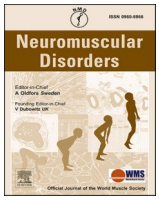
Neuromuscular Disorders 60 (2026) 106336

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd



# Refining functional phenotypes in an international cohort of untreated paediatric type 2 and 3 SMA patients using the Revised Hammersmith Scale

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ARTICLE INFO

*Key words:*
Sma
Longitudinal
Disease functional phenotype
Revised hammersmith scale

ABSTRACT

Spinal muscular atrophy types 2 and 3 encompass a wide spectrum of motor abilities ranging from non-sitting to sitting and walking. This study refines a functional group termed high functioning sitter-standers, positioned between traditional categories, and examined in relation to both the Revised Hammersmith Scale and a World Health Organization motor milestone-based framework. Among 178 participants completing 618 assessments, 109 were classified as type 2, 59 as type 3a, and 10 as type 3b, with ages ranging from 1 to 17.5 years. Twenty-seven non-sitters completed 54 assessments, 110 sitters completed 347, and 50 walkers completed 169, while the high functioning sitter-standers accounted for 48 assessments of 21 individuals. This newly defined group scored significantly lower than walkers and higher than both sitters and non-sitters, highlighting a distinct and measurable functional profile. Although no significant differences in age distribution were observed between the high functioning sitter-standers and walkers or non-sitters, sitters were notably younger. This intermediate phenotype captures patients with partial standing and assisted walking abilities, often overlooked in previous analyses. Recognition of this group is important for understanding emerging functional trajectories in treated spinal muscular atrophy and for informing future outcome measures and quality of life assessments.

## 1. Introduction

Spinal muscular atrophy (SMA) is a neuromuscular disorder caused by mutations of the survival motor neuron 1 (*SMN1*) gene, with the resultant SMN protein deficiency leading to degeneration of the alpha motor neurons in the spinal cord [1,2]. This disease manifests with a heterogenous clinical phenotype incorporating types 0–4 SMA [2–5], to capture the spectrum of maximum motor function achieved, from never achieving independent sitting to independent ambulation. The treatment landscape in SMA has changed drastically in the last 8 years [6–8], and consequently patients' disease progression trajectories now deviate from those previously established for each type.

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https://doi.org/10.1016/j.nmd.2026.106336
Received 10 October 2025; Received in revised form 30 December 2025; Accepted 12 January 2026
Available online 3 February 2026

Whereas the classic SMA types 0–4 reflect a patient's historical level of maximal motor milestones, motor function scales have been created to describe current level of motor function in more granular detail. The Revised Hammersmith Scale (RHS) for SMA is a psychometrically sound and versatile clinical outcome that was developed by an international panel of SMA experts to assess the physical abilities of people with SMA types 2 and 3 [9,10]. The RHS extends the range of functional abilities captured by the Hammersmith Functional Motor Scale Expanded (HFMSE) [11]. It captures the full range of physical abilities in SMA from very weak SMA type 2 patients who are no longer able to achieve sitting to stronger ambulant patients with SMA type 3. The RHS consists of a 36-item ordinal scale (total score 69, with a higher score reflecting a higher level of motor function), including two timed tests (Runs 10 m and Rise from floor), and it is often completed in conjunction with the World Health Organization (WHO) motor milestones, to enable greater description of functional characteristics in SMA. The International SMA Consortium (iSMAC) (SMA REACH UK, PNCRN USA and Italian Telethon) have been collecting natural history data on the RHS since its initial pilot in March 2015, and this cohort study represents the largest cohort of untreated type 2 and 3 SMA patients. Previous work analysing up-to 2-year change in RHS, in part by baseline motor function, utilised four WHO-derived functional phenotypes, and these groups are presented and characterised in this analysis [12–14].

The current functional characterisation of SMA has some limitations in capturing patients who may be in a transitional phase between sitting/ standing and walking. In other neuromuscular conditions such as Duchenne mMuscular dystrophy, recent research has highlighted the need to recognise and include "the transfer state", which adds a separate functional group of patients who cannot walk anymore but are able to shift own weight or stand supported [15]. These patients are particularly vulnerable to biomechanical risks due to profound weakness, where a change in tightness, contracture, or muscle strength could lead to a loss of the ability to stand or walk. This additional functional classification can help clinicians, parents and carers to plan for events of transferring, toileting, healthcare assistance support and other medical and personal needs.

### 1.1. Aims

The aim of this retrospective study is to refine and formally define the previously noted intermediate group historically referred to as SMA 2/3 or SMA 2.8–2.9, here labelled as high functioning sitter-standers (HFSS). The HFSS group, is contextualised with respect to historic SMA subtypes, and described fully with regards to their relative performance on the RHS. We propose that this revised functional phenotyping becomes more relevant given the observed disease trajectories in treated SMA patients.

## 2. Materials and methods

### 2.1. Inclusion criteria

Patients were recruited from the International SMA Consortium (iSMAC) if they met the following inclusion criteria: 1) genetically confirmed diagnosis of SMA classified as either type 2 or type 3 SMA; SMA type 3 was further sub-divided into 3a and 3b where SMA type 3a presents with symptoms before the age of 3, whereas type 3b shows symptoms after the age of 3; 2) receiving Standards of Care for SMA [16–18], 3) no prior/ongoing treatment with novel therapeutics, and 4) with at least two repeated RHS assessments during the period 17th March 2015 to 29th July 2019 [19]. In this paper, we restrict analysis to the paediatric population only.

### 2.2. Revised Hammersmith Scale and WHO assessments

RHS assessments were conducted by experienced neuromuscular physiotherapists from the iSMAC who originally designed and piloted the RHS, or who had been trained by these expert physiotherapists. These physiotherapists continued to receive regular refresher training via their individual national networks annually, and expert physiotherapists continued to participate in regular iSMAC meetings [19]. Physiotherapists across the iSMAC clinical sites in Europe and the United States evaluated patients using the RHS manual of testing procedures version 1.0 dated 17th March 2015 and the corresponding testing forms. Participants from the United Kingdom, Italy and USA were assessed at routine clinical appointments or during natural history study visits, approximately every 6 months with some variability due to changes in clinical status, logistical limitations or missed appointments. While assessments were scheduled in accordance to international standards of care, some differences might present in local clinical practices and service organisations [16–18]. The RHS is an ordinal scale which can be scored 0,1 and 2 where a score of 2 is given when a task is completed without any compensation, a score of 1 is given when item is completed with compensation; score of 0 is recorded when patients are unable to perform any part of the item.

Alongside the RHS, the WHO motor milestone descriptors for the acquisition of key motor abilities are documented and were used to enable the investigation and stratification of the wider spectrum of functional presentations seen within SMA types 2 and 3. The six WHO motor milestones have been used universally in SMA populations, as they are easy to use, and provide functional segregation [20]. However, due to SMA Type classifications, which rely on peak functional abilities, the functional abilities of patients with intermediate functional skills beyond sitting, such as crawling, standing independently and standing and walking with assistance have traditionally been under analysed in SMA. One earlier suggestion to divide type 2 into 2a (sitting without support) and 2b (standing with or without support) failed to gain widespread utilization [20]. Instead, we propose using the WHO functional status to yield four WHO-derived functional groups - non-sitters (scoring 0/6 on the WHO motor milestones), sitters (1/6 on the WHO motor milestones), high functioning sitter-standers (HFSS; crawlers, stand and walk with assistance and stands alone, score of 2–5 on the WHO motor milestones), and walkers (6/6 on the WHO motor milestones).

### 2.3. Analysis

The descriptive analysis in this paper uses medians and Inter Quartile Range (IQR) to capture the full distribution of the data. Demographic and cross-sectional data are presented using descriptive statistics.

A conservative approach was taken to determine the quantile scoring ranges for the WHO-derived SMA functional phenotypes, by using the IQR, representing the 50 % percentile of data. Cross-sectional analysis of the RHS scores for different subgroups was completed using the student *t*-test for non-paired data. The pairwise comparison of achievement of RHS items by functional group was performed using the Fischer Exact and Chi-Squared tests, where those with expected cell value under five were tested using the Fischer exact test. For all pairwise comparisons, the Bonferroni correction was used. To estimate the median loss of walking time by SMA type, the Kaplan-Meier estimator was used. All analysis was performed using R 4.2.2.

## 3. Results

### 3.1. Participants

This retrospective study included a total of 178 untreated patients contributed to 618 assessments in this study. The cohort included 109 patients with SMA type 2, 59 with SMA type 3a, and 10 with SMA type 3b; 84 participants were female and 94 were male. The time between assessments ranged from 0.2 to 3.7 years following the initial assessment. At baseline, participant ages ranged from 1 to 17.5 years, with a

median age of 7.7 years (IQR: 4–10.6).

Based on motor function, 27 participants were classified as non-sitters across 54 assessments. Sitters comprised 110 participants across 347 assessments, while walkers included 50 participants across 169 assessments. Additionally, there were 21 participants in the HFSS group with 48 assessments. Within this group, the highest WHO motor milestone achieved was: crawling (5 participants, 15 assessments), standing with assistance (5 participants, 5 assessments), standing independently (8 participants, 11 assessments), and walking with assistance (11 participants, 17 assessments).

### 3.2. RHS total score by functional phenotype

The individual patient trajectories across the cohort are shown in Fig. 1a, whilst the cross-sectional RHS scores for each of the functional phenotypes are displayed in Fig. 1b Notably, while some of the patients classified as HFSS are on a declining trajectory from walkers to HFSS, and others gain from sitters to HFSS, the majority of patients are fairly stable in this group. This suggests that this group is not an intermediate phenotypic stage for patients gaining or losing function, but also a functionally distinct stage of gross motor acquisition, at least for the period of time that they were followed (mean follow-up 7.64 months). Fig. 2 shows that when considered by type, the 3a and 3b patients are not separable, but by looking at function we can describe more clearly the expected score by group.

The RHS values achieved by patients in each of the four WHO-derived functional groups were significantly different from each other ($p < 0.001$). In pairwise comparisons the newly identified HFSS group scored significantly lower than the walkers ($p < 0.001$), and significantly higher than the sitters ($p < 0.001$) and non-sitters ($p < 0.001$). Notably, there was no significant difference in the distribution of ages between the HFSS group and non-sitters ($p = 0.054$) and walkers ($p = 0.563$), although the sitters were significantly younger on average than the HFSS group ($p = 0.006$). Similarly, the RHS values achieved by patients in each of the three SMA types were significantly different from each other overall ($p < 0.001$ for all). Additionally, the age ranges represented across the three SMA types were significantly different ($p < 0.001$ for all). Notably, there is variability in the RHS score achieved by functional group across age groups although this is limited by N small numbers in many of the groups (see Supplementary Figure 1). There was a significant statistical difference in RHS scores in sitters who were classified as type 2 or 3a ($p < 0.001$), the HFSS patients who were classified as type 2 or type 3a ($p < 0.001$), but not the HFSS patients classified as type 3a or 3b ($p = 0.339$). There was a significant difference in the RHS total scores between the walker 3a's and 3b's ($p < 0.001$). The full presentation of RHS scores by functional group and subtype are presented in Table 1.

### 3.3. RHS item scores by functional phenotype

Nearly all of the HFSS participants were able to achieve compensated or full scores on items 1–6, which was significantly different from the sitters, who these patients are more traditionally grouped with. In items 5–7, the HFSS participants were significantly worse than the walkers, with the HFSS group more likely to achieve a score of 1, whilst the walker often achieving a score of 2. In items 8, 9, 11, 13, and 14, the HFSS patients score significantly differently from sitters. HFSS patients are significantly stronger than sitters but weaker than walkers in items 15–19, and 22–24. In the rest of the items (19–21, 25–30), the HFSS patients have a similar phenotype to the sitters and are weaker than the walkers (Table 2). These distinctions underscore the functional differences between the different groups and support the classification of HFSS as a distinct subgroup with abilities that lie between those of traditional sitters and walkers.

#### 3.3.1. HFSS group as an intermediary functional group

Overall, only 2 % of sitters (2 out of 96) were observed to gain function and transition into the HFSS group. Both of these patients were 2.2 years at baseline and gained walking with assistance by 2.9 years. Within the HFSS group, seven patients consistently remained in this category throughout the observation period, while three lost function

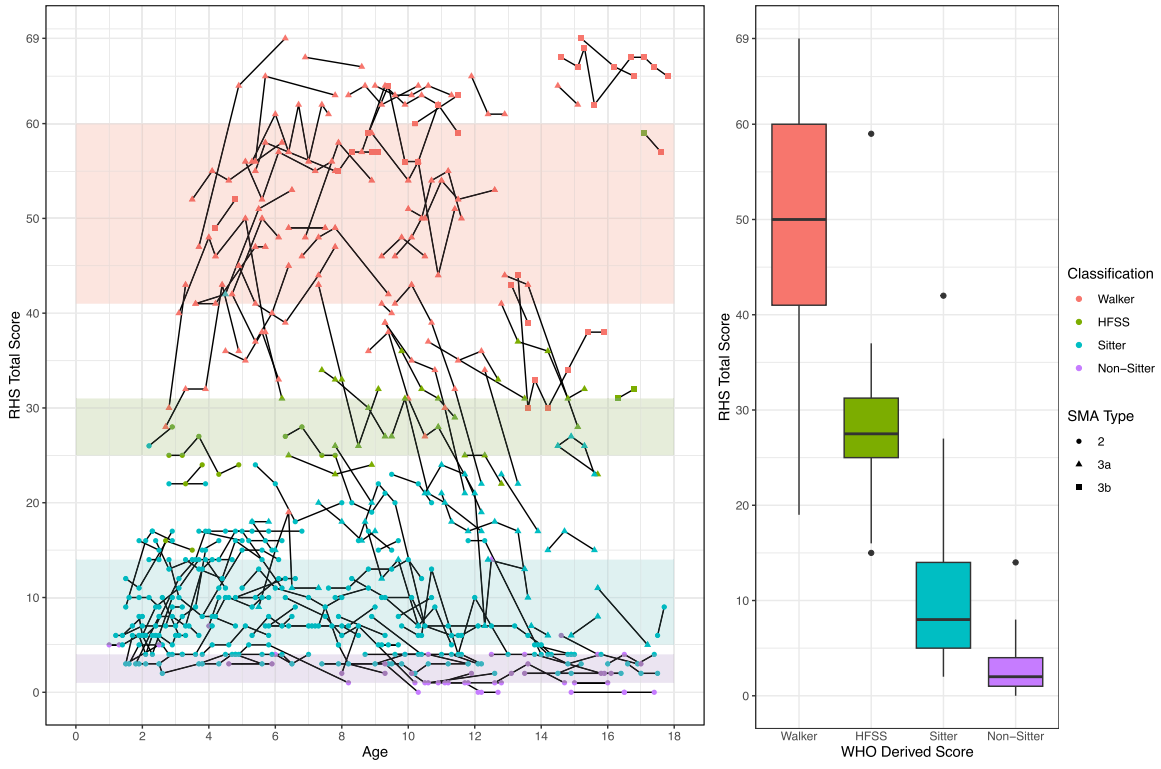


**Fig. 1.** RHS total scores by functional status.

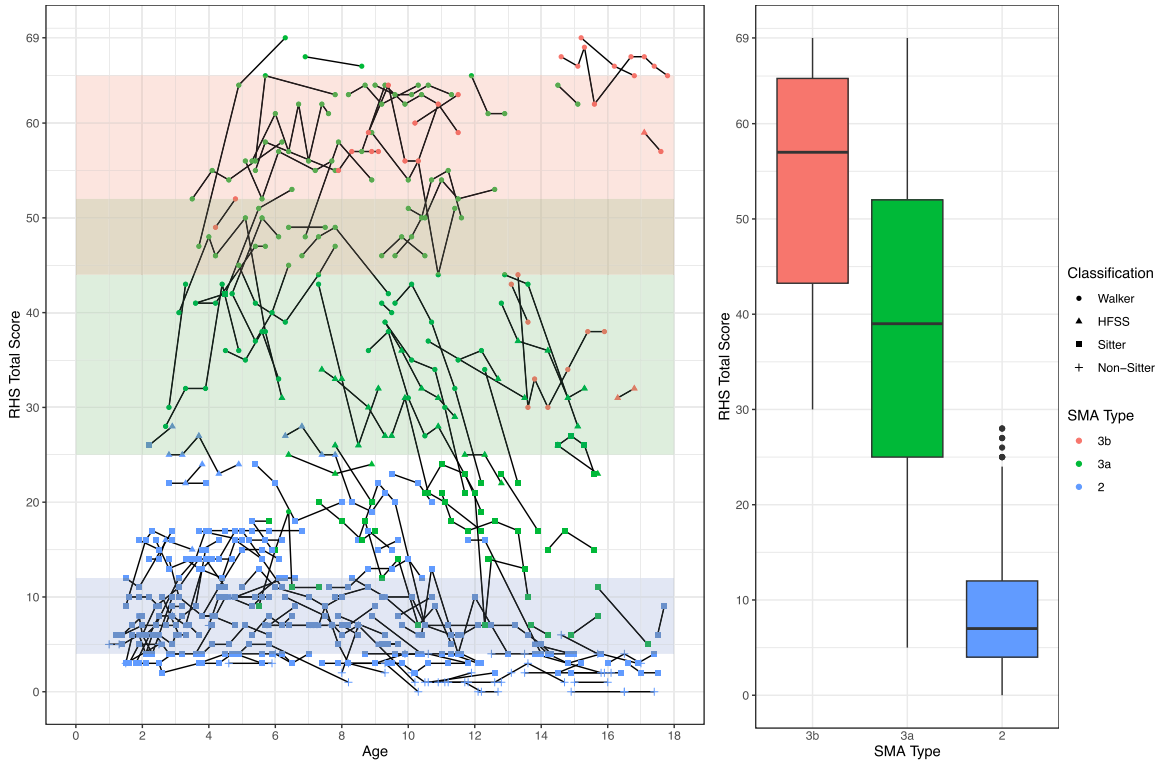


**Fig. 2.** RHS Total by SMA Type.

and became sitters. The three patients who moved from HFSS to sitter were aged 6.3, 7.8 and 9.5 years at baseline, and had a highest function of standing with assistance, standing independently and walking with assistance. All three had no recorded spinal surgery and recorded peak functional status of sitting 1.1 years after inclusion in the study. One patient who was 17.1 years at inclusion to the study was recorded as HFSS at baseline, scoring a 1 on item 18 of the RHS (able to take <5 independent steps), and was recorded as a walker at 17.6 years, scoring a 2 on the same item (able to take ≥ 5 independent steps).

Among the 48 participants who were walking at baseline, 11 (23 %) lost the ability to walk during the observation period; of these, one later regained the ability. Of the 11 who lost walking ability, 7 (64 %) transitioned to the HFSS group, 3 (17 %) became sitters, and 1 progressed through all four functional classifications. All bar one participant who lost walking ability were diagnosed with SMA type 3a, with a Kaplan-Meier estimate of the average age of loss ambulation of 11.6 (95 % CI: 10.8, NA) in this cohort (see supplementary figure SF2).

## 4. Discussion

Our study shows that integrating the well-established RHS with the WHO motor milestones, enables more detailed functional analysis and patient stratification beyond traditional SMA subtype classifications [9, 21]. Building on this framework, the current study further refines these classifications into four WHO-derived SMA functional groups: non-sitters, sitters, HFSS, and walkers. These may represent a useful reference metric for both clinical and research settings, and health care provision.

The initial description of the RHS introduced the concept of the non-sitter as a distinct subgroup within the SMA type 2 population. These individuals represent the weaker end of the SMA type 2 spectrum, having at some point acquired the ability to sit unaided, necessary for classification as type 2, but subsequently having lost this ability over time [9]. In the current study, non-sitters accounted for 8.7 % of all assessments. The 25th and 75th percentile RHS scores for this group suggest that the 50 % percentile of non-sitters typically score between 1 and 4. However, caution should be applied when inferring a non-sitter or weaker sitter classification in children under five years of age, as younger non-sitters may achieve scores that overlap with those of sitters as they might be still gaining skills. This pattern is consistent with the natural history of SMA type 2, where individuals must have achieved independent sitting at some stage to meet the diagnostic criteria, but later lose this ability and are subsequently categorised as non-sitters.

In the sitter population the 25th and 75th centile scores give a conservative estimate that the 50 % percentile of this population will achieve scores in the range of 5–14. This quantile range reflects the range of abilities across the age groups, with lower RHS values observed in the ≥15-year group which continue to lie within the quantile range. It is important to note that the sitter population consist of a mixture of SMA types. Fig. 2 suggest there may be a difference in the range of sitter scores for SMA 2 and SMA 3a patients during childhood and adolescence, and patients with SMA 3b do not appear in the sitter range until adulthood, but this was not analysed in our study as the scope was limited to paediatric population only but should be explored in future research. Further exploration of the nuances within sitters and SMA type may be beneficial also in view of earlier suggestions of subdivision of SMA 2 between 2a and 2b [20].

This study has identified and described a distinctly separate functional HFSS group. Such functional status have previously been described as having a 'borderline type 2/3′, type '2.8 or 2.9′ form of SMA, and this group often represents the stronger end of SMA type 2 spectrum [22–26]. The WHO-derived functional types within this study represent a step wise progression or regression of abilities of non-sitter, sitter, HFSS and walker, and uses a different approach of functional classification than SMA type which uses highest ability ever achieved. The estimate of the 50 % percentile of the HFSS subgroup scored 25 to 31 on the RHS. This stepwise progression/regression of functional type means the HFSS within this study also captures type 3 patients who have lost ambulation. The HFSS group demonstrates a level of abilities and RHS scores that are distinctly separate from the 'non-sitter', 'sitter' and

**Table 1**
RHS total score by motor function and SMA Type (* omitted due to identifying data).

| | | All | 2 | 3a | 3b |
|---|---|---|---|---|---|
| All | N (M) | 178 (618) | 109 (363) | 59 (217) | 10 (38) |
| | RHS Median (IQR) | 14 (6, 35.75) | 7 (4,12) | 39 (25, 52) | 57 (43.25, 64.75) |
| | RHS Range | 0–69 | 0–28 | 5–69 | 30–69 |
| | Age Median (IQR) | 8.2 (4.8, 11.375) | 6.3 (3.65, 10.4) | 9.3 (6.4, 11.5) | 14 (10.225, 16.125) |
| | Age Range (years) | 1–17.8 | 1–17.7 | 2.7–17.2 | 4.2–17.8 |
| Non-Sitter | N (M) | 27 (54) | 26 (53) | 1 (1) | 0 |
| | RHS Median (IQR) | 2 (1,4) | 2 (1,4) | * | |
| | RHS Range | * | 0–8 | * | |
| | Age Median (IQR) | 11.75 (8.7, 14.35) | 11.7 (8.5, 14.6) | * | |
| | Age Range (years) | 1–17.4 | 1–17.4 | * | |
| Sitter | N (M) | 110 (347) | 90 (296) | 20 (51) | 0 |
| | RHS Median (IQR) | 8 (5, 14) | 7 (4,12) | 17 (12.5, 21) | |
| | RHS Range | 2–24 | 2–26 | 5–42 | |
| | Age Median (IQR) | 6.6 (3.8, 10.6) | 5.8 (3.3, 9.525) | 12 (9.1, 13.8) | |
| | Age Range (years) | 1.2–17.7 | 1.2–17.7 | 4.5–17.2 | |
| HFSS | N (M) | 21 (48) | 5 (14) | 14 (31) | 2 (3) |
| | RHS Median (IQR) | 27.5 (25,31.25) | 25 (23.25, 26.5) | 30 (26,32) | 32 (31.5,45.5) |
| | RHS Range | 15–59 | 15–28 | 22–37 | 31–59 |
| | Age Median (IQR) | 9 (6.375, 12.725) | 3.75 (3.225, 5.95) | 10.4 (8.65, 13.05) | 16.8 (16.55, 16.95) |
| | Age Range (years) | 2.7–17.1 | 2.7–7.8 | 6.2–15.7 | 16.3–17.1 |
| Walker | N (M) | 50 (169) | 0 | 41 (134) | 9 (35) |
| | RHS Median (IQR) | 50 (41,60) | | 48.5 (41,57) | 57 (46.5, 65) |
| | RHS Range | 19–69 | | 19–69 | 30–69 |
| | Age Median (IQR) | 9 (5.9, 11) | | 7.8 (5.6, 10.25) | 13.6 (10.05, 15.5) |
| | Age Range (years) | 2.7–17.8 | | 2.7–15.1 | 4.2–17.8 |

'walker' WHO-derived SMA functional groups. In our study, classification within the HFSS group is based on current functional status as it evolves over time, rather than the highest motor abilities ever achieved. As a result, the HFSS category may reflect not only distinct functional capabilities, but also individuals in a phase of functional decline or improvement - for instance, those transitioning from ambulant to non-ambulant status, or those who are no longer able to rise from the floor independently or very young children learning to crawl or stand, or adolescents and young adults whose increasing contractures and scoliosis demand greater strength to maintain an upright posture and may lead to functional loss. Although the HFSS subgroup sample size was relatively small, it is plausible that in treated type 2 and weaker type 3 SMA patients, therapeutic interventions may expand this transitional functional continuum.

The walker population, which consistently demonstrate the highest functional scores, show a 25th to 75th percentile RHS score range of 41 to 60. This interquartile range offers a conservative estimate of the 50 % percentile of scores and reflects the broad spectrum of abilities present across age groups within this functional category.

Our results have highlighted that looking at SMA type alone may mask individual functional differences, which are likely more meaningful to patients and carers, within and between types. Furthermore, a more detailed characterisation of the functional groups may be helpful in predicting functional gains or losses especially in the DMTs era. For example, if looking at potential prognostic capabilities of the RHS for type 2 SMA you may expect an "average" patient to score between 4 and 12 on the RHS, however a non-sitter may score 1 to 4, a sitter may score 4 to 12 and the HFSS group may score 23 to 27. This study has highlighted the potential of the scale to detect four different WHO-derived functional types. This scale, therefore, may be a more accessible frame of reference than transitioning between non-ambulant to ambulant or from 'a type 2′ to 'a type 3a' to 'a type 3b' for example. The RHS with the WHO-derived functional types and functional ranges presented in this paper anchor a scoring quantile range to a functional type, with important implications for qualifying the functional significance of changes observed on the RHS. The changing functional phenotype in treated SMA patients (with any of the currently approved disease modifying therapies (DMT): nusinersen, risdiplam, or onasemnogene abeparvovec) and the likelihood of initiating a DMT treatment soon after symptom onset (where a type cannot be assigned) may indicate that a move away from SMA type and towards functional type is warranted.

There is further work to be done to investigate the effect of motor skills acquisition on the RHS scale, and an age at which the RHS is appropriate has not yet been determined. We also acknowledge, that our results should be interpreted with caution due to the apparent functional stability observed in the HFSS group, compared to the other subgroups, this can be influenced by the relatively short mean follow-up and limited number of participants with repeated assessments. Confirmation of these findings will require larger cohorts with extended longitudinal follow-up. Additionally, although we have 618 assessments for our cross-sectional data indicative of a large untreated SMA population representative sample, future work would need to assess how sensitive to change the RHS is in treated populations. We have also opted to utilise a conservative approach regarding our provision of cross-sectional 25th and 75th centile quantile ranges for this scale. The findings of this study should be taken in conjunction with works which analyse the RHS scores with respect to age [12] and time [14].

## 5. Conclusion

This study highlights that the RHS can effectively distinguish between different functional phenotypes in paediatric SMA patients, including a newly defined HFSS group, providing a more relevant framework for patient classification in the era of new treatments. As a psychometrically validated, SMA-specific scale, the RHS has demonstrated strong sensitivity in distinguishing among clearly established functional subgroups (non-sitter, sitter, walker). Given the complementary strengths of the HFSS in capturing functional differences, we recommend that HFSS be considered for incorporation into future SMA typing classification to enhance diagnostic precision and functional stratification. We suggest that using the WHO-derived SMA functional types and the RHS in combination may provide an additional useful clinical tool for prognostic estimation; however, we acknowledge this is cross sectional paper and prognostic factors in SMA patients treated with DMTs may be different. The use of quantile ranges for inclusion/exclusion criteria in clinical trials may enable a more sensitive and refined

**Table 2**
Item performance by Motor Function Phenotype. The comparisons were using the $\chi^2$test, unless expected cell sizes were <5, in which case the Fisher exact test was used. The Fisher exact test is marked by *.

| | Non-Sitter | | | | Sitter | | | | HFSS | | | | Walker | | | | p-value for comparison of HFSS vs. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | N | 0 | 1 | 0 | 1 | 2 | N | 0 | N | 0 | 1 | 2 | N | 0 | Sitters | 0 |
| Item: 1 sitting | 28 (51.9%) | 17 (31.5%) | 9 (16.7%) | 54 | 0 (0%) | 0 (0%) | 346 (100%) | 346 | 0 (0%) | 0 (0%) | 48 (100%) | 48 | 0 (0%) | 0 (0%) | 169 (100%) | 169 | 0 X | 1 F | 1 F |
| Item: 2 hands to head in sitting | 48 (88.9%) | 5 (9.3%) | 1 (1.9%) | 54 | 172 (49.6%) | 43 (12.4%) | 132 (38%) | 347 | 0 (0%) | 3 (6.2%) | 45 (93.8%) | 48 | 1 (0.6%) | 1 (0.6%) | 167 (98.8%) | 169 | 0 F | 0 X | 0.0347 F |
| Item: 3 Sitting to lying | 51 (98.1%) | 1 (1.9%) | 0 (0%) | 52 | 210 (60.7%) | 67 (19.4%) | 69 (19.9%) | 346 | 2 (4.2%) | 7 (14.6%) | 39 (81.2%) | 48 | 0 (0%) | 8 (4.7%) | 161 (95.3%) | 169 | 0 F | 0 X | 0.0021 F |
| Item: 4 Add from crook | 18 (33.3%) | 18 (33.3%) | 18 (33.3%) | 54 | 28 (8.1%) | 127 (36.7%) | 191 (55.2%) | 346 | 0 (0%) | 1 (2.1%) | 47 (97.9%) | 48 | 1 (0.6%) | 2 (1.2%) | 166 (98.2%) | 169 | 0 X | 0 F | 0.635 F |
| Item: 5 Right hip flexion | 44 (81.5%) | 10 (18.5%) | 0 (0%) | 54 | 121 (35.2%) | 207 (60.2%) | 16 (4.7%) | 344 | 0 (0%) | 31 (64.6%) | 17 (35.4%) | 48 | 0 (0%) | 41 (24.4%) | 127 (75.6%) | 168 | 0 X | 0 F | 0 F |
| Item: 6 Left hip flexion | 46 (85.2%) | 8 (14.8%) | 0 (0%) | 54 | 126 (36.5%) | 209 (60.6%) | 10 (2.9%) | 345 | 0 (0%) | 35 (72.9%) | 13 (27.1%) | 48 | 0 (0%) | 43 (25.7%) | 124 (74.3%) | 167 | 0 X | 0 F | 0 F |
| Item: 7 Lifts head in supine | 53 (98.1%) | 1 (1.9%) | 0 (0%) | 54 | 290 (83.6%) | 32 (9.2%) | 25 (7.2%) | 347 | 15 (31.2%) | 11 (22.9%) | 22 (45.8%) | 48 | 6 (3.6%) | 31 (18.3%) | 132 (78.1%) | 169 | 0 X | 0 X | 0 F |
| Item: 8 Supine to side lying | 38 (71.7%) | 15 (28.3%) | | 53 | 72 (20.9%) | 273 (79.1%) | | 345 | 0 (0%) | 47 (100%) | | 47 | 0 (0%) | 169 (100%) | | 169 | 0 F | 1e-04 F | NA |
| Item: 9 Rolls sup to pr | 50 (94.3%) | 3 (5.7%) | 0 (0%) | 53 | 181 (52.2%) | 91 (26.2%) | 75 (21.6%) | 347 | 0 (0%) | 2 (4.2%) | 46 (95.8%) | 48 | 0 (0%) | 4 (2.4%) | 165 (97.6%) | 169 | 0 F | 0 X | 0.6159 F |
| Item: 10 Prone lifts head | 49 (96.1%) | 1 (2%) | 1 (2%) | 51 | 254 (73.6%) | 41 (11.9%) | 50 (14.5%) | 345 | 3 (6.2%) | 2 (4.2%) | 43 (89.6%) | 48 | 2 (1.2%) | 1 (0.6%) | 165 (98.2%) | 168 | 0 F | 0 X | 0.0265 F |
| Item: 11 props forearms | 48 (94.1%) | 2 (3.9%) | 1 (2%) | 51 | 210 (61.2%) | 52 (15.2%) | 81 (23.6%) | 343 | 2 (4.2%) | 1 (2.1%) | 45 (93.8%) | 48 | 0 (0%) | 1 (0.6%) | 168 (99.4%) | 169 | 0 F | 0 X | 0.0347 F |
| Item: 12 Four point crawl | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 308 (89.5%) | 23 (6.7%) | 13 (3.8%) | 344 | 2 (4.2%) | 3 (6.2%) | 43 (89.6%) | 48 | 6 (3.6%) | 3 (1.8%) | 160 (94.7%) | 169 | 0 F | 0 F | 0.184 F |
| Item: 13 Rolls pr to s | 47 (92.2%) | 4 (7.8%) | 0 (0%) | 51 | 189 (54.8%) | 117 (33.9%) | 39 (11.3%) | 345 | 0 (0%) | 10 (20.8%) | 38 (79.2%) | 48 | 0 (0%) | 8 (4.7%) | 161 (95.3%) | 169 | 0 X | 0 X | 0.0013 F |
| Item: 14 Lie to sit | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 303 (87.6%) | 34 (9.8%) | 9 (2.6%) | 346 | 6 (12.5%) | 23 (47.9%) | 19 (39.6%) | 48 | 9 (5.3%) | 44 (26%) | 116 (68.6%) | 169 | 0 X | 0 F | 8e-04 F |
| Item: 15 Sit to std | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 343 (99.1%) | 2 (0.6%) | 1 (0.3%) | 346 | 29 (60.4%) | 18 (37.5%) | 1 (2.1%) | 48 | 8 (4.8%) | 116 (69.5%) | 43 (25.7%) | 167 | 0 F | 0 F | 0 X |
| RHS 16 Stand cruise | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 339 (98.5%) | 5 (1.5%) | 0 (0%) | 344 | 15 (31.9%) | 7 (14.9%) | 25 (53.2%) | 47 | 0 (0%) | 1 (0.6%) | 168 (99.4%) | 169 | 0 F | 0 F | 0 F |
| Item: 17 Standing | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 344 (99.4%) | 2 (0.6%) | 0 (0%) | 346 | 28 (58.3%) | 12 (25%) | 8 (16.7%) | 48 | 1 (0.6%) | 24 (14.3%) | 143 (85.1%) | 168 | 0 F | 0 F | 0 X |
| Item: 18 Walking | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 1 (0.3%) | 0 (0%) | 346 | 41 (85.4%) | 5 (10.4%) | 2 (4.2%) | 48 | 1 (0.6%) | 0 (0%) | 168 (99.4%) | 169 | 0.0046 F | 0 F | 0 F |

(*continued on next page*)

**Table 2** (*continued*)

| | Non-Sitter | | | | Sitter | | | | HFSS | | | | Walker | | | | p-value for comparison of HFSS vs. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | N | 0 | 1 | 0 | 1 | 2 | N | 0 | N | 0 | 1 | 2 | N | 0 | Sitters | 0 |
| Item: 19 Run | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 0 (0%) | 1 (0.3%) | 346 | 48 (100%) | 0 (0%) | 0 (0%) | 48 | 47 (29.2%) | 81 (50.3%) | 33 (20.5%) | 161 | 1 F | 1 F | 0 X |
| Item: 20 Squat up and down | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 0 (0%) | 1 (0.3%) | 346 | 45 (93.8%) | 3 (6.2%) | 0 (0%) | 48 | 34 (20.1%) | 129 (76.3%) | 6 (3.6%) | 169 | 0.107 F | 0.0017 F | 0 F |
| Item: 21 Std to sit on floor | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 343 (99.1%) | 3 (0.9%) | 0 (0%) | 346 | 44 (91.7%) | 3 (6.2%) | 1 (2.1%) | 48 | 36 (21.3%) | 104 (61.5%) | 29 (17.2%) | 169 | 0.0496 F | 0.0052 F | 0 X |
| Item: 22 High kneeling | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 337 (98%) | 6 (1.7%) | 1 (0.3%) | 344 | 16 (34%) | 6 (12.8%) | 25 (53.2%) | 47 | 9 (5.3%) | 26 (15.4%) | 134 (79.3%) | 169 | 0 F | 0 F | 0 X |
| Item: 23 High kneel to R half kneel | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 339 (98.3%) | 4 (1.2%) | 2 (0.6%) | 345 | 27 (56.2%) | 19 (39.6%) | 2 (4.2%) | 48 | 18 (10.7%) | 62 (36.9%) | 88 (52.4%) | 168 | 0 F | 0 F | 0 X |
| Item: 24 High kneel to L half kneel | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 340 (98.6%) | 4 (1.2%) | 1 (0.3%) | 345 | 26 (54.2%) | 17 (35.4%) | 5 (10.4%) | 48 | 18 (10.7%) | 63 (37.5%) | 87 (51.8%) | 168 | 0 F | 0 F | 0 X |
| Item: 25 Rise from floor | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 346 (100%) | 0 (0%) | 0 (0%) | 346 | 48 (100%) | 0 (0%) | 0 (0%) | 48 | 53 (31.5%) | 105 (62.5%) | 10 (6%) | 168 | 1 F | 1 F | 0 F |
| Item: 26 Stand on R leg | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 346 (100%) | 0 (0%) | 0 (0%) | 346 | 45 (93.8%) | 3 (6.2%) | 0 (0%) | 48 | 25 (14.9%) | 70 (41.7%) | 73 (43.5%) | 168 | 0.107 F | 0.0017 F | 0 X |
| Item: 27 Stand on L leg | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 346 (100%) | 0 (0%) | 0 (0%) | 346 | 43 (89.6%) | 5 (10.4%) | 0 (0%) | 48 | 30 (17.9%) | 69 (41.1%) | 69 (41.1%) | 168 | 0.0227 F | 0 F | 0 X |
| Item: 28 Hops on R leg | 52 (100%) | 0 (0%) | | 52 | 346 (100%) | 0 (0%) | | 346 | 47 (97.9%) | 1 (2.1%) | | 48 | 122 (72.6%) | 46 (26.8%) | | 168 | 0.48 F | 0.1218 F | 1e-04 F |
| Item: 29 Hops on L leg | 52 (100%) | 0 (0%) | | 52 | 346 (100%) | 0 (0%) | | 346 | 47 (97.9%) | 1 (2.1%) | | 48 | 119 (70.8%) | 49 (28.6%) | | 168 | 0.48 F | 0.1218 F | 0 F |
| Item: 30 Ascend 4 stairs | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 1 (0.3%) | 0 (0%) | 346 | 45 (93.8%) | 3 (6.2%) | 0 (0%) | 48 | 36 (22.1%) | 85 (52.1%) | 42 (25.8%) | 163 | 0.107 F | 0.0062 F | 0 X |
| Item: 31 Descend 4 stairs | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 1 (0.3%) | 0 (0%) | 346 | 44 (91.7%) | 3 (6.2%) | 1 (2.1%) | 48 | 34 (20.9%) | 76 (46.6%) | 53 (32.5%) | 163 | 0.0496 F | 9e-04 F | 0 X |
| Item: 32 Climb box step R | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 1 (0.3%) | 0 (0%) | 346 | 47 (97.9%) | 0 (0%) | 1 (2.1%) | 48 | 59 (36%) | 49 (29.9%) | 56 (34.1%) | 164 | 0.48 F | 0.2291 F | 0 X |
| Item: 33 Descend box step R | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 1 (0.3%) | 0 (0%) | 346 | 47 (97.9%) | 0 (0%) | 1 (2.1%) | 48 | 46 (28%) | 73 (44.5%) | 45 (27.4%) | 164 | 0.48 F | 0.2291 F | 0 X |
| Item: 34 Climb box step L | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 1 (0.3%) | 0 (0%) | 346 | 47 (97.9%) | 0 (0%) | 1 (2.1%) | 48 | 60 (36.6%) | 49 (29.9%) | 55 (33.5%) | 164 | 0.48 F | 0.2291 F | 0 X |
| Item: 35 Descend box step L | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 345 (99.7%) | 1 (0.3%) | 0 (0%) | 346 | 47 (97.9%) | 0 (0%) | 1 (2.1%) | 48 | 47 (28.7%) | 75 (45.7%) | 42 (25.6%) | 164 | 0.48 F | 0.2291 F | 0 X |
| Item: 36 Jump forward | 52 (100%) | 0 (0%) | 0 (0%) | 52 | 346 (100%) | 0 (0%) | 0 (0%) | 346 | 47 (97.9%) | 0 (0%) | 1 (2.1%) | 48 | 88 (54%) | 43 (26.4%) | 32 (19.6%) | 163 | 0.48 F | 0.1218 F | 0 X |

approach regarding the potential response to treatment. Future studies may give further indication regarding the value of the RHS to assess treatment efficacy.

The HFSS phenotype is a distinctly different SMA functional group characterised by a greater loss of abilities, relative to walkers, based on previously reported natural history data, yet showing potential for greater gains with treatment in children. It may be possible that with treatment the HFSS functional type becomes more prevalent. Furthermore, our study can guide clinicians, parents and caregivers to clinically important changes in patient care by allowing for phenotype-specific management, monitoring and goal setting. This functional phenotype encompasses a different skill set and it is important to be aware of it for health-related quality of life purposes.

## CRediT authorship contribution statement

**E Milev:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. **G Stimpson:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **D Ramsey:** Writing – review & editing, Writing – original draft, Conceptualization. **A Mayhew:** Writing – review & editing. **M Scoto:** Writing – review & editing. **G Baranello:** Writing – review & editing. **R Muni Lofra:** Writing – review & editing. **E O'Reilly:** Writing – review & editing. **Wolfe Amy:** Writing – review & editing. **M Main:** Writing – review & editing. **ES Mazzone:** Writing – review & editing. **J Montes:** Writing – review & editing. **AM Glanzman:** Writing – review & editing. **A Pasternak:** Writing – review & editing. **T Duong:** Writing – review & editing. **M Civitello:** Writing – review & editing. **G Coratti:** Writing – review & editing. **C Marini-Bettolo:** Writing – review & editing. **J Day:** Writing – review & editing. **BT Darras:** Writing – review & editing. **D De Vivo:** Writing – review & editing. **RS Finkel:** Writing – review & editing. **E Mercuri:** Writing – review & editing. **F Muntoni:** Writing – review & editing, Supervision, Conceptualization.

## Declaration of competing interest

Evelin Milev provides consultancy services through ATOM International Ltd for Amicus Therapeutics Pty Ltd, Genethon, Italfarmaco, NS Pharma, Pfizer, Edgewise Therapeutics, Sarepta, and Dyne Therapeutics.

D. Ramsey reports participation in teaching initiatives for Roche.

E. O'Reilly reports participation in advisory boards for Roche.

M. Scoto has provided consultancy services, lectures, and participated in advisory boards for Biogen, Roche, and Novartis; she is also co-Principal Investigator of the SMA REACH UK, currently supported by Biogen, Roche, and Novartis.

F. Muntoni has participated in advisory boards for Biogen, Roche, and Novartis, presented at industry symposia for these companies, and is the Principal Investigator of the paediatric SMA REACH UK network supported by Biogen, Roche, and Novartis.

E. Mercuri has participated in advisory boards for Biogen, Roche, Scholar Rock, and Novartis, presented at industry symposia for Biogen, Roche, and Novartis, and is the Principal Investigator of the paediatric ITASMAC network supported by Biogen, Roche, and Novartis.

A. Pasternak has participated in advisory boards for Biogen, Roche, and Scholar Rock, and presented at industry symposia for Biogen.

J. Montes has received grant support from Genentech, Scholar Rock, Biogen, the National Institute of Child Health and Human Development, the Muscular Dystrophy Association, and Cure SMA; she has received honoraria for non-CME events from F. Hoffmann-La Roche and Scholar Rock, and served on advisory boards for Biogen, Scholar Rock, Argenx, NMD Pharma, and F. Hoffmann-La Roche.

T.T. Duong has served as a consultant for Astellas, Roche, Dyne, Biogen, Trinds, Juvena, Avidity, and Genzyme, and has received grants or served on advisory boards for Scholar Rock, Biogen, Sanofi, Cure SMA, Duchenne UK, and Parent Project Muscular Dystrophy.

G. Coratti has participated in advisory boards, steering committees, and served as a consultant/speaker for Biogen, Roche, Solid, Novartis, and Scholar Rock.

R. Muni Lofra has participated in advisory boards for Roche and Biogen, provided consultancy services for Roche and Biogen, and is Principal Investigator for grants supported by these companies.

R.S. Finkel declares personal compensation for advisory board participation from Astellas, Biogen, Dyne, Genentech, Ionis, Italfarmaco, Novartis, NS Pharma, ReveraGen, Roche, Sarepta, Satellos, and Scholar Rock; research funding from Biogen, Dyne, Genentech, Genethon, Insmed, Italfarmaco, Roche, Sarepta, and Scholar Rock; editorial fees from Elsevier for co-editing a neurology textbook; and license fees from the Children's Hospital of Philadelphia.

A. Glanzman provides AMD consulting, participates in advisory boards for Biogen, and holds licensing rights for the CHOP INTEND scale.

E.S. Mazzone has participated in advisory boards for Biogen and Scholar Rock and presented at industry symposia for Biogen.

All other authors declare no competing interests.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2026.106336.

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