0.619	-0.468	1.968	0.227
Motor: walker	-0.292	0.863	-1.99	1.406	0.735
Male sex	1.028	0.502	0.041	2.015	0.041
Age	-0.03	0.018	-0.065	0.005	0.092
Salbutamol/pyrid.	0.057	0.512	-0.949	1.064	0.911

In adjusted analyses, *SMN2* copy number was independently associated with fatigue, with **a higher copy number indicating lower fatigue** (3 vs. 2 copies; $p = 0.011$). **Male sex** was also independently associated with **lower fatigue scores** ($p = 0.041$). **Motor function status was not independently associated** with perceived fatigue after adjustment.

Multivariable Model for the Aggregated Score of Perceived Fatigability Items (6-19)

Variables	Estimate	Std Error	Lower 95	Upper 95	*P*-value
(Intercept)	41.762	3.481	34.912	48.611	<0.001
SMN2 copies: 3	6.289	1.593	3.154	9.424	<0.001
SMN2 copies: 4	7.064	2.681	1.787	12.34	0.009
DMT	0.497	2.888	-5.187	6.182	0.863
Motor: sitter	13.314	1.575	10.215	16.414	<0.001
Motor: walker	14.532	2.189	10.225	18.839	<0.001
Male sex	-1.421	1.267	-3.913	1.072	0.263
Age	-0.115	0.045	-0.203	-0.027	0.011
Salbutamol/pyrid.	1.267	1.289	-1.27	3.804	0.326

By contrast, perceived fatigability showed a strong and independent **association with disease severity**. Compared with non-sitters, **sitters and walkers reported significantly lower fatigability** ($p < 0.001$). A **higher *SMN2* copy number** (3 and 4 copies) was associated with **lower fatigability** ($p < 0.001$). **Increasing age** was associated with **greater global fatigability** ($p = 0.011$), although the effect size was small.

Conclusions

Perceived fatigue and perceived fatigability are statistically and clinically distinct constructs in pwSMA, with divergent patterns of association. Both were related to *SMN2* copy number; however, perceived fatigue showed only a weak association with disease severity and instead exhibited an independent sex effect, whereas perceived fatigability closely reflected functional status and genetic burden and increased modestly with age. These findings support the separate measurement and analysis of fatigue and fatigability using disease-specific PROMs.

Acknowledgements:
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