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Original research

Loss of ambulation in SMA III at the time of disease-modifying treatments: an international study

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ABSTRACT

Background Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder caused by survival motor neuron (SMN1) deletion. While loss of ambulation in SMA type III typically occurs at a median age of 13.4 years, outcomes in the treatment era remain unclear. This study aims to address that gap by investigating ambulation outcomes in individuals with type III receiving disease-modifying therapies.

Methods This retrospective study analysed prospectively collected international data. Time-dependent Cox models assessed the association between treatment initiation and age at loss of ambulation, adjusting for age at onset, sex, SMN2 copies, birth year and country. Treatment was modelled as a time-dependent covariate to avoid immortal time bias. Descriptive analyses used Mann-Whitney U and χ^2 tests.

Results Among 555 individuals with type III, treatment halved the risk of ambulation loss (HR=0.50), with median loss at 44 vs 32 years in treated and untreated groups. Later onset, ≥4 SMN2 copies and female sex were also protective. The treatment effect was significant in type IIIA (HR=0.34) but not IIIB, with no significant interactions by sex, country or SMN2, though effects remained directionally protective.

Conclusions Treatment in type III reduced the risk of ambulation loss by 50%, extending median ambulation by 12 years, with the greatest benefit in type IIIA. Later onset, female sex and higher SMN2 copy number were also protective but did not modify treatment effect. These findings underscore the value of early treatment and support its broad use to preserve ambulation across clinical subgroups.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type III usually leads to ambulation loss in adolescence, but the impact of disease-modifying therapies on this outcome has not been systematically studied.

WHAT THIS STUDY ADDS

⇒ Disease-modifying therapies halve the risk of ambulation loss and extend walking ability by more than a decade, with the greatest benefit in type IIIA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results support early and widespread treatment to preserve ambulation and provide new benchmarks for care, counselling and trial design.

INTRODUCTION

Spinal muscular atrophy (SMA) is a genetically determined neuromuscular disorder that impacts motor neurons and their associated motor units, leading to muscle atrophy and weakness.[1] The primary cause of the SMA phenotype is related to mutations in the survival motor neuron (*SMN1*) gene situated on chromosome 5q13.[2] Individuals with the mildest SMA type, type III or IV, acquire the ability to walk independently.[3 4] Type III is further subclassified into type IIIA, with symptom onset before age 3, and type IIIB, with onset after age 3.[5] Motor function is progressively compromised even in type III, with persistent weakness, leading to gait impairments, fatigue and, in many cases, eventual loss of ambulation (LOA).[3 5 6] In a recent review synthesised natural history data from 22 arms across 7 studies,[7] the median time to LOA in the overall population was estimated to be 13.4 years, encompassing a total population of 1327 individuals with type III.

Further stratification based on SMA subtype revealed that for type IIIA, the median time to LOA was 13.4 years, while for type IIIB, it extended significantly to 44.2 years. Nonetheless, the 25th percentiles for the risk of LOA varied substantially—from 7.0 to 25.0 years—across different pooling scenarios, highlighting the heterogeneity within the type III population.

The therapeutic landscape of SMA has been transformed by the advent of disease-modifying therapies (DMTs),[8–12] which target the underlying genetic deficiency of the SMN protein. Currently approved DMTs—including nusinersen,[13] onasemnogene abeparvovec[14] and risdiplam[15]—increase SMN protein levels through different mechanisms and have shown significant clinical benefit, particularly when initiated early in the disease course.

Several studies have reported the beneficial effects of the available drugs using functional scales,[16–20] but a critical gap remains in understanding the extent to which these therapies influence the timing or likelihood of losing ambulation in comparison with the well-known natural history of LOA in type III.[21–27]

Given that maintaining ambulation is a major functional priority, understanding the impact of treatment on this outcome is critical for both clinical management and individual counselling regarding the expectations for individuals living with type III.

This study aims to address this gap by evaluating the risk of LOA in individuals with type III undergoing DMTs.

METHODS

This study is a retrospective analysis of prospectively collected data from the International Spinal Muscular Atrophy Consortium registry,[28] which includes centres from Italy, the UK and the USA.

Within this framework, data were systematically gathered prospectively through a structured electronic case report form (eCRF).[28] Data were extracted from the registry from January 2025 to April 2025.

Participants were eligible for inclusion if they had a confirmed diagnosis of type III,[3] known age of symptom onset and known *SMN2* copy number. Individuals of any age and any sex assigned at birth were considered. Participants receiving DMTs were included only if they were being treated with approved therapies, in the countries where this study was conducted, both nusinersen and risdiplam are approved to be used commercially for type III. Follow-up data from individuals who initiated investigational products were censored at the time investigational treatment began. Individuals who received DMTs prior to symptom onset were also excluded. LOA was defined as the inability to walk 10 m unassisted.

Statistical analysis

Data are presented as median and IQR for continuous variables and as frequency and percentage for categorical variables. To compare characteristics between included and excluded individuals, a χ^2/Fisher's exact test was used for categorical variables, while the Mann-Whitney U test was applied for continuous variables. Age at LOA was calculated from the date of birth to the date of the event. For those who remained ambulatory, follow-up was censored at the date of last contact. The association between DMT initiation and LOA was estimated using time-dependent Cox proportional hazards models. In these models, DMTs were included as a time-dependent covariate: individuals were assigned a value of 0 before DMT initiation and 1 after treatment began. This approach was necessary to avoid immortal time bias—that is, the period during which individuals must survive to receive treatment, which would otherwise be incorrectly attributed to the treatment group and artificially inflate its apparent benefit. By modelling treatment as time-dependent, individuals contributed person-time to the untreated group until the actual start of treatment, serving as appropriate controls for those receiving treatment during the same period. The following covariates were considered and selected a priori: age at symptom onset, sex, *SMN2* copy number, year of birth and country. The year of birth was included to account for calendar bias, as access to diagnosis, standards of care and treatment availability have evolved over time and may influence outcomes independently of treatment. Adjustment for age at symptom onset further helps control for differences in disease severity and timing of clinical presentation—even among individuals born in the same year—ensuring a more accurate comparison of treatment effects across individuals with different disease trajectories.

Statistical tests were conducted using R (V.4.3.2) and SAS (V.9.4; SAS Institute). A $p \leq 0.05$ was considered statistically significant.

RESULTS

The initial cohort included 655 individuals with type III, 388 classified as type IIIA and 265 as type IIIB (table 1).

Their median age at last follow-up was 28.76 (22.9 in IIIA and 36.1 in IIIB) years.

Of the 655 individuals, 218 (33%) lost ambulation (156 with type IIIA and 62 with type IIIB). Among the 156 IIIA, 148 (95%) lost ambulation before DMT initiation (n=144, 97%) or within 1 year after starting DMTs (n=4, 3%). Among the 62 IIIB, 54 (87%) lost ambulation before DMT initiation (n=53, 98%) or within 1 year after starting DMT (n=1, 2%).

Among the 304 IIIA and IIIB individuals who had been on DMTs for more than 1 year, 283 (93%) remained ambulatory.

Table 2 presents details on age at first DMTs as well as the time from DMTs to LOA or last follow-up categorised by SMA subtypes IIIA and IIIB and ambulatory status.

Figure 1 shows the percentage of individuals losing or not losing ambulation subdivided by treatment status (treated vs not treated) at event and by age groups at LOA or last follow-up.

Figure 2 shows individual details of ambulatory status according to age at DMT initiation and DMT duration at event.

Survival analysis

Of the 655 individuals with type III eligible for survival analysis, *SMN2* copy number was not available in 100 individuals, resulting in a final sample of 555 individuals (84.7%).

Baseline characteristics of individuals included and excluded from the analysis are shown in table 1.

503 of the 555 individuals (90.6%) started DMTs at a median age of 17.41 years (IQR 9.49, 33.00), while 52 (9.4%) individuals did not receive any DMTs. No significant differences were found between individuals who received and those who did not receive DMTs during the follow-up and individuals who never received DMTs in terms of sex, age at diagnosis, age at symptoms onset, year of birth and copy number. Of the 503 who received DMTs, 105 were on risdiplam-only, 333 were on nusinersen-only and 65 switched from nusinersen to risdiplam.

Online supplemental table 1 presents the demographic characteristics of treated-population and never treated groups.

The median age at LOA in all type III was 32 years in untreated periods and 44 years during DMTs (figure 3A).

Table 1 Comparison of demographic and clinical characteristics at baseline and follow-up

	Level	Overall (n=655)	Excluded (n=100)	Included (n=555)	P value
Registry country (%)	ITA	488 (74.5)	66 (66.0)	422 (76.0)	<0.001
	UK*	27 (4.1)	17 (17.0)	10 (1.8)	
	USA	140 (21.4)	17 (17.0)	123 (22.2)	
Sex assigned at birth (%)	Female	315 (48.1)	52 (52.0)	263 (47.4)	0.46
	Male	340 (51.9)	48 (48.0)	292 (52.6)	
SMN2 copy number (%)	1	1 (0.2)	0 (0.0)	1 (0.2)	<0.001
	2	41 (6.3)	0 (0.0)	41 (7.4)	
	3	281 (42.9)	0 (0.0)	281 (50.6)	
	4+	232 (35.4)	0 (0.0)	232 (41.8)	
	Unknown	100 (15.3)	100 (100.0)	0 (0.0)	
SMA III subtype (%)	A	388 (59.4)	65 (65.7)	323 (58.3)	0.20
	B	265 (40.6)	34 (34.3)	231 (41.7)	
Median age at treatment initiation, years (IQR)		24.49 (11.33, 41.08)	29.68 (14.32, 46.23)	24.17 (11.14, 40.55)	0.05
Year of birth† (%)	Pre-2007	477 (72.82)	79 (79.0)	398 (71.71)	0.04
	2007–2017	153 (23.36)	21 (21.0)	132 (23.78)	
	Post-2017	25 (3.82)	0 (0.0)	25 (4.51)	
Median age at diagnosis, years (IQR)		5.00 (2.50, 15.00)	4.37 (2.50, 13.54)	5.70 (2.52, 15.00)	0.56
Median age at symptoms onset, years (IQR)		2.69 (1.58, 6.90)	2.13 (1.50, 3.98)	2.75 (1.59, 7.00)	0.06
Median age at last follow-up, years (IQR)		28.76 (15.95, 45.86)	32.02 (18.02, 49.91)	28.41 (15.55, 44.71)	0.15
Treated individuals during the follow-up, n (%)	Never treated	68 (10.4)	16 (16.0)	52 (9.4)	0.068
	Treated	587 (89.6)	84 (84.0)	503 (90.6)	

*Only one centre from the UK participated in the study (Great Ormond Street Hospital for Children).
†Stratified according to standards of care publications.[36–38]
ITA, Italy; SMA, spinal muscular atrophy.

Exposure to DMTs was significantly associated with a reduced risk of ambulation loss (HR=0.50; 95% CI 0.30 to 0.80; p=0.004). Older age at symptom onset was associated with a lower risk of ambulation loss (HR=0.82 per year; 95% CI 0.78 to 0.85; p<0.0001). The risk of LOA was more than twice as high in males, indicating that females had a significantly lower hazard (HR=2.05; 95% CI 1.56 to 2.70; p<0.0001).

Individuals with four or more *SMN2* copies had a significantly lower risk compared with those with two copies (HR=0.29; 95% CI 0.18 to 0.48; p<0.0001), while no significant difference was observed in individuals with three copies (HR=0.82; 95% CI 0.51 to 1.30; p=0.391). No significant differences in risk were observed across countries.

Table 3 summarises results from the multivariable Cox proportional hazards regression model, where treatment status was modelled as a time-dependent variable.

Green lines represent periods during which patients were treated; red lines represent periods during which patients were untreated. Each patient is represented at the time LOA (or remained ambulant) occurred, based on their treatment status during that period. These curves are time-dependent: a patient may contribute to both treated and untreated curves if their treatment status changed over time when still ambulant.

Subgroup analysis indicated that the protective effect of DMTs against LOA was generally consistent across most subgroups. A significant interaction was observed between DMTs and SMA III subtype (p=0.029; figure 4). In type IIIA, DMTs were associated with a significantly lower risk of LOA (HR=0.34; 95% CI 0.18 to 0.64; figure 3B). In contrast, no significant association between DMTs and LOA was found in type IIIB (HR=0.93; 95% CI 0.42 to 2.06; figure 3C). No significant interactions were observed for sex (p=0.573), country of care (p=0.816), or *SMN2* copy number (p=0.672).

Figure 4 summarises the effect of DMTs on LOA across clinically relevant subgroups.

Among the 105 individuals treated with risdiplam-only, 2 (2%) lost ambulation during treatment. Of the 333 treated with nusinersen-only, 16 (4.8%) lost ambulation during treatment.

Table 2 Age at first DMTs and time from DMTs to LOA or last FU, stratified by SMA type III subclassification and ambulatory status

		SMA III A		SMA III B	
		LOA (N=12)	Remained ambulant (N=137)	LOA (N=9)	Remained ambulant (N=144)
Time from first DMTs to event (LOA or last FU)	Mean (SD)	2.86 (2.09)	4.32 (2.15)	3.38 (1.61)	3.95 (2.04)
	Median (IQR)	3.19 (3.24)	4.96 (3.55)	2.87(2.27)	4.25 (3.79)
Age at first DMTs	Mean (SD)	12.3 (10.3)	11.2 (11.7)	47.7 (12.2)	29.2 (17.1)
	Median (IQR)	8.68 (7.32)	6.99 (10.9)	51.4 (13.4)	25.3 (23.0)

Age at LOA was used for the patients who lost ambulation over FU, while age at last FU was used for the patient who remained ambulant at their last FU visit.
DMTs, disease-modifying therapies; FU, follow-up; LOA, loss of ambulation; SMA, spinal muscular atrophy.

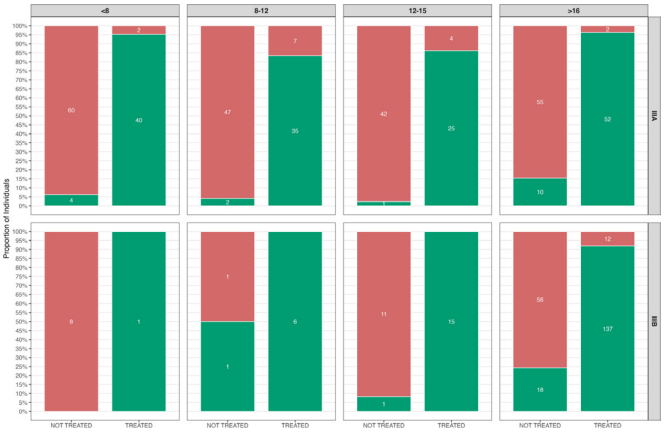

Figure 1 Individuals losing or not losing ambulation subdivided by treatment status at event. Percentage of individuals losing or not losing ambulation subdivided by treatment status at event (red=lost ambulation, green=not lost ambulation).

Among the 65 who received both DMTs, 3 (4.6%) lost ambulation during DMTs (all occurred while on nusinersen, the first DMTs received). Due to the small number of events, along with notable differences in group sizes and baseline demographic and clinical characteristics, formal statistical comparisons were not performed, as they would likely lack sufficient power and could be misleading. Future studies specifically designed to capture DMT effects, including through the use of exclusively treated cohorts, would be necessary to facilitate a meaningful comparative analysis.

DISCUSSION

Several studies have reported LOA in type III individuals.[7 21 22 24–26 29] Zerres *et al* reported that the risk of losing ambulation increased over time in individuals with type III.[5 26] Specifically, in type IIIA, the probabilities of remaining ambulatory at 10, 20 and 40 years after disease onset were 73%, 44% and 34%, respectively. In contrast, individuals with type IIIB had a more favourable prognosis, with 97%, 89% and 67% still ambulatory at the same time points.[5] As confirmed by a recent meta-analysis, LOA is still a frequent finding even in more recent natural history studies performed before the advent of the DMTs[7] with a median age of LOA of 13.4 years for IIIA and 44.2 years for IIIB.

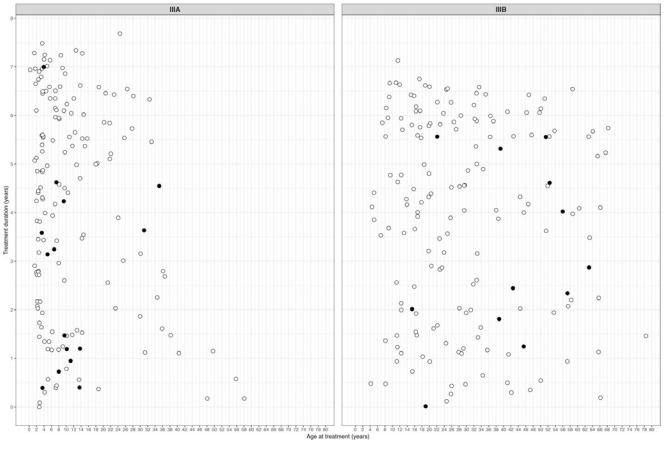

Figure 2 Treatment duration at event versus age at treatment in treated individuals. Black dot=individual who lost ambulation, White dot=individual who did not lose ambulation.

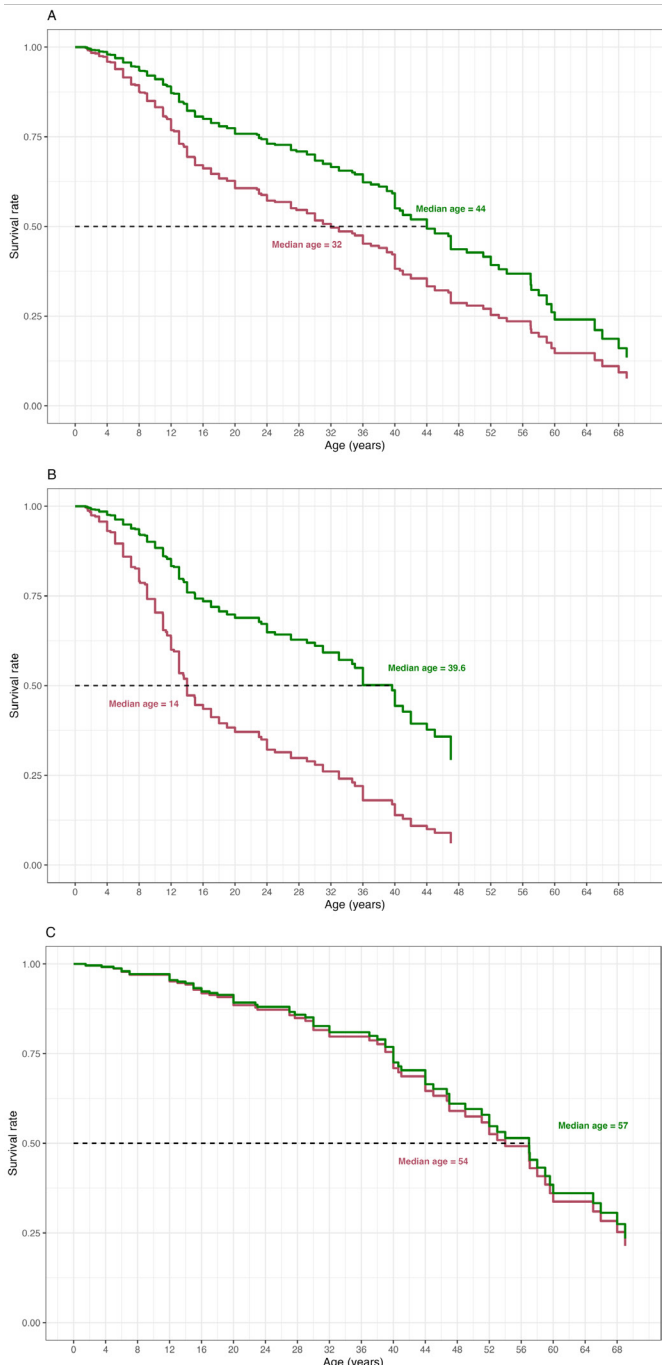

Figure 3 Adjusted time-dependent Kaplan-Meier curves by treatment status. (A) Whole SMA type III cohort; (B) SMA type IIIA; (C) SMA type IIIB. SMA, spinal muscular atrophy.

The full extent to which DMTs may change LOA has not been well defined as yet.[30] While the short-term efficacy of the new DMTs on motor function has been reported by several studies,[16–20] few studies have concentrated on LOA as this requires a longer period of observation. As DMTs have been available for nearly a decade, it is now possible to start analysing the data obtained in children and adults with type III to explore the possible effect of the DMTs on LOA. Interestingly, across our whole cohort of type III individuals, the percentage of treated individuals who lost ambulation was very low. This held true for

Table 3 Time-dependent cox regression model

	HR (95% CI)	P value
Treatment status	0.50 (0.30 to 0.80)	0.004
Age at symptom onset	0.82 (0.78 to 0.85)	<0.0001
Sex assigned at birth (male vs female)	2.05 (1.56 to 2.70)	<0.0001
Copy number (3 vs 2)	0.82 (0.51 to 1.30)	0.391
Copy number (4+ vs 2)	0.29 (0.18 to 0.48)	<0.0001
Country (UK vs ITA)	0.73 (0.18 to 2.99)	0.660
Country (USA vs ITA)	0.75 (0.52 to 1.09)	0.131
Year of birth	1.01 (1.00 to 1.02)	0.152

The only individual with one *SMN2* copy and a modifier gene was grouped with those having two copies.
ITA, Italy; SMN2, survival motor neuron type II.

the great majority of type III individuals, including those with type IIIA reaching puberty, who in natural history had a much higher risk of losing ambulation.[7] It should be noted that in the small group of 21 treated individuals who lost ambulation, 5 lost ambulation within a year from starting DMTs. All individuals in this subgroup, even if able to walk more than 10 m independently, were only able to perform very limited distances on the 6 min walk test or were unable to complete it for safety reasons, these findings suggesting the need for early treatment.

In order to better quantify the possible effect of DMTs on LOA, we performed a time-dependent analysis. As most individuals in our cohort transitioned from being untreated to receiving DMTs during follow-up, a time-dependent Cox regression model was chosen to account for immortal time bias. This approach was essential to avoid overestimating treatment effects by properly accounting for the time individuals spent untreated before starting therapy.

The analysis provided strong evidence of the effectiveness of DMTs in reducing the risk of LOA among individuals with type III. In the overall type III cohort, exposure to DMTs was associated with a 50% reduction in the hazard of LOA (HR=0.50; 95% CI 0.30 to 0.80; p=0.004), when compared with untreated individuals. This demonstrates a substantial therapeutic benefit when administered during the ambulatory phase.

In addition to DMTs, other key prognostic factors were identified. Males and individuals with 2 *SMN2* copies had a significantly higher risk of LOA compared with females and individuals with four copies. Prior studies have documented more severe

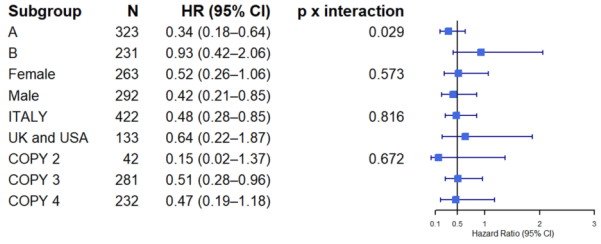

Figure 4 Forest plot of treatment effect on LOA by clinical subgroup. Each horizontal line represents the estimated treatment effect with its 95% CI. The vertical line at 0.5 reflects the total treatment effect observed in the analysed cohort. Estimates to the left of this line suggest a reduced risk of LOA with treatment, while those to the right suggest no benefit. The plot includes p values for interaction, indicating whether the treatment effect significantly differs between subgroups. Interpretation focuses on CIs crossing 0.5 and the interaction p values to assess subgroup differences in treatment response. LOA, loss of ambulation.

phenotypes in affected males compared with female siblings, and sex-specific differences in ambulatory ratios among SMA type III patients.[31–33] Several mechanisms may contribute to this sex difference, including potential neuroprotective effects of oestrogen, sex-specific differences in SMN protein regulation, or differential expression of modifier genes on sex chromosomes.

There were no significant differences in risk of LOA adjusting by country or year of birth, suggesting that variations in standards of care across countries and potential calendar bias did not significantly affect the risk of LOA in this cohort.

The significantly reduced risk of LOA with later age at symptom onset (18% lower risk of LOA per additional year) (HR=0.82; 95% CI 0.78 to 0.85; p<0.0001) likely suggested a possible difference between IIIA (onset before 3 years) and IIIB (onset after 3 years). This was confirmed by the subgroup analyses revealing a significant interaction emerging between DMTs and type III subtype (p=0.029).

The change in median age at ambulation loss in the whole type III cohort, increasing from 32 years in untreated individuals to 44 years in treated individuals, was mainly driven by the III A subgroup who showed a much lower risk of LOA (66%). In type IIIA, the median age at LOA changed from 14 years in untreated to 39.6 years in treated individuals, suggesting that the exposure to DMTs was strongly protective in this subgroup (HR=0.34; 95% CI 0.18 to 0.64).

In contrast, the effect of exposure to DMTs was not significant in type IIIB (HR=0.93; 95% CI 0.42 to 2.06). This likely reflects the potentially slower progression of this subtype[32 34 35] in which LOA does not always occur or, when this happens, may occur very late in life.

Although males and individuals with fewer *SMN2* copies (2 *SMN2* vs 4+*SMN2*) had a higher baseline risk of LOA, the relative benefit of DMTs is consistent across these groups. As part of the subgroup analysis considering the interaction with DMTs, no significant interactions were observed between DMTs and sex assigned at birth (p=0.573) or *SMN2* copy number (p=0.672). These results support the generalisability of therapeutic benefit irrespective of these individual characteristics.

Overall, these findings, even if limited to a relatively short follow-up period, provide initial evidence that DMTs in type III individuals have an impact on LOA. In approximately a third of the individuals who lost ambulation, this occurred in individuals who already had limited mobility at the time when DMT was started, suggesting that early treatment—particularly in type IIIA—may prevent or delay LOA.

The use of time-dependent survival analysis provided further information on the influence of other variables. Individual risk factors such as sex, *SMN2* copy number and age at symptom onset influence the overall progression and risk of LOA. However, these factors do not appear to significantly modify the therapeutic response as this can be observed in the whole group of treated individuals irrespective of these variables. These results highlight the sustained benefit of treatment across a broad spectrum of individuals and reinforce the role of early and proactive management to preserve motor function and long-term mobility in type III.

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Contributors GC and FB contributed equally to this work as co-first authors. GC was responsible for study conceptualisation, data curation, formal analysis, investigation, methodology, project administration and writing the original draft. FB conducted all statistical analyses, developed the statistical methodology, performed data validation and contributed to writing the original draft. VF, JM, VAS, SDY, CC, AP, MCP, MP, AG, EP, TD, ES, MS, SM, EC, MCS, AD'A, RR-T, TM, LM, MC, MF, RZ, RM, GR, CB, LR, VV, ED'e, LV, VN, GS, MG, MT, CT, AB, CA, FR and ZZ-C were responsible for patient recruitment, clinical assessments, data collection at their respective centres, and writing the original draft. BTD, JD, MH, FM and RSF contributed to study design, provided scientific oversight, secured funding and revised the manuscript for important intellectual content. EM conceived and designed the study, supervised all aspects of the research, obtained funding, contributed to the writing of the original draft and takes responsibility as guarantor for the integrity of the work as a whole.

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REFERENCES

1 D'Amico A, Mercuri E, Tiziano FD, *et al*. Spinal muscular atrophy. *Orphanet J Rare Dis* 2011;6:71.
2 Lefebvre S, Bürglen L, Reboullet S, *et al*. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell* 1995;80:155–65.
3 Salort-Campana E, Quijano-Roy S. Clinical features of spinal muscular atrophy (SMA) type 3 (Kugelberg-Welander disease). *Arch Pediatr* 2020;27:7S23–8.
4 Dubowitz V. Chaos in classification of the spinal muscular atrophies of childhood. *Neuromuscul Disord* 1991;1:77–80.
5 Zerres K, Rudnik-Schöneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. *Arch Neurol* 1995;52:518–23.
6 Montes J, McDermott MP, Mirek E, *et al*. Ambulatory function in spinal muscular atrophy: Age-related patterns of progression. *PLoS One* 2018;13:e0199657.
7 Aponte Ribero V, Marti Y, Batson S, *et al*. Systematic Literature Review of the Natural History of Spinal Muscular Atrophy: Motor Function, Scoliosis, and Contractures. *Neurology (ECronicon)* 2023;101:e2103–13.
8 Messina S, Sframeli M. New Treatments in Spinal Muscular Atrophy: Positive Results and New Challenges. *J Clin Med* 2020;9.
9 Angilletta I, Ferrante R, Giansante R, *et al*. Spinal Muscular Atrophy: An Evolving Scenario through New Perspectives in Diagnosis and Advances in Therapies. *Int J Mol Sci* 2023;24.
10 Armengol VD, Darras BT, Abulaban AA, *et al*. Life-Saving Treatments for Spinal Muscular Atrophy: Global Access and Availability. *Neurol Clin Pract* 2024;14:e200224.
11 Audic F. Gene therapy in spinal muscular atrophy. *Arch Pediatr* 2023;30:8S12–7.
12 Farrar MA, Park SB, Vucic S, *et al*. Emerging therapies and challenges in spinal muscular atrophy. *Ann Neurol* 2017;81:355–68.
13 Aartsma-Rus A. FDA Approval of Nusinersen for Spinal Muscular Atrophy Makes 2016 the Year of Splice Modulating Oligonucleotides. *Nucleic Acid Ther* 2017;27:67–9.
14 Naveed A, Calderon H. Onasemnogene Abeparvovec (AVXS-101) for the Treatment of Spinal Muscular Atrophy. *J Pediatr Pharmacol Ther* 2021;26:437–44.
15 Paik J. Risdiplam: A Review in Spinal Muscular Atrophy. *CNS Drugs* 2022;36:401–10.
16 Coratti G, Cutrona C, Pera MC, *et al*. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. *Orphanet J Rare Dis* 2021;16:430.
17 Hagenacker T, Maggi L, Coratti G, *et al*. Effectiveness of Nusinersen in Adolescents and Adults with Spinal Muscular Atrophy: Systematic Review and Meta-analysis. *Neurol Ther* 2024;13:1483–504.
18 Pascual-Morena C, Cavero-Redondo I, Lucerón-Lucas-Torres M, *et al*. Onasemnogene Abeparvovec in Type 1 Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis. *Hum Gene Ther* 2023;34:129–38.
19 Pascual-Morena C, Martínez-Vizcaíno V, Cavero-Redondo I, *et al*. Efficacy of risdiplam in spinal muscular atrophy: A systematic review and meta-analysis. *Pharmacotherapy* 2024;44:97–105.
20 Qiao Y, Chi Y, Gu J, *et al*. Safety and Efficacy of Nusinersen and Risdiplam for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Brain Sci* 2023;13:1419.
21 Kaneko K, Arakawa R, Urano M, *et al*. Relationships between long-term observations of motor milestones and genotype analysis results in childhood-onset Japanese spinal muscular atrophy patients. *Brain Dev* 2017;39:763–73.
22 Wadman RI, Stam M, Gijzen M, *et al*. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0-4. *J Neurol Neurosurg Psychiatry* 2017;88:365–7.
23 Russman BS, Buncher CR, White M, *et al*. Function changes in spinal muscular atrophy II and III. The DCN/SMA Group. *Neurology (ECronicon)* 1996;47:973–6.
24 Chung BHY, Wong VCN, Ip P. Spinal muscular atrophy: survival pattern and functional status. *Pediatrics* 2004;114:e548–53.
25 Lusakowska A, Jedrzejowska M, Kaminska A, *et al*. Observation of the natural course of type 3 spinal muscular atrophy: data from the polish registry of spinal muscular atrophy. *Orphanet J Rare Dis* 2021;16:150.
26 Zerres K, Rudnik-Schöneborn S, Forrest E, *et al*. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. *J Neurol Sci* 1997;146:67–72.
27 Hu C, Li X, Shi Y, *et al*. Comprehensive profile and natural history of pediatric patients with spinal muscular atrophy: A large retrospective study from China. *Front Neurol* 2022;13:1038012.
28 Mercuri E, Finkel R, Scoto M, *et al*. Development of an academic disease registry for spinal muscular atrophy. *Neuromuscul Disord* 2019;29:794–9.
29 Rudnik-Schöneborn S, Hausmanowa-Petrusewicz I, Borkowska J, *et al*. The predictive value of achieved motor milestones assessed in 441 patients with infantile spinal muscular atrophy types II and III. *Eur Neurol* 2001;45:174–81.
30 Pechmann A, Behrens M, Dörnbrack K, *et al*. Improvements in Walking Distance during Nusinersen Treatment - A Prospective 3-year SMArtCARE Registry Study. *J Neuromuscul Dis* 2023;10:29–40.
31 Maggi L, Bello L, Bonanno S, *et al*. Adults with spinal muscular atrophy: a large-scale natural history study shows gender effect on disease. *J Neurol Neurosurg Psychiatry* 2022;93:1253–61.
32 Coratti G, Messina S, Lucibello S, *et al*. Clinical Variability in Spinal Muscular Atrophy Type III. *Ann Neurol* 2020;88:1109–17.
33 Sun J, Harrington MA, Porter B, *et al*. Sex Difference in Spinal Muscular Atrophy Patients - are Males More Vulnerable? *J Neuromuscul Dis* 2023;10:847–67.
34 Deymeer F, Serdaroglu P, Parman Y, *et al*. Natural history of SMA IIIb: muscle strength decreases in a predictable sequence and magnitude. *Neurology (ECronicon)* 2008;71:644–9.
35 Ricci M, Cicala G, Capasso A, *et al*. Clinical Phenotype of Pediatric and Adult Patients With Spinal Muscular Atrophy With Four SMN2 Copies: Are They Really All Stable? *Ann Neurol* 2023;94:1126–35.
36 Mercuri E, Finkel RS, Muntoni F, *et al*. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord* 2018;28:103–15.
37 Finkel RS, Mercuri E, Meyer OH, *et al*. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord* 2018;28:197–207.
38 Wang CH, Finkel RS, Bertini ES, *et al*. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol* 2007;22:1027–49.