Disease Trajectories in the Revised Hammersmith Scale in a Cohort of Untreated Patients with Spinal Muscular Atrophy types 2 and 3

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Abstract.

Background: Spinal muscular atrophy (SMA) is a neuromuscular disorder characterised by progressive motor function decline. Motor function is assessed using several functional outcome measures including the Revised Hammersmith Scale (RHS).

Objective: In this study, we present longitudinal trajectories for the RHS in an international cohort of 149 untreated paediatric SMA 2 and 3 patients (across 531 assessments collected between March 2015 and July 2019).

Methods: We contextualise these trajectories using both the Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM). At baseline, this cohort included 50% females and 15% of patients had undergone spinal fusion surgery. Patient trajectories were modelled using a natural cubic spline with age, sex, and random effects for each patient.

Results: RHS and HFMSE scores show similar trends over time in this cohort not receiving disease modifying therapies. The results confirm the strong correlation between the RHS and RULM previously observed in SMA types 2 and 3a. Scoliosis surgery is associated with a reduction of 3 points in the RHS, 4.5 points in the HFMSE for the SMA 2 population, and a reduction of 11.8 points in the RHS, and 13.4 points in the HFMSE for the SMA 3a populations. When comparing the RHS and RULM, there is a lower correlation in the type 3a's than the type 2 patients. In the SMA 2 population, there is no significant difference between the sexes in either the RHS or HFMSE trajectories. There is no significant difference in the RULM trajectory in the SMA 2 or 3a participants by sex.

Conclusions: This study demonstrates that the RHS could be used in conjunction with other functional measures such as the RULM to holistically detect SMA disease progression. This will assist with fully understanding changes that occur with treatments, further defining trajectories and therapy outcomes.

Keywords: Spinal muscular atrophy, scoliosis, outcome measure, physical therapists

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by mutations in the *survival motor neuron 1 (SMN1)* gene resulting in SMN protein deficiency [1–3]. This leads to muscle atrophy and a progressive decline in motor function due to muscle weakness. Secondary complications include scoliosis, joint contractures, fatigability, and progressive respiratory decline [3, 4].

SMA has historically been classified into types defined by age of onset and the maximum motor milestone achieved. Type 1 children never achieved independent sitting, type 2 children achieved independent sitting but never walked and type 3 achieved independent walking but would lose motor function over time and many became wheelchair dependant [3]. The type 3 has further subgroups of type 3a, with disease onset before 3 years and type 3b with onset after 3 years [5].

The introduction and approval of three disease modifying treatments for SMA (nusinersen, risdiplam and onasemnogene aberparvovec) has underscored the need for a robust understanding of the longitudinal natural history of SMA and how this natural history is represented across functional outcome measures [6–12].

The SMA specific outcome measures commonly used to assess gross motor function for clinical trials in patients with later-onset type 2 and 3 SMA are the Hammersmith Functional Motor Scale Expanded (HFMSE) and more recently the Revised Hammersmith Scale (RHS) [13, 14]. The RHS was developed more recently to expand the HFMSE at both ends of the scale, including an item from the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) which has been shown to reduce floor effect and several items including timed tests from the North Star Ambulatory Assessment (NSAA) to reduce the ceiling effect [13, 15]. Upper limb function is assessed using the Revised Upper Limb Module (RULM) [16, 17]. The RULM and HFMSE when used independently are appropriate for different age and functional groups however it has been shown that when used in conjunction, they are more sensitive to detecting functional changes [18]. As the RHS is being used clinically and more recently as a trial outcome measure it is important to understand the relationship between HFMSE, RULM, and RHS and how the RHS can be used in conjunction with other motor function outcomes.

Aims

With this analysis, we aim to characterise for the first time the longitudinal trajectories for the RHS in an international cohort of SMA 2 and 3 patients not receiving disease modifying therapies (DMT), establish patterns of progression. We contextualise

these trajectories by providing the corresponding trajectory in the HFMSE on the same untreated cohort, with the aim of assessing the impact of the differences in items of the two scales to capture disease progression. We also analyse the impact of sex and spinal surgical intervention on these trajectories. We also aim to demonstrate that the RHS score can be used in conjunction with other functional measures such as the RULM to understand this cohort's disease progression.

MATERIALS AND METHODS

Inclusion criteria

The participants included in this analysis are recruited from the International SMA Consortium (iSMAC) natural history studies (SMA REACH UK, PNCRN USA and Italian Telethon) [19]. Cohort inclusion criteria included no prior or active treatment with any disease modifying therapy, available information on sex, scoliosis surgery status, and a complete RHS and HFMSE assessment. All participants had a genetically confirmed diagnosis of SMA, clinically classified as type 2, 3a or 3b, were receiving SMA Standards of Care treatment [20], had no previous involvement in clinical trials, and had at least two RHS assessments performed between the 17th of March 2015 and the 29th of July 2019. This study is a longitudinal reanalysis of previously published cross-sectional natural history data [15]. The inclusion criteria included those who had all fully completed HFMSE and RHS assessments, known spinal surgery status and known sex. The restriction to complete RHS assessments, as per the instruction manuals, led to the exclusion of 42 assessments and the restriction to complete HFMSE led to a further 4 assessments being excluded.

The RHS, HFMSE, and RULM assessments were conducted by iSMAC trained neuromuscular physiotherapists in the standardised assessment administration. Inter and intra-rater reliability have previously been reported for the HFMSE, RHS and RULM [16, 21–23]. The RHS, HFMSE, and RULM scores were collected in clinics every 6 months as recommended in the international standards of care [20]. The RHS is a 36-item ordinal scale with a maximum score of 69 points (33 items are scored 0–2, and three 0–1) [13]. The HFMSE is a 33-item ordinal scale with a maximum score of 66 points (33 items are scored 0–2) [14]. The RHS and HFMSE can be scored simultaneously, as many items are similar or identical

between scales. The RULM is a 20-item scale with a maximum total score of 37. It includes an entry item that does not contribute to the total score but identifies the functional level of the participant. The 19 other items are scores 0–2, with only one exception scored 0–1 [16].

Statistical analysis

Median and range summary statistics are presented for the variables of interest. The correlations between the RHS and HFMSE were performed using Spearman correlations, with *p*-values calculated using the asymptotic *t* approximation. A random effects model was fitted separately for both the RHS and the HFMSE by SMA type, with a random intercept for patients. A natural cubic spline was fitted separately for age for both male and female children, and scoliosis surgery was included as a factor. This is a flexible model, which consists of a series of cubic polynomials connected at knots. The polynomials fitted to the youngest and oldest groups are enforced as linear, which prevents overfitting in the sparse RHS and HFMSE assessments in the youngest and oldest patients. The model degrees of freedom were selected as parameter which minimised the Bayesian Information Criterion (a conservative assessment of model fit)– this was 3 across all 4 models (SMA 2 s male and female and SMA 3 s male and female). Significance between nested models was assessed using ANOVA. Residual fits and Quantile-Quantile plots were assessed for the suitability of the model assumptions. No model was fitted for the SMA 3b's, and instead the trajectories are presented graphically due to the smaller sample size. A binary indicator was added to the model for scoliosis surgery. This leads to a discontinuity when patients undergo scoliosis but due to the visiting process, it wasn't possible to model the impact of scoliosis surgery on motor function with respect to time. The ages for yearly change estimates are the mid-points of the age group summaries previously presented [15]. RStudio version 2022.07.2 Build 576 was used for this analysis.

RESULTS

Participants

We analysed 531 assessments across 149 paediatric SMA patients. The median number assessments were 3 (IQR: 2–5), this cohort included 96 with SMA type 2, 47 with SMA type 3a and 6 with SMA Type
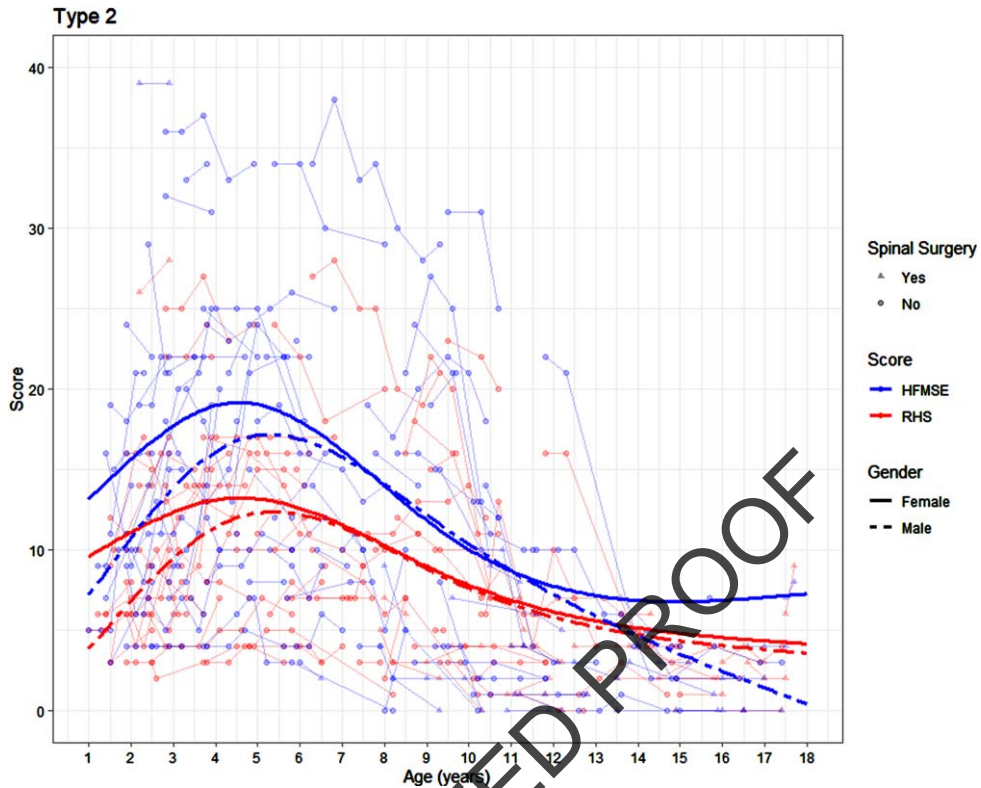
3b. There were 74 females and 75 males overall. In the patients with type 2 there were 40 female and 56 male participants, in those with type 3a there were 32 female and 15 male participants and there were 2 female and 4 male participants with type 3b.

The median age at the first assessment was 7.2 years [IQR: (3.8, 10.9). range: (1, 17.5)], the median RHS at first assessments was 11 [IQR: (5, 28). range: (0, 69)] and the median HFMSE at first assessments was 17 [IQR: (7, 39). range: (0, 66)]. The RULM total score was recorded in 196 (40%) of assessments and the median RULM at first assessments was 23.5 [IQR: (14.75, 30). range: (0, 37)]. The distribution of age, RHS total score, HFMSE total score and RULM total score by SMA type, sex and spinal surgery status are presented in Table 1.

The RHS and HFMSE total scores were very highly correlated overall $\rho = 0.99$ ($p < 0.001$). The correlation between the RHS and the HFMSE in the type 2's was $\rho = 0.96$ ($p < 0.001$) and in the type 3a's $\rho = 0.98$ ($p < 0.001$). The correlation between the RHS and the HFMSE in the type 3b's was $\rho = 0.77$ ($p < 0.001$).

In assessments where the RULM was performed, the overall correlation between the RULM and the RHS/HFMSE across the cohort was $\rho = 0.895$, ($p < 0.001$) and 0.895, ($p < 0.001$), respectively. The correlation between the RULM and the RHS/HFMSE in the type 2's was $\rho = 0.799$, ($p < 0.001$) and 0.812, ($p < 0.001$), respectively. The correlation between the RULM and the RHS/HFMSE in the type 3a's was $\rho = 0.697$, ($p < 0.001$) and 0.711, ($p < 0.001$), respectively. There was a significant difference in the RHS score of participants who completed the RULM compared to those who did not (median 10, IQR: 4.25–16 in the group with a RULM assessment, median 6, IQR: 4–10 in the group without, $p < 0.001$).

SMA 2's

There was no significant difference in either the RHS or the HFMSE trajectory in the SMA 2 participants by sex ($p = 0.096$ and $p = 0.13$ respectively). In girls with SMA 2, an average peak RHS score of 13 was achieved between the age of 3.25 and 6.08 years. In the same cohort, an average peak HFMSE score of 19 was achieved in girls between the age of 3.58 and 5.58 years. In boys with SMA 2, the peak RHS score of 12 was achieved slightly later, between the age of 4.08 and 6.83 years. In the same cohort, a peak HFMSE score of 17 was achieved between the age of 4.33 and 6.42 years (Fig. 1). The aver-

Table 1
Summary statistics of patient cohort

|		Number of Participants	Number of Assessments	Age Median (IQR)	Age Range	RHS Median (IQR)	RHS Range	HFMSE Median (IQR)	HFMSE Range	RULM N	RULM M	RULM Median (IQR)	RULM Range
All		149	531	8.2 (4.8, 11.4)	1–17.8	14 (6, 33)	0–69	19 (7, 41)	0–66	66 (44%)	196 (40%)	26 (16, 34)	0–37
SMA Type	2	96	324	6.45 (3.6, 10.5)	1–17.7	7 (4, 13)	0–28	10 (4, 18.25)	0–39	27 (39%)	102 (31%)	16 (11, 20)	0–33
	3a	47	178	9.5 (6.4, 11.6)	2.7–17.2	39 (25, 51.8)	5–69	47 (35, 53)	6–66	29 (62%)	94 (53%)	34 (29, 36)	17–37
	3b	6	29	14.8 (10.9, 16.2)	7.9–17.8	59 (55, 66)	30–69	61 (56, 63)	36–66	0	0		
Sex	F	74	266	8.8 (4.9, 11.5)	1.2–17.8	17 (7, 36)	0–68	23 (9, 43.75)	0–64	35 (47%)	106 (40%)	28 (17.25, 35)	2–37
	M	75	265	7.8 (4.7, 11.2)	1–17.7	11 (4, 23)	0–69	15 (5, 32)	0–66	31 (41%)	90 (34%)	19.5 (13, 31)	0–37
Spinal Surgery	Yes	33	74	12.4 (10, 15.2)	2.2–17.7	4 (2, 9)	0–69	4 (2, 9.75)	0–66	18 (55%)	30 (41%)	16 (9.5, 18.75)	0–37
	No	126	457	7.4 (4.3, 10.6)	1–17.8	16 (7, 36)	0–69	22 (10, 43)	0–66	55 (44%)	166 (36%)	27 (18, 34.75)	0–37

Fig. 1. Average SMA 2 trajectories on the RHS and HFMSE by age and sex (average presented for participants who have not undergone scoliosis surgery) surgery).

age yearly change on the RHS in the female SMA 2 patients is +1.04, –0.58, –0.83 and –0.21 at 2.5 years, 5 years, 10.5 years, and 16 years respectively, with corresponding changes of +1.72, –1.06, –1.13 and +0.18 on the HFMSE. The average yearly change on the RHS in the male SMA 2 participants is +2.33, –0.09, –0.89 and –0.25 at 2.5 years, 5 years, 10.5 years, and 16 years respectively, with corresponding changes of +2.74, –0.22, –1.56 and –1.03 on the HFMSE.

There was no significant difference in the RULM trajectory in the SMA 2 participants by sex ($p = 0.302$). In girls the average peak RULM score of 18 was achieved between the age of 5.42 and 10.17 years. In boys the average peak RULM score of 17 was achieved between the age of 5.5 and 9.5 years (Fig. 2).

Scoliosis surgery in the patients with SMA 2 was associated with a reduction of 2.96 (95% CI: 1.56, 4.36) points in the RHS trajectory, 4.51 (95% CI: 2.55, 6.47) points in the HFMSE and 2.71 (95% CI: 0.08, 5.33) points reduction in the RULM. In the patients with SMA type 2, after scoliosis surgery,

RHS items 2 (hands to head in sitting), 3 (sitting to lying), 9 (rolls supine to prone), 10 (lifting head from prone), 11 (props on forearms) and 13 (rolls prone to supine) were mostly scored as a 0 (83%, 94%, 92%, 98%, 92% and 94% respectively), which is significantly different ($p < 0.001$ for all) to the pre scoliosis surgery cohort (53%, 64%, 52%, 77%, 61% and 56%).

SMA 3a's

There was no significant difference in the RHS trajectory in the participants with SMA 3a by sex ($p = 0.088$), but there is a significant difference in the HFMSE trajectory by sex ($p = 0.019$). In girls with SMA 3a, the peak RHS score of 44 was achieved between the age of 5.83 and 7.67 years. In the same cohort, a peak HFMSE score of 49 was achieved in girls between the age of 5.67 and 7.58 years. In boys with SMA 3a, the peak RHS score of 48 was achieved in boys between the age of 7.25 and 9.92 years. The peak HFMSE score of 52 was achieved in boys between the age of 8.17 and 10.08 years
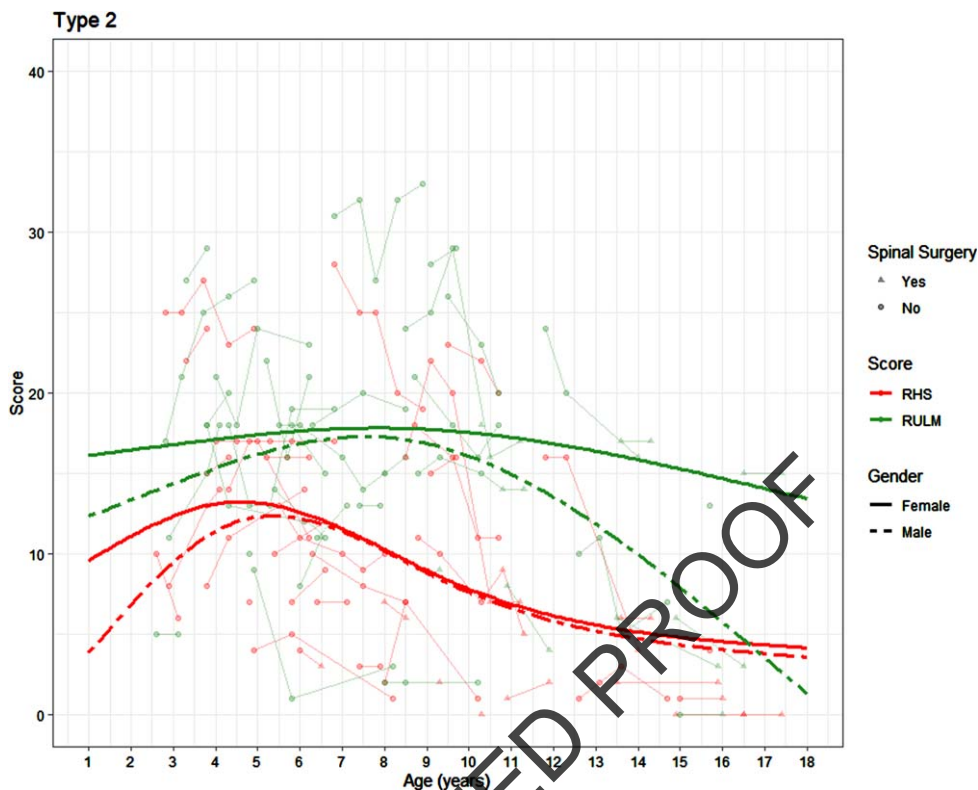
Fig. 2. Average SMA 2 trajectories on the RHS and RULM by age and sex (average presented for participants who have not undergone scoliosis surgery).

(Fig. 3). The average yearly change on the RHS in the female SMA 3a patients is +3.16, +1.67, –3.36 and –2.28 at 2.5 years, 5 years, 10.5 years and 16 years respectively, with corresponding changes of +3.01, +1.15, –3.34 and –2.16 on the HFMSE. The average yearly change on the RHS in the male SMA 3a participants is +3.98, +3.03, –2.52 and –5.52 at 2.5 years, 5 years, 10.5 years and 16 years respectively, with corresponding changes of +2.53, +2.1, –2.18 and –6.31 on the HFMSE.

In the assessments of the 3a's where a RULM was recorded 51% were ambulatory. There was no significant difference in the RULM trajectory in the participants with SMA 3a by sex ($p = 0.549$)(Fig. 4). In girls with SMA 3a, the peak RULM score of 33 was achieved between the age of 10.75 and 13.67 years, whilst in boys the average peak RULM score of 33 is achieved between the age of 6.17 and 11.83 years.

Scoliosis surgery in the SMA 3a patients was associated with a reduction of 11.75 (95% CI: 5.94, 17.56) points in the RHS trajectory, 13.39 (95% CI: 8.34, 18.4) points in the HFMSE and 3.56 (95% CI: 0.87, 6.28) points reduction in the RULM.

In the SMA 3a patients, after scoliosis surgery, RHS items 3 (sitting to lying), 9 (rolls supine to prone), 10 (lifting head from prone), 11 (props on forearms) and 13 (rolls prone to supine) were scored significantly differently ($p < 0.001$) in the cohort post scoliosis surgery (32%, 32%, 42%, 53% and 32% scored as 0 respectively) compared to pre scoliosis surgery (1%, 3%, 5%, 5% and 4% scored as 0 respectively).

SMA 3b's

The SMA 3b participants displayed stability over time (Fig. 5), although statistical modelling was not possible due to the small sample size ($n = 6$).

DISCUSSION

Our results indicate that this cohort of later-onset SMA demonstrates a time of relative stability prior to a decline in functional skills. The scores on the RHS and HFMSE show similar trends over time in this cohort not receiving DMT. Our analysis has shown
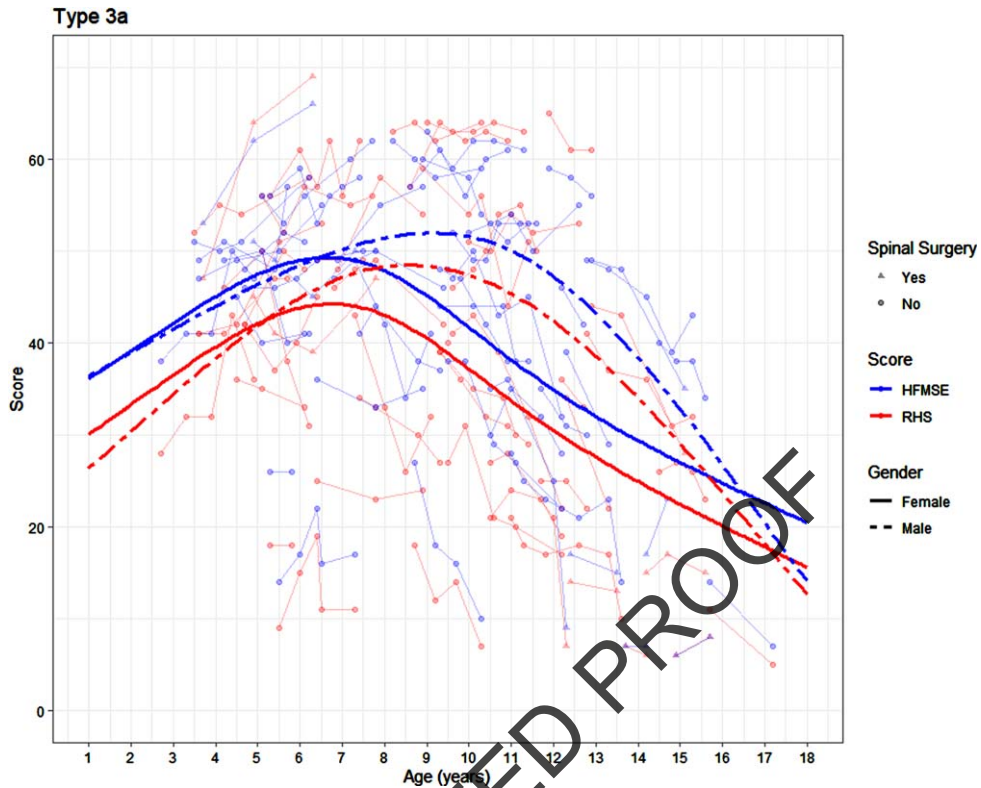
Fig. 3. Average SMA 3a trajectory on the RHS and HFMSE by age and sex (average is presented for participants who have not undergone scoliosis surgery).

a broad age window to achieve the peak score, with deterioration often being linked to growth [3, 24]. In the RHS we observe a stable peak in the SMA type 2 s between 3.25–6 years and in the SMA 3a between 5.6–7.7 years. Previous work on the RHS has reported positive slopes before the age of 5 in those with type 2 SMA followed by a negative slope, whereas the patients with SMA 3a demonstrated an increase in scores before 5 years, stability between ages 5–7 and then a negative trend after 7 years [15].

When comparing the RHS and RULM, there is a lower correlation in the type 3a's than for the type 2 patients, suggesting a decrease in correlation as function improves. The original upper limb module was specifically designed for a non-ambulant population [25], however the RULM was designed to be suitable for both ambulant and non-ambulant cohorts, which is reflected in this dataset [16, 17]. We identified a significant difference in the RHS score of participants who completed the RULM compared to those who did not. It's important to consider that this is historical natural history data and prior to the introduction of disease modifying treatments the RULM

was not routinely completed in the clinical settings across all sites. We acknowledge that there could be an element of selective bias, as the RULM may not always be completed either in the strongest patients, or in the weakest ones due to lack of perceived usefulness. This limits the interpretation of the results of this study, but as there are very few untreated patients remaining in the respective networks, we consider these results to reflect as accurately as possible the relationship between the RHS and RULM in the natural history of SMA. Despite the limitations these results will help the interpretation of disease modifying therapies in patients who can sit with and without support across the networks. Figures 1 and 2 show that in the SMA type 2 the RHS plateaus at approximately 7 points. This score could be used to inform clinical decision making when selecting the use of scales to capture functional changes and therefore to consider prioritising the RULM at this stage instead.

Overall, the magnitude of the RHS is lower than the HFMSE with more of a marked reduction in the SMA 2 cohort. However, in the SMA 2 cohort we observed a steeper decline in HFMSE, likely repre-
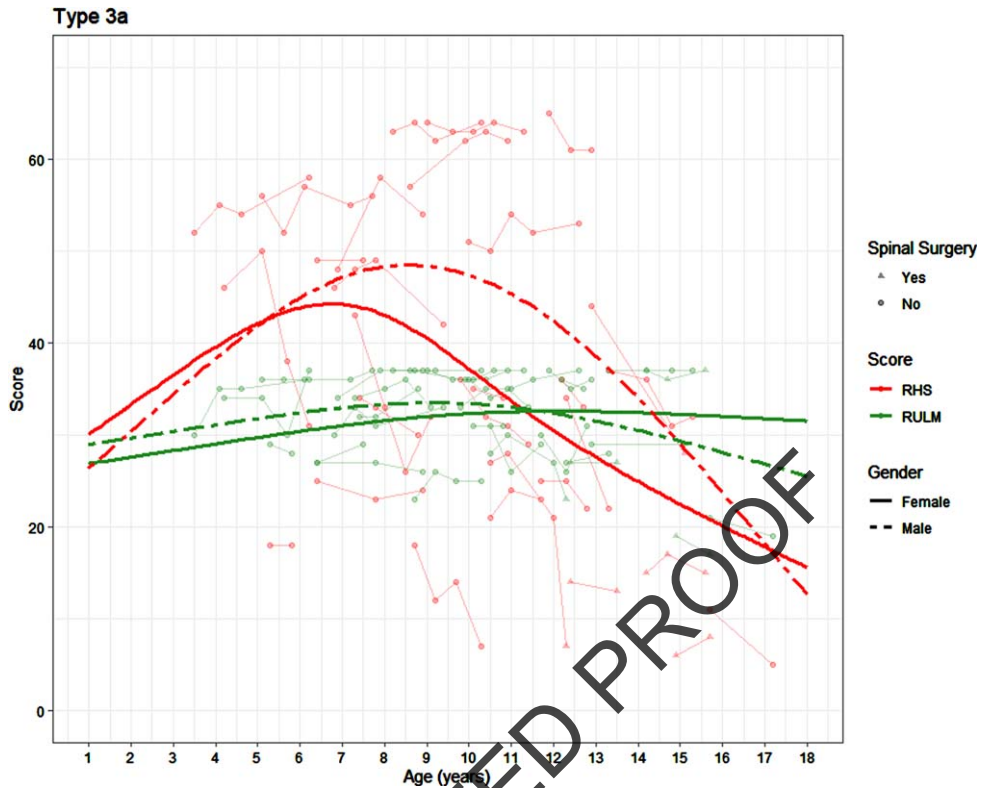
Fig. 4. Average SMA 3a trajectories on the RHS and RULM by age and sex (average presented for participants who have not undergone scoliosis surgery).

senting the larger reduction in score due to the loss of the same item bilaterally. Rasch analysis identified validity issues in some SMA phenotypes for the HFMSE, resulting in the creation of the RHS by remove the duplicated items and reducing the floor and ceiling effect. The RHS is a more compact scale, but this does not reduce its meaningfulness [13, 26]. Indeed, in the type 2 cohort the average peak score of the HFMSE is approximately 5 points higher than in the RHS. This is likely due to items which are tested on both sides in the HFMSE (rolling, items 6–9) and the duplication of items in the HFMSE (sitting independently and hands to head, items 1–4). In the SMA 3a's, the average peak of the HFMSE is approximately 5 points higher than in the RHS. This is also likely due to other items duplicated (the 4 propping and crawling) items on the HFMSE being merged into 2 items on the RHS. This may indicate either over measurement of certain levels of ability in the HFMSE, or loss of sensitivity in the RHS. As the RHS only collects assessment of one side, further work will need to explore these differences. This change (from bilateral data collection to unilateral collection) was

deliberately introduced to avoid discontinuities in the scale and overrepresentation of scores for specific changes. It will nevertheless be important to understand the sensitivity in these cohorts by looking at the relative minimal clinically important difference (MCID) and the minimum detectable change (MDC) in the RHS and compare this to the HFMSE. The MDC for the HFMSE has been reported on but this is likely to be different in the RHS [27, 28].

When analysing the impact of scoliosis surgery, it was clear that this was associated with a reduction in scores in all three scales. It is important to note that also an increase in scoliosis Cobb angle would also negatively impact scores [29]. The reduction due to scoliosis surgery was larger in the HFMSE than the RHS, again due to the bilateral items (4.5 vs 3 in those with SMA 2, 13.4 vs 11.8 in those with SMA 3a), representing similar reductions in total score of between 23% and 27% respectively across SMA type, sex, and total score. In this cohort there were 8 SMA 2 patients for whom an assessment was available both pre and post spinal surgery. Two of these had lost the ability to get their hands to their head in sitting (item 2) and two
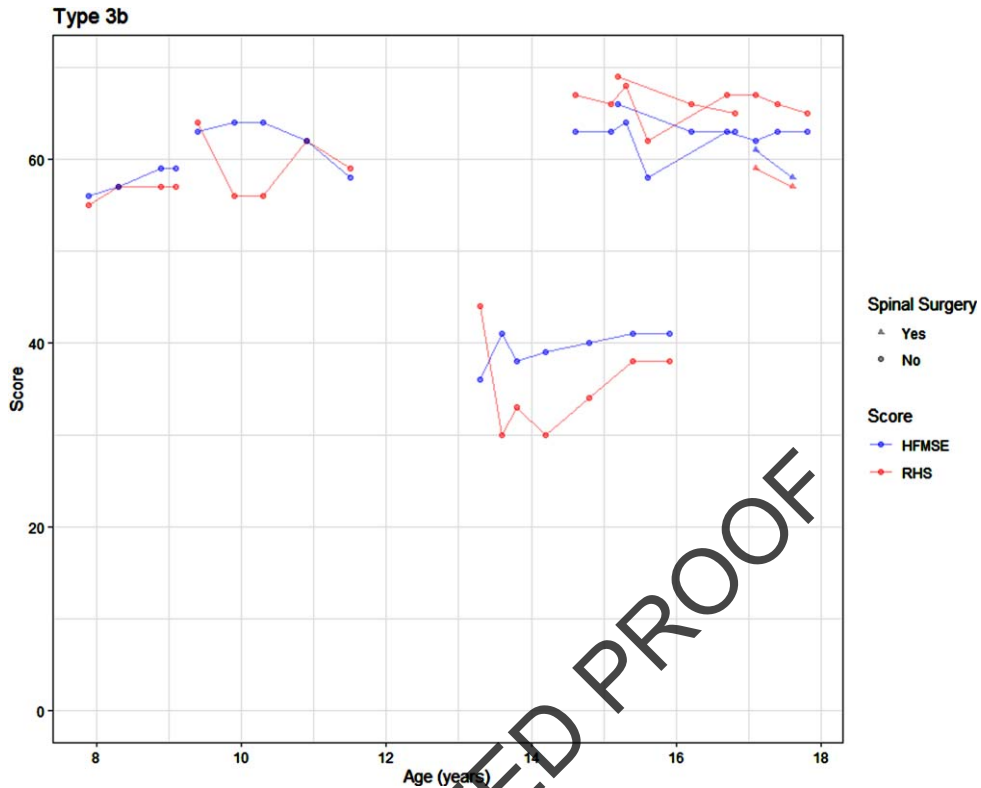
Fig. 5. Average SMA 3b trajectory on the RHS and HFMSE by age.

lost the ability to transition from sitting to lying (item 3). One patient lost the ability to roll from supine to prone and one needed compensation to achieve this (item 9). One patient lost the ability to lift their head from prone and one needed compensation to achieve this (item 10), one lost the ability to prop on their forearms and two needed assistance to achieve this (item 11). One patient lost the ability to roll from prone to supine and one needed compensation to achieve this (item 13).

In our cohort sex did not significantly impact the SMA 2 cohort peak score for either the RHS or HFMSE. The same was true with the RULM trajectory in the SMA 2's and SMA 3a's. There was no significant difference in the RHS trajectory in the SMA 3a participants by sex but there is a significant difference in the HFMSE trajectory by sex. In girls with SMA 3a the peak HFMSE score of 49 was achieved between the age of 5.67 and 7.58 years. In boys with SMA 3a the peak HFMSE score of 52 was achieved between the age of 8.17 and 10.08 years. There is a disparity between sex groups in our 3a cohort with 32 females and 15 males, and this small sample size may be the reason for observed

differences. Alternatively, some studies have linked differential motor function in SMA to growth. In SMA growth has been found to be more linear in females compared to males, which could explain the later peak for males [30]. However, it's been previously found that the typical sex differences in strength are not applicable to SMA due to the muscle atrophy, so this might not necessarily explain the higher peak in the male cohort [31].

In paediatric SMA, type 3b is a rare sub-type in an already rare condition, with disease onset anywhere between 3 and 18 years, and our cohort did not have many patients in this category [5, 32]. Due to this the cohort size in this study is very small and statistical analysis could not be performed on the type 3b group which is a limitation. It appears this cohort remains stable in both their RHS and HFMSE scores.

This longitudinal multicentre natural history study showed that the RHS can be used across SMA type and could be used in conjunction with other functional measures such as the RULM to holistically detect disease progression. This will assist with fully understanding changes that occur with treatments, and with defining trajectories and proactive therapy

recommendations. Further work is needed to look at the MDC and MCID for the RHS.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

INSTITUTIONAL REVIEW BOARD STATEMENT

This study was conducted in accordance with the Declaration of Helsinki. Each of the International SMA Consortium natural history study sites had ethical approval in place permitting collection of RHS natural history data. SMA REACH UK: National Research Ethics Committee (REC) London Bromley, Health Research Authority REC reference 13/LO/1748. PNCR USA Institutional Review Boards (IRB) and Numbers: IRB Numbers—Columbia University Medical Center Human Research Protection Office IRB reference AAAE8252, The Children's Hospital of Philadelphia IRB reference 10-007816, Boston Children's Hospital Office of Clinical Investigations IRB reference 05-02-028, Stanford University Re-search Compliance Office IRB reference 31140, Nemours Children's Hospital reference number 1004092. The Italian SMA Network is co-ordinated by Catholic University of Sacred Heart, Fondazione Policlinico Universitario Agostino Gemelli IRCCS (IRB protocol number 2533/18) and includes: University of Messina; IRCCS Bambino Gesù Children's; University of Milan, Niguarda Hospital; IRCCS Istituto Giannina Gaslini.

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