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ORIGINAL ARTICLE

Long-term natural history in type II and III spinal muscular atrophy: a 4-year international study on the Hammersmith Functional Motor Scale Expanded

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Abstract

Background and purpose: Spinal muscular atrophy (SMA) is a genetic disorder caused by *SMN1* gene mutations. Although studies on available disease-modifying treatments have reported their efficacy and safety, long-term natural history data are lacking for comparison. The aim of this prospective study was to report 4-year changes on the Hammersmith Functional Motor Scale Expanded (HFMSE) in type II and III SMA in relation to several variables such as age, functional status and *SMN2* copy number.

Methods: The study involves retrospective analysis of prospectively collected data from international datasets (Belgium, Italy, Spain, USA, UK). HFMSE longitudinal changes were analyzed using linear mixed effect models, examining annualized HFMSE change and its association with variables such as age at baseline, sex, motor function, *SMN2* copy number.

Results: In SMA type II ($n = 226$), the 4-year mean change was −2.20 points. The largest mean changes were observed in sitters aged 5–14 years and the lowest in those who lost the ability to sit unsupported. In SMA type III ($n = 162$), the 4-year mean change was −2.75

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points. The largest mean changes were in those aged 7–15 years, whilst the lowest were in those below 7 and in the SMA type IIIa subgroup over 15. Age and score at baseline were predictive of 4-year changes.

Conclusions: Our findings provide natural history reference data for comparison with long-term follow-up of clinical trials or real-world data, highlighting the need to define patterns of changes in smaller SMA subgroups instead of reporting mean changes across an entire SMA cohort.

KEYWORDS
Hammersmith Functional Motor Scale Expanded, long-term results, motor function, spinal muscular atrophy

INTRODUCTION

Spinal muscular atrophy (SMA) is a genetic progressive disorder caused by mutations in the *SMN1* gene. Historically, SMA is classified according to the onset of clinical signs and the maximum motor function achieved [1]. The advent of disease-modifying treatments (DMTs) has completely altered the disease progression in SMA [2]. These drugs have now been available for over 7 years and several studies have reported efficacy and safety data. In SMA type I infants [3, 4], survival beyond 2 years, acquisition of motor milestones and durability of effect provide clear evidence of the efficacy of the DMTs [5–8] compared to the invariable progression with limited survival beyond the age of 2 years in untreated infants. In contrast in SMA type II, and even more in SMA type III, the wide variability in progression reported in untreated individuals [9–13] makes the interpretation of efficacy less obvious. Recent studies have reported that in participants with type II and III SMA the observed relative stabilization or minimal improvement observed in the treated cohorts can be better interpreted by comparing these findings to subgroups matched for age and functional status available from natural history studies [14–19].

The interpretation of long-term results is complicated by the paucity of natural history studies reporting progression of the disease beyond 1 or 2 years. The aim of this study was to report 4-year changes in a large cohort of untreated type II and type III SMA individuals as part of a large international effort. In consideration of the variability of changes observed in shorter follow-up studies amongst these patients, the rate of changes in relation to a number of variables such as age, functional status, *SMN2* copy number and sex was also explored in an attempt to identify how each of these variables contribute to the progression of the disease.

METHODS

The study involves retrospective analysis of prospectively collected data from various international datasets, which encompassed the three networks affiliated with the international SMA consortium [20]. These include the Pediatric Neuromuscular Clinical Research Network for SMA in the United States, Italy and the UK-SMA REACH (with data collected from July 2003 to July 2022), a natural history network in Spain (data collected from September 2015 to May 2021) and another in Belgium (data collected from June 2006 to June 2018).

All individuals who had a confirmed genetic diagnosis of SMA and a clinical diagnosis of type II or III SMA were considered for inclusion in the study. This encompassed all participants who had been examined at the neuromuscular clinics of the participating centers, using the same criteria employed in our previous collaborative study on progression patterns [10, 16, 21]. Participants who were participating in clinical trials or received any available DMTs were excluded from the analysis.

To comply with the procedures of the participating networks, all participants and legal guardians provided written informed consent or assent as appropriate, which was approved by the respective institutional review boards.

Hammersmith Functional Motor Scale Expanded (HFMSE)

The HFMSE [22] comprises 33 items that assess the child's capacity to engage in various activities. Each activity (item) is evaluated using a 3-point scoring system. A score of 2 indicates that the child can perform the activity without any modifications, a score of 1 indicates that the child can perform the activity with modifications or adaptations, and a score of 0 indicates that the child is unable to perform the activity. By adding up the scores for all the individual items, a total score can be obtained. The total score can range from 0, indicating failure in all activities, to 66, indicating successful completion of all activities. It is mandatory to conduct the assessments for all items without the use of spinal jackets or orthoses. HFMSE was administered at each center at least every 6 months, in accordance with the standards of care.

The HFMSE was employed as the outcome measure throughout the study, utilizing a pilot version before its official release, which occurred in 2007 [22].

Training sessions

A standardized HFMSE manual was distributed amongst all the networks taking part in the study. As part of their respective network

activities, evaluators from each network received training during in-person meetings held in the United States and Europe [23]. The evaluators who conducted the assessments included in the current study were the same individuals who participated in the reliability studies. In both Europe and the United States, evaluators undergo regular annual refresher training that involves reviewing the scale items and scoring methods.

Statistical analysis

Baseline participant characteristics were described as proportions (percentages) for categorical variables and means with standard deviation or median and interquartile range (IQR) for continuous variables. Due to the presence of missing at random values, multiple imputation was used to maximize the use of available information. Imputation was performed on participants who had at least 6 months of follow-up, using the chained equations approach with 10 imputations, where each incomplete variable is imputed by a separate model and implemented through the Multiple Imputation by Chained Equation algorithm. In the imputation models age and HFMSE at baseline, sex, SMA type and functional level, and *SMN2* copy number were included as predictors.

Longitudinal changes in HFMSE were obtained using linear mixed effect models to account for repeated measures over the follow-up period. Cumulative changes at 1, 2, 3 and 4 years (±3 months) from baseline were estimated using time as fixed effect and a random intercept to account for individual differences. All the analyses were adjusted for baseline HFMSE values and for the registry where participants were enrolled.

Following previous literature findings, the cohort was further subdivided by functional level at baseline (non-sitters/sitters/walkers), by *SMN2* copy number (2, 3, 4+) and by age at baseline (SMA II, <5/5–13/14–18/>18; SMA III, <7/7–15/≥15) [10, 24]. Ability to sit independently was defined as a score of 2 on item 1 of the HFMSE and ability to walk independently was defined as participant able to walk 10 m without any help or support. The cut-off point for age was chosen based on our previous observation reporting slopes of progression in SMA type II and III at different age points [10, 21].

A linear mixed model analysis was conducted to examine the association between the annualized slopes of HFMSE change in participants with SMA type II and type III included in the longitudinal analysis and the following variables: age at baseline, sex, motor function, *SMN2* copy number and age of symptom onset (only for SMA type III, IIIa and IIIb).

RESULTS

The final dataset included 388 subjects. Of these, 226 were SMA type II (median follow-up 2.40, IQR 1.45–5.50, years) and 162 were SMA type III (median follow-up 2.45, IQR 1.48–4.62, years); 59.3% of the SMA type III were classified as SMA type IIIa (i.e., with onset of clinical signs before the age of 3 years) and 23.5% as SMA type IIIb (onset after the age of 3 years). Table 1 describes the baseline characteristics of the populations. Figure 1 shows individual trajectories for SMA type II and III patients.

Four-year HFMSE changes

Type II

Table 2 describes yearly changes from first visit (T0).

The 4-year change in the whole cohort of SMA type II was −2.20 (Figure 2), with an estimated annualized change of −0.58 points per year.

Sensitivity analysis for type II SMA

In a sensitivity analysis conducted using non-imputed data the 4-year change in the whole cohort of SMA type II was −3.34 (95% confidence interval [CI] −4.29 to −2.39), with an estimated annualized change of −0.69 (95% CI −0.87 to −0.50) points per year.

Type III

The 4-year change in the whole cohort of SMA type III was −2.75 (Table 3), with an estimated annualized change of −0.82 points per year.

Sensitivity analysis for type III SMA

In a sensitivity analysis, conducted using non-imputed data, the 4-year change in the whole cohort of SMA type III was −2.82 (95% CI −4.29 to −1.34), with an estimated annualized change of −0.81 (95% CI −1.11 to −0.52) points per year.

Predictors of disease progression

A linear mixed model analysis was conducted to examine the association between variables and HFMSE scores in participants with SMA type II and SMA type III included in the longitudinal analysis. The whole length of follow-up was included in the model. Since the *SMN2* copy number was included in the model as a possible predictor of disease progression, participants with unknown *SMN2* copies were excluded from the analysis ($n = 71$).

For SMA type II, the model included sex, *SMN2* copy number, age at first visit, initial HFMSE score, time since first visit, and patient-specific random intercepts. For SMA type III, the model included sex, current functional status, *SMN2* copy number, age at first

TABLE 1 Baseline characteristics of the participants.

	Overall population	SMA type II	SMA type III
	N = 388	*N* = 226	*N* = 162
Age at baseline (years)			
Mean (SD)	14.78 (14.24)	11.41 (10.52)	19.48 (17.15)
Median (range)	9.80 (2.50–79.24)	8.41 (2.50–64.63)	12.89 (2.50–79.24)
Sex, *n* (%)			
Male	195 (50.26)	122 (53.98)	73 (45.06)
Female	193 (49.74)	104 (46.02)	89 (54.94)
SMA function, *n* (%)			
Non-sitter	84 (21.65)	74 (32.74)	10 (6.17)
Sitter	199 (51.29)	152 (67.26)	47 (29.01)
Walker	105 (27.06)	0 (0.00)	105 (64.81)
HFMSE at baseline			
Mean (SD)	21.47 (20.47)	9.67 (9.76)	37.94 (20.13)
Median (range)	14.50 (0–66)	8.00 (0–40)	42.50 (0–66)
SMN2 copy number, *n* (%)			
2	41 (10.57)	30 (13.27)	11 (6.79)
3	220 (56.70)	150 (66.37)	70 (43.21)
≥4	56 (14.43)	5 (2.21)	51 (31.48)
Unknown	71 (18.30)	41 (18.14)	30 (18.52)
Type IIIa/b, *n* (%)			
a	N/A	N/A	86 (53.09)
b	N/A	N/A	50 (30.86)
Unknown	N/A	N/A	26 (16.05)
Registry, *n* (%)			
Belgium	6 (1.53)	1 (0.44)	5 (3.09)
Italy	206 (53.09)	110 (48.67)	96 (59.26)
Spain	59 (15.21)	48 (21.24)	11 (6.79)
UK	56 (14.43)	27 (11.95)	29 (17.90)
USA	61 (15.72)	40 (17.70)	21 (12.96)

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; SMA, spinal muscular atrophy.

visit, subset (IIIa, IIIb), initial HFMSE score, time since first visit, and patient-specific random intercepts (Table 4).

DISCUSSION

With clinical trials having a limited duration with a placebo group for comparison, long-term efficacy of drugs treatment can be better interpreted by comparing the long-term results of the clinical trials and real-world data to natural history data collected in untreated cohorts using the same measures [15, 16, 18]. This paper provides, for the first time, 4-year longitudinal data in untreated SMA type II and III participants using the HFMSE as the result of a large international effort. Our findings show that the progression is very variable with differences not only between SMA type II and III but also within each type, providing evidence of the complexity of study design when recruiting participants with a wide range of clinical severity.

The mean values observed in each SMA type are associated with very large standard deviations to demonstrate the broad range of changes observed.

In SMA type II, the largest changes were observed in sitters between the age of 5 and 13 years, at the age when they are known to progressively lose most of the aspects of motor function assessed by the HFMSE [25] due to increased growth, scoliosis/surgery and contracture development [26, 27]. Interesting results could be observed, however, at either end of the age spectrum. A longer follow-up period in very young children showed that, after the reported stability or minimal improvement observed after 1 or 2 years of follow-up, loss of points and function can be observed at the 3-year and even more at the 4-year follow-up. In older sitters aged between 7 and 15 years of age at baseline the changes were smaller, as at baseline they have very few activities left to be lost on the scale, but further reduction can nevertheless be observed after 3 and 4 years. This did not hold true for the sitters

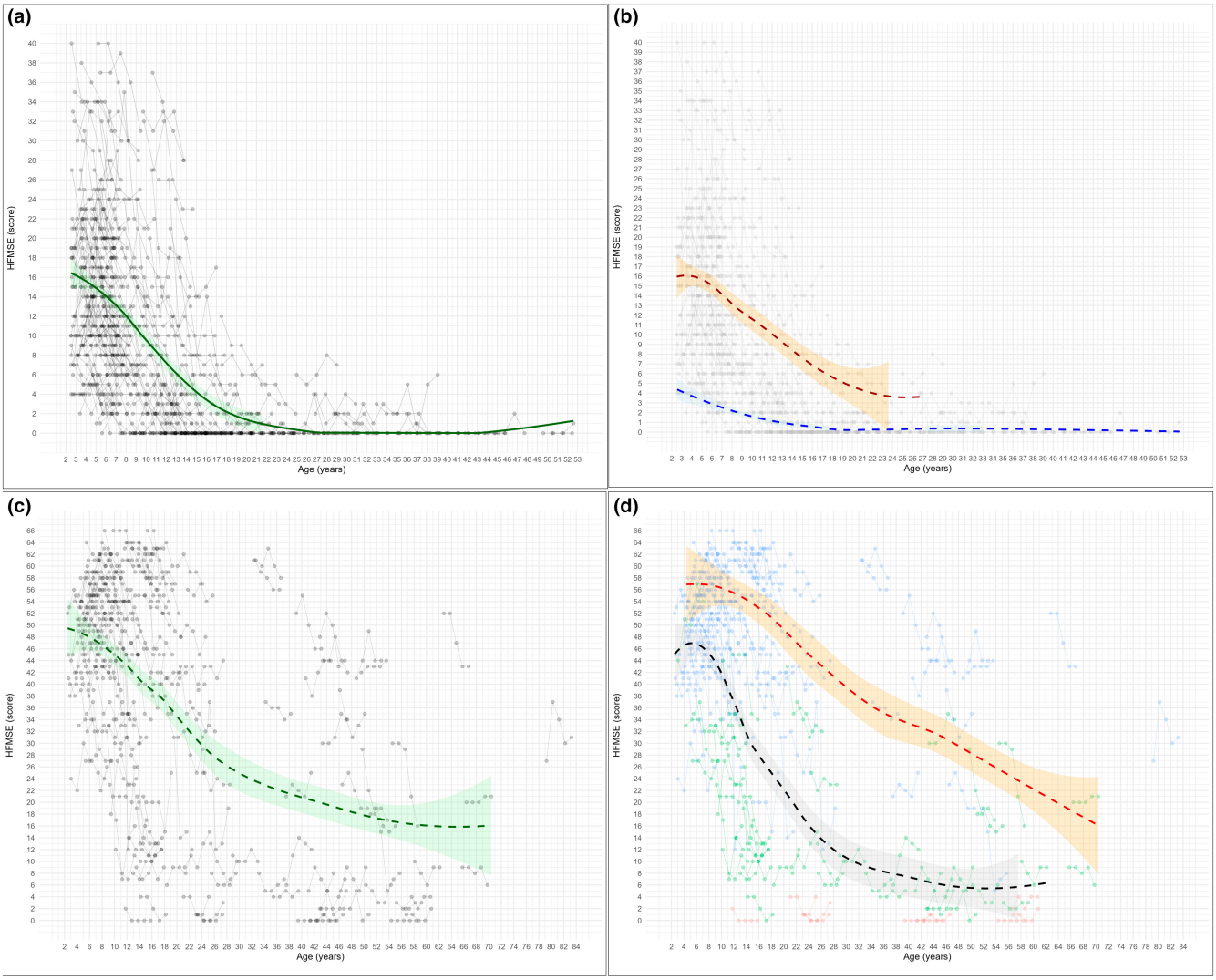

FIGURE 1 Individual trajectories of SMA type II and III patients. (a) SMA type II, (b) SMA type II subdivided into non-sitters (blue polynomial line) and sitters (dark red polynomial line), (c) SMA type III, (d) SMA type III subdivided into IIIa (black polynomial line) and IIIb (orange polynomial line), non-sitters (red individual trajectories), sitters (green individual trajectories) and walkers (blue individual trajectories).

after the age of 15 who have essentially reached the floor of the scale, having already lost most of their abilities. Similarly, individuals who had lost the ability to sit at baseline (non-sitters) also had the same profile. It is interesting that in the group of SMA type II <5 years, those who had two SMN2 copies had a worse performance over time than those with three SMN2 copies.

In SMA type III, there were different profiles in type IIIa and IIIb, with type IIIb showing overall larger changes than type IIIa. In both, the largest changes were observed after the age of 7 years and before puberty. As in SMA type IIIa the mean scores at the age of 7 were lower than in type IIIb (approximately 40 vs. 60), even a small reduction in scores in type IIIa was associated with an increased risk of losing ambulation. In SMA type IIIb further changes were observed after the age of 15 in participants who were still ambulant at baseline.

Although the analysis was limited by a relatively high number of participants with missing *SMN2* copy numbers, the available results did not appear to indicate that *SMN2* copy number could predict the magnitude of changes in both SMA types. Similarly, sex was also not predictive. In contrast, age and HFMSE scores at baseline were predictive of changes at 4 years, confirming previous observations of their predictive value at 1 and 2 years in both SMA type II and III [15].

Our findings expand the existing literature on longitudinal data obtained using the HFMSE and, more generally, on motor function in SMA type II and III. Our data confirm the broad variability of findings observed in both SMA type II and type III [10, 21, 28–30] with the largest changes observed in the more able subgroups within each type (sitters in SMA type II and walkers in SMA type III) who have relatively high scores that are progressively lost over time from baseline. In the less able subgroups, such as those who have lost

TABLE 2 SMA type II yearly changes.

SMA type II				
Year	**Estimate change**	**Pr > |t|**	**Lower**	**Upper**
1	0.02732	0.9163	−0.4827	0.5374
2	−0.8798	0.0007	−1.3898	−0.3697
3	−1.4262	<0.0001	−1.9363	−0.9162
4	−2.1967	<0.0001	−2.7068	−1.6867

	Mean change from baseline to 1 year (95% CI)	**Mean change from baseline to 2 years (95% CI)**	**Mean change from baseline to 3 years (95% CI)**	**Mean change from baseline to 4 lenyears (95% CI)**
SMA type II subdivided by age				
<5 (*N* = 79)	0.89 (0.02; 1.75)	−0.15 (−1.02; 0.72)	−1.18 (−2.04; −0.31)	−1.95 (−2.82; −1.08)
≥5 and <14 (*N* = 88)	−0.92 (1.69; −0.15)	−2.29 (−3.07; −1.52)	−2.93 (−3.70; −2.16)	−3.87 (−4.65; −3.10)
≥14 and <18 (*N* = 17)	0.35 (−0.60; 1.30)	−0.59 (−1.54; 0.36)	−1.12 (−2.07; −0.16)	−1.23 (−2.19; −0.28)
≥18 (*N* = 42)	0.24 (−0.09; 0.57)	0.00 (−0.33; 0.33)	0.43 (−0.01; 0.26)	−0.007 (−0.40; 0.26)
SMA type II subdivided by functional status and age				
Non-sitter (*N* = 74)	0.20 (−0.08; 0.48)	−0.22 (−0.49; 0.06)	0.11 (−0.17; 0.39)	−0.50 (−0.78; −0.22)
<5 (*N* = 2)	−0.50 (−2.89; 1.89)	−2.5 (−4.89; −0.11)	−1.0 (−3.39; 1.39)	−3.5 (−5.89; −1.11)
≥5 and <14 (*N* = 27)	0.26 (−0.32; 0.84)	−0.52 (−1.10; 0.06)	−0.18 (−0.77; 0.40)	−0.89 (−1.47; −0.31)
≥14 and <18 (*N* = 10)	0.10 (−0.50; 0.70)	−0.20 (−0.80; 0.40)	0.20 (−0.40; 0.80)	−0.50 (−1.10; 0.10)
≥18 (*N* = 35)	0.23 (−0.05; 0.50)	0.14 (−0.13; 0.42)	0.37 (0.09; 0.65)	−0.03 (−0.30; 0.25)
Sitter (*N* = 152)	−0.04 (−0.68; 0.68)	−1.31 (−1.95; −0.67)	−2.32 (−2.96; −1.68)	−3.15 (−3.79; −2.50)
<5 (*N* = 77)	0.92 (0.03; 1.81)	−0.09 (−0.98; 0.80)	−1.18 (−2.07; −0.29)	−1.91 (−2.80; −1.02)
≥5 and <14 (*N* = 61)	−1.44 (−2.47; −0.41)	−3.08 (−4.11; −2.05)	−4.15 (−5.18; −3.12)	−5.20 (−6.23; −4.17)
≥14 and <18 (*N* = 7)	0.71 (−1.12; 2.55)	−1.14 (−2.98; 0.69)	−3.00 (−4.84; −1.16)	−2.29 (−4.12; −0.45)
≥18 (*N* = 7)	0.29 (−1.16; 1.73)	−0.71 (−2.16; 0.73)	0.71 (−0.73; 2.16)	−0.29 (−1.73; 1.16)
SMA type II subdivided by *SMN2* copy number and age				
2 copies (*N* = 30)	−0.70 (−1.92; 0.52)	−1.53 (−2.75; −0.31)	−1.13 (−2.35; 0.09)	−2.40 (−3.62; −1.18)
<5 (*N* = 13)	−2.77 (−4.93; −0.60)	−2.77 (−4.93; −0.60)	−1.92 (−4.09; 0.24)	−3.77 (−5.93; −1.60)
≥5 and <14 (*N* = 7)	1.86 (−0.66; 4.37)	−1.43 (−3.95; 1.09)	−2.43 (−4.95; 0.09)	−3.00 (−5.52; −0.48)
≥14 and <18 (*N* = 4)	0.50 (−0.62; 1.62)	0.00 (−1.12; 1.12)	0.25 (−0.87; 1.37)	−0.75 (−1.87; 0.37)
≥18 (*N* = 6)	0.00 (−0.79; 0.79)	0.00 (−0.79; 0.79)	1.17 (0.37; 1.96)	0.17 (−0.63; 0.96)
3 copies (*N* = 150)	0.20 (−0.37; 0.77)	−0.73 (−1.30; −0.16)	−1.48 (−2.05; −0.91)	−2.14 (−2.71; −1.57)
<5 (*N* = 61)	1.64 (0.68–2.60)	0.49 (−0.47; 1.45)	−0.92 (−1.88;0.04)	−1.34 (−2.31; −0.38)
≥5 and <14 (*N* = 59)	−1.19 (−2.14; −0.23)	−2.15 (−3.10; −1.20)	−2.83 (−3.78; −1.88)	−3.88 (−4.83; −2.93)
≥14 and <18 (*N* = 9)	−0.33 (−1.23; 0.57)	−0.78 (−1.68; 0.12)	−0.56 (−1.46: 0.35)	−1.00 (−1.90; −0.10)
≥18 (*N* = 21)	0.14 (−0.38; 0.67)	−0.24 (−0.76; 0.29)	0.29 (−0.24; 0.81)	−0.05 (−0.57; 0.48)
≥4 copies (*N* = 5)	−0.80 (−2.23; 0.63)	−1.20 (−2.63; 0.23)	−1.00 (−2.43; 0.43)	−1.80 (−3.23; −0.37)
<5 (*N* = 2)	−0.50 (−1.92; 0.92)	−0.50 (−1.92; 0.92)	0.00 (−1.42; 1.42)	−2.50 (−3.92; −1.08)
≥5 and <14 (*N* = 3)	−1.00 (−3.05; 1.05)	−1.67 (−3.72; 0.39)	−1.67 (−3.72; 0.39)	−1.33 (−3.39; 0.72)

Note: Linear mixed effect models were used to calculate yearly changes in the whole SMA type II population; due to the limited sample size, the results showing yearly change per age, functional status and *SMN2* copy number subgroups should be mainly interpreted as descriptive.

Abbreviations: CI, confidence interval; SMA, spinal muscular atrophy; Pr>|t|, *p*-value.

sitting, changes are limited by their very low HFMSE scores at baseline. In these patients, other changes are more likely to be captured on the additional modules such as the RULM [31] as also shown in weaker non-ambulant SMA individuals treated with DMTs [32, 33]. Similarly, the revised Hammersmith Scale (RHS) and the Adaptive Test for Neuromuscular Disorders (ATEND) [34–36] are also useful tools for detecting changes in this specific population.

These findings highlight the clinical significance of accounting for variables like age and baseline function in data interpretation, as recently reported in the calculation of the HFMSE Minimal Clinical

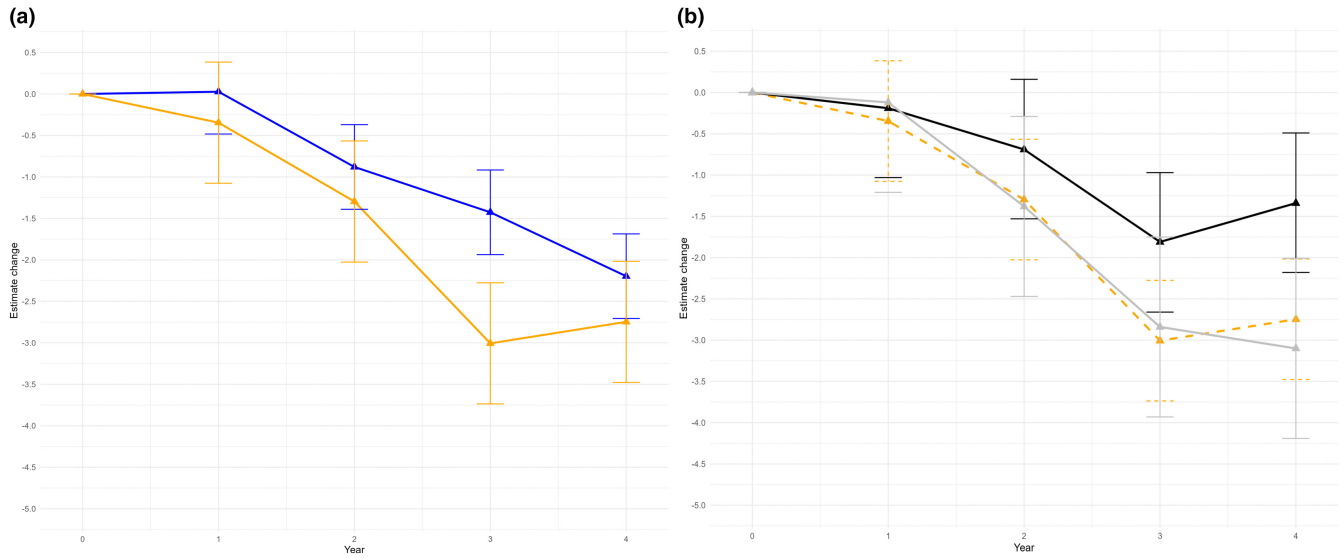

FIGURE 2 HFMSE 4-year changes in SMA type II and SMA type III: (a) blue line, SMA type II; yellow line, SMA type III; (b) yellow dotted line, SMA type III; black line, SMA type IIIa; grey line, SMA type IIIb.

TABLE 3 SMA type III yearly changes.

SMA type III				
Year	**Estimate change**	**Pr > |t|**	**Lower**	**Upper**
1	−0.3457	0.3528	−1.0758	0.3844
2	−1.2963	0.0005	−2.0264	−0.5662
3	−3.0062	<0.0001	−3.7362	−2.2761
4	−2.7469	<0.0001	−3.477	−2.0168

	Mean change from baseline to 1 year (95% CI)	**Mean change from baseline to 2 years (95% CI)**	**Mean change from baseline to 3 years (95% CI)**	**Mean change from baseline to 4 years (95% CI)**
SMA type III subdivided by age				
<7 (*N* = 40)	1.27 (0.08; 2.47)	0.87 (−0.32; 2.07)	−0.62 (−1.82; 0.57)	−0.70 (−1.89; 0.49)
≥7 and <15 (*N* = 55)	−1.64 (−3.07; −0.20)	−2.78 (−4.21; −1.35)	−5.25 (−6.69; −3.82)	−5.38 (−6.81; −3.95)
≥15 (*N* = 67)	−0.25 (−1.28; 0.77)	−1.37 (−2.40; −0.35)	−2.58 (−3.61; −1.56)	−1.81 (−2.83; −0.78)
SMA type III subdivided by subtype and age				
A (*N* = 86)	−0.19 (−1.03; 0.66)	−0.69 (−1.53; 0.16)	−1.81 (−2.66; −0.97)	−1.34 (−2.18; −0.49)
<7 (*N* = 31)	1.39 (0.13; 2.64)	1.32 (0.07; 2.58)	0.29 (−0.97; 1.55)	−0.10 (−1.35; 1.16)
≥7 and <15 (*N* = 27)	−2.56 (−4.38; −0.73)	−3.26 (−5.08; −1.43)	−4.74 (−6.57; −2.92)	−4.78 (−6.60; −2.95)
≥15 (*N* = 28)	0.36 (−0.63; 1.35)	−0.43 (−1.42; 0.56)	−1.32 (−2.31; −0.33)	0.61 (−0.38; 1.60)
B (*N* = 50)	−0.12 (−1.21; 0.97)	−1.38 (−2.47; −0.29)	−2.84 (−3.93; −1.75)	−3.10 (−4.19; −2.01)
<7 (*N* = 3)	0.00 (−2.21; 2.21)	0.67 (−1.55; 2.88)	−3.00 (−5.21; −0.79)	−1.67 (−3.88; 0.55)
≥7 and <15 (*N* = 16)	−0.44 (−1.97; 1.09)	−1.87 (−3.40; −0.34)	−3.50 (−5.03; −1.97)	−4.56 (−6.09; −3.03)
≥15 (*N* = 31)	0.03 (−1.51; 1.57)	−1.32 (−2.86; 0.22)	−2.48 (−4.02; −0.94)	−2.48 (−4.02; −0.94)
SMA type III subdivided by functional status and age				
Non-sitter (*N* = 10)	−0.10 (0.75; 0.55)	−0.80 (−1.46; −0.14)	−0.50 (−1.16; 0.16)	0.50 (−1.16; 0.16)
≥7 and <15 (*N* = 1)	−2	−2	−2	−2
≥15 (*N* = 9)	0.11 (−0.55; 0.77)	−0.67 (−1.33; −0.005)	−0.33 (−0.99; 0.33)	0.78 (0.12; 1.44)

(Continues)

TABLE 3 (Continued)

	Mean change from baseline to 1 year (95% CI)	Mean change from baseline to 2 years (95% CI)	Mean change from baseline to 3 years (95% CI)	Mean change from baseline to 4 years (95% CI)
Sitter (*N* = 47)	−1.15 (−2.42; 0.13)	−2.32 (−3.59; −1.04)	−2.89 (−4.17; −1.62)	−2.36 (−3.64; −1.09)
<7 (*N* = 4)	2.50 (−2.58; 7.58)	−0.25 (−5.33; 4.83)	0.25 (−4.83; 5.33)	0.25 (−4.83; 5.33)
≥7 and <15 (*N* = 18)	−2.89 (−5.21; −0.56)	−4.39 (−6.71: −2.06)	−5.94 (−8.27; −3.62)	−5.33 (−7.66; −3.01)
≥15 (*N* = 25)	−0.48 (−1.85; 0.89)	−1.16 (−2.53; 0.21)	−1.20 (−2.57; 0.17)	−0.68 (−2.05; 0.69)
Walker (*N* = 105)	−0.01 (−0.96; 0.94)	−0.89 (−1.83; 0.06)	−3.29 (−4.24; −2.35)	−3.23 (−4.18; −2.28)
<7 (*N* = 36)	1.14 (−0.07; 2.35)	1.00 (−0.21; 2.21)	−0.72 (−1.93; 0.49)	−0.83 (−2.04; 0.38)
≥7 and <15 (*N* = 36)	−1.00 (−2.84; 0.84)	−2.00 (−3.84: −0.16)	−5.00 (−6.84; −3.16)	−5.50 (−7.34; −3.66)
≥15 (*N* = 33)	−0.18 (−1.89; 1.53)	−1.73 (−3.43; −0.02)	−4.24 (−5.95; −2.53)	−3.36 (−5.07; −1.65)
SMA type III subdivided by *SMN2* copy number and age				
2 (*N* = 11)	−0.91 (−3.13; 1.31)	−0.73 (−2.95; 1.49)	−3.09 (−5.31; −0.87)	−2.36 (−4.58; −0.14)
<7 (*N* = 3)	−1.67 (−6.26; 2.93)	1.67 (−2.93; 6.26)	−3.00 (−7.59; 1.59)	−2.33 (−6.93; 2.26)
≥7 and <15 (*N* = 2)	−3.50 (−10.05; 3.05)	−3.50 (−10.05; 3.05)	−8.50 (−15.05; −1.95)	−6.50 (−13.05; 0.05)
≥15 (*N* = 6)	0.33 (−1.95; 2.61)	−1.00 (−3.28; 1.28)	−1.33 (−3.61; 0.95)	−1.00 (−3.28; 1.28)
3 (*N* = 70)	−0.17 (−1.23; 0.89)	−1.31 (−2.37; −0.26)	−2.50 (−3.56; −1.44)	−2.20 (−3.26; −1.14)
<7 (*N* = 23)	2.09 (0.61; 3.56)	0.83 (−0.65; 2.30)	0.04 (−1.43; 1.52)	−0.61 (−2.08; 0.87)
≥7 and <15 (*N* = 23)	−3.26 (−5.27; −1.25)	−3.91 (−5.92; −1.91)	−5.96 (−7.96; −3.95)	−6.04 (−8.05;−4.04)
≥15 (*N* = 24)	0.62 (−1.03; 2.28)	−0.87 (−2.53; 0.78)	−1.62 (−3.28; 0.03)	−0.04 (−1.69; 1.61)
≥4 (*N* = 51)	−0.45 (−1.87; 0.97)	−1.08 (−2.50; 0.35)	−3.27 (−4.70; −1.85)	−2.84 (−4.27; −1.42)
<7 (*N* = 11)	−0.09 (−2.68; 2.49)	0.09 (−2.49; 2.68)	−1.18 (−3.77; 1.40)	−0.73 (−3.31; 1.86)
≥7 and <15 (*N* = 17)	−0.06 (−3.19; 3.08)	−1.71 (−4.84; 1.43)	−5.94 (−9.08; −2.81)	−5.59 (−8.72; −2.45)
≥15 (*N* = 23)	−0.91 (−2.49; 0.66)	−1.17 (−2.75; 0.40)	−2.30 (−3.88; −0.73)	−1.83 (−3.40; −0.25)

Note: Linear mixed effect models were used to calculate yearly changes in the whole SMA type III population; due to the limited sample size, the results showing yearly change per age, functional status and *SMN2* copy number subgroups should be mainly interpreted as descriptive.
Abbreviations: CI, confidence interval; SMA, spinal muscular atrophy; Pr>|t|, *p*-value.

Important Difference (MCID) [37]. For instance, the MCID for SMA II (−2) was reached in our cohort at the 2-year follow-up for patients aged 5–14, but also appeared later in other subgroups. Similarly, the MCID for SMA II (−4) was reached at the 3-year follow-up for patients aged 7–15. Whilst this information helps understand when deterioration is perceived as clinically meaningful by individuals or caregivers, the observed variability also reinforces the idea that mean changes across different SMA cohorts are not reliable benchmarks, as they encompass a wide spectrum of individual variations in disease progression and treatment response.

A notable strength of this study is the prospective collection of data as part of an international effort using the same measures utilized in most clinical trials and real-world data collections. Whilst the use of multiple imputation techniques allowed more patients to be included in the analysis, it is important to note that imputation could introduce some degree of uncertainty. However, our sensitivity analyses comparing results obtained using imputed data to those using only non-imputed data demonstrated that the overall findings were robust and not substantially influenced by the imputation process. These data are highly valuable, as they were collected in the years immediately preceding the approval of DMTs for SMA, and in some cases concurrently collected, as some groups continued to collect natural history data whilst DMTs were more readily available in other countries. As, according to recent surveys, over 90% of the existing SMA individuals are now treated [38] it will no longer be possible to obtain new data to expand or replicate this dataset. Our findings, characterizing the long-term changes in different age and functional subgroups of SMA, provide reference data that can be used for future comparisons and facilitate the interpretation of long-term clinical trial results and real-world data.

AUTHOR CONTRIBUTIONS

Giorgia Coratti: Conceptualization; methodology; data curation; formal analysis; writing – original draft; writing – review and editing. **Francesca Bovis:** Methodology; formal analysis; data curation; writing – original draft; writing – review and editing; funding acquisition. **Maria Carmela Pera:** Methodology; supervision; writing – original draft; writing – review and editing; funding acquisition. **Matthew Civitello:** Conceptualization; supervision; resources; writing – review and editing. **Annemarie Rohwer:** Conceptualization; supervision; writing – review and editing; resources. **Francesca Salmin:** Investigation; visualization; data curation. **Allan M. Glanzman:** Investigation; visualization; data curation. **Jacqueline Montes:** Investigation; visualization; data curation. **Amy Pasternak:**

TABLE 4 Output of the two mixed models.

Term	Estimate (95% CI)	*p* value
SMA type II (*N* = 185)		
Time	−0.58 (−0.69;-0.46)	<0.0001
HFMSE baseline	0.83 (0.78;0.88)	<0.0001
Age at baseline	−0.05 (−0.11;-0.003)	0.039
Sex (male vs. female)	−0.67 (−1.41;0.07)	0.075
Functional status (sitter vs. non-sitter)	0.52 (−0.64;1.68)	0.378
SMN2 copy number		
3 versus 2	0.24 (−0.76;1.24)	0.891
4+ versus 2	0.06 (−2.35;2.47)	
SMA type III (*N* = 116)		
Time	−0.58 (−0.75;-0.41)	<0.0001
HFMSE baseline	0.92 (0.86;0.98)	<0.0001
Age at baseline	−0.008 (−0.06;0.05)	0.766
Sex (male vs. female)	−0.51 (−1.70;0.68)	0.398
Onset B versus A	−0.41 (−1.93;1.10)	0.591
Motor function		
Sitter versus non-sitter	0.15 (−2.54;2.84)	0.022
Walker versus non-sitter	2.94 (−0.49;6.36)	
SMN2 copy number		
3 versus 2	0.59 (−1.59;2.77)	0.536
4+ versus 2	1.18 (−1.16;3.51)	

Abbreviations: CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; SMA, spinal muscular atrophy.

Investigation; visualization; data curation. **Roberto De Sanctis:** Investigation; visualization; data curation. **Sally Dunaway Young:** Investigation; visualization; data curation. **Tina Duong:** Investigation; visualization; data curation. **Irene Mizzoni:** Visualization; investigation; data curation. **Evelin Milev:** Visualization; data curation; investigation. **Maria Sframeli:** Data curation; visualization; validation. **Simone Morando:** Data curation; visualization; investigation. **Emilio Albamonte:** Data curation; visualization; validation. **Adele D'Amico:** Data curation; visualization; validation. **Michela Catteruccia:** Data curation; visualization; validation. **Noemi Brolatti:** Data curation; visualization; validation. **Marika Pane:** Data curation; visualization; validation. **Mariacristina Scoto:** Data curation; visualization; validation. **Sonia Messina:** Data curation; visualization; validation. **Jesica Exposito Escudero:** Validation; visualization; data curation. **Liesbeth De Waele:** Data curation; visualization; validation. **Michio Hirano:** Data curation; validation; visualization. **Zarazuela Zolkipli-Cunningham:** Data curation; visualization; validation. **Basil T. Darras:** Data curation; visualization; validation. **Enrico Bertini:** Data curation; visualization; validation; funding acquisition. **Andres Nascimiento Osorio:** Data curation; visualization; validation. **Claudio Bruno:** Data curation; visualization; validation. **Natalie Goemans:** Data curation; visualization; validation. **Valeria A. Sansone:** Data curation; visualization; validation. **John Day:** Data curation; visualization; validation. **Giovanni Baranello:** Data curation; visualization; validation. **Francesco Muntoni:** Data curation; visualization; validation. **Richard Finkel:** Data curation; visualization; validation. **Eugenio Mercuri:** Data curation; visualization; methodology; validation; writing – review and editing; writing – original draft; supervision; project administration.

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CONFLICT OF INTEREST STATEMENT

Coratti G, Pera MC, Glanzman A, Scoto M, Montes J, Pasternak A, De Sanctis R, Duong T, Dunaway Young S, Civitello M, Pane M, Albamonte E, Sansone AV, D'Amico A, Bruno C, Messina S, Bertini E, De Waele L, Baranello G, Day J, Muntoni F, Finkel R, Mercuri E report personal fees for advisory boards, steering committee, speaker fees or consultancies from Biogen S.R.L., Roche, Avexis and/or Novartis outside the submitted work; Zolkipli-Cunningham Z reports support from Cure SMA outside the submitted work; Bovis F, Rohwer A, Goemans N, Darras BT, Nascimiento Osorio A, Hirano M, Sframeli M, Catteruccia M, Mizzoni I, Milev E, Morando S, Brolatti N, Exposito Escudero J, Salmin F have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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