Published Ahead of Print on October 16, 2020 as 10.1212/WNL.0000000000011051

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000011051

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Neurology -2020-099077 R1

Original Article

Respiratory trajectories in type 2 and non-ambulant 3 Spinal muscular atrophy in the iSMAC cohort study

The Article Processing Charge was funded by National Institute of Health Research (NIHR).

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Word count: 4047 (4500 allowed)
Title: 97 characters (96 allowed)
Abstract: 250 (250 allowed)
References: 37(40 allowed)
Figures and Tables: 7 (7 allowed)
Data available from Dryad (Supplementary eFigure 1-3): doi:10.5061/dryad.1jwstqjs8

The statistical analysis was conducted by DR - Population, Policy and Practice Programme, UCL GOS Institute of Child Health, London

Search terms: Spinal muscular atrophy, Forced Vital Capacity, Hammersmith Functional Motor Scale, Revised Upper Limb Module

Study funding: The support of Biogen and advocacy group SMA TRUST and Muscular Dystrophy UK to the Neuromuscular Centre at UCL and to the SMA REACH network (**Error! Hyperlink reference not valid.** is gratefully acknowledged. FM is supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health, University College London, & Great Ormond Street Hospital Trust, London, UK. The views expressed in this manuscript are those of the authors and not necessarily of the NIHR.

Disclosure

Dr. F. Trucco, Dr. D. Ridout, Dr. M. Main, Dr. M. Ong and Dr. A Navas Nazario report no disclosures.

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ABSTRACT

Objective. To describe the respiratory trajectories and their correlation with motor function in an international paediatric cohort of patients with type 2 and non-ambulant type 3 spinal muscular atrophy (SMA).

Methods. Eight-year retrospective observational study of patients in the iSMAc natural history study. We retrieved anthropometrics, forced vital capacity (FVC) absolute, FVC% predicted (FVC%P.), Non-Invasive ventilation (NIV) requirement. Hammersmith functional motor scale (HFMS) and Revised performance of upper limb (RULM) were correlated with respiratory function. We excluded patients in interventional clinical trials and on Nusinersen commercial therapy.

Results. There were 437 patients with SMA: 348 type 2, 89 non-ambulant type 3. Mean age at first visit was 6.9(±4.4) and 11.1(±4) years. In SMA type 2 FVC%P declined by 4.2%/year from 5 to 13 years, followed by a slower decline (1.0%/year). In type 3 FVC%P declined by 6.3%/year between 8 and 13 years, followed by a slower decline (0.9%/year). 39% SMA type 2 and 9% type 3 required NIV at median age 5.0(1.8-16.6) and 15.1(13.8-16.3) years. 84% SMA type 2 and 80% type 3 had scoliosis, 54% and 46% required surgery, which did not significantly affect respiratory decline. FVC%P positively correlated with HFMS and RULM in both subtypes.

Conclusions. In SMA type 2 and non-ambulant type 3 lung function declines differently, with a common levelling after age 13 years. Lung and motor function correlated in both subtypes. Our data further defines the milder SMA phenotypes and provides novel information to benchmark the long-term efficacy of new treatments for SMA.

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INTRODUCTION

Spinal Muscular Atrophy (SMA) is an autosomal recessive neurodegenerative disorder characterized by progressive muscle wasting due to motor neuron degeneration, secondary to mutations in the survival motor neuron 1 (*SMN1*) gene [1]. SMA is classified according to age of onset and maximal motor functional status achieved: weak infants unable to sit unsupported (type 1), non-ambulant patients (type 2), ambulant patients with childhood (type 3) and -adult onset (type 4) [2] [3].

Respiratory impairment is the most frequent non-neurologic complication and the leading cause of mortality in SMA [4]. Patients with SMA present with variable severity of chest wall distortion, paradoxical breathing and impaired airway clearance and cough, compounded by bulbar muscle weakness [5, 6]. The assessment of respiratory function has gained interest in infants with SMA type 1 [7, 8] as recently available treatments have improved patients' motor function and life expectancy [9-11]. In contrast, very few studies have focused on the long-term respiratory progression in SMA type 2 and 3 [12-14]. The correlation between ~~with~~ respiratory and motor function in these milder subtypes is ~~particularly~~ interesting in light of the new therapeutic options [15-18]. Intrathecal Nusinersen and adeno-associated viral vector gene replacement therapy are commercially available (the latter currently only for patients aged <2 years). Small molecules orally administered (*NCT02908685)* [19] or intrathecal gene replacement ~~therapies~~ are currently both in clinical trials *(NCT03381729)*.

Aim of our work is to describe the respiratory features of paediatric patients with SMA type 2 and non-ambulant SMA type 3 and their correlation with motor function in a multicentre international cohort.

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METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Institutional Review Board (Ethics Committee) at each participating study site. Written informed consent was obtained from all participants (or guardians of participants) in the study (consent for research).

Study population

Eight-year (June 2010-September 2018) retrospective observational study of SMA type 2 and non-ambulant SMA type 3 paediatric patients (age<18years). The data used in this study is part of the International SMA Consortium (iSMAc) [20] composed by SMA REACH-UK (NCT03520179), Italian SMA and US PNCR Networks and by additional centres: UK SMARTNET and C. Mondino and C. Besta Neurological Institutes (Italy).

Patients with SMA type 2 were classified as sitters and non-sitters (those who lost the ability to sit unsupported) at each recorded visit. Only non-ambulant SMA type 3 were included in this study in order to compare homogeneous respiratory trajectories not affected by changes in ambulatory status.

We subsequently excluded patients recruited in any interventional clinical trials or receiving Nusinersen or Onasemnogene abeparvovec, either commercially available or within Expanded Access Programme. *SMN 1* gene mutations and *SMN 2* copies were recorded. Anthropometrics were collected. Either arm span, recumbent or ulnar length were used as surrogate for height in Forced Vital Capacity % predicted (FVC%P) calculation [21]. Co-morbidities affecting lung function such as aspiration, either identified clinically or by videofluoroscopy (VF) were collected. Patients' nutritional status was postulated by body mass index (BMI) expressed as kg/m^2. Patients' feeding status (oral nutrition, naso-gastric

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tube (NG) or gastrostomy) was recorded. Scoliosis was defined as Cobb angle>10°. Scoliosis surgery technique was collected.

Respiratory function

Spirometry was performed at each site by either physiotherapists or respiratory physiologists who had received appropriate training and certification in the context of clinical trials. The best out of three efforts deemed reliable by the operator was recorded according to international guidelines [22]. Forced vital capacity (FVC) absolute (L) and FVC%P, Peak expiratory flow (PEF) absolute (l/min) and PEF% predicted (PEF%P) with the patient tested in a sitting position were collected.

Ventilation requirement either non-invasive (NIV) or invasive (tracheostomy) and the use of assisted airway clearance were recorded.

Motor function

Motor function outcomes, namely Hammersmith functional motor scale (HFMS) and Revised performance of upper limb (RULM) were collected. HFMS was developed to assess the physical abilities of SMA type 2 and type 3 with limited ambulation. It is composed of 20 items with a maximal score of 40 [23]. The upper limb module (ULM) was the first tool to assess the upper limb function in non-ambulant SMA. It was created and validated in 2011 for non-ambulant children from 30 months to adults [24]. In 2017 ULM was critically re-evaluated and the RULM was developed to tackle the ceiling effect observed with the ULM in non-ambulant patients. RULM detects changes in upper limb function in a wide spectrum of weak and strong SMA. The RULM has a total of 19 items plus an entry item, not included in the total score that serves as functional class identification. Its maximum total score is 37 [25]. A higher score on the HFMS, ULM and RULM represents a higher level of function.

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Statistical analysis

The primary outcome was the annual variation of FVC%P in SMA type 2 and non-ambulant type 3 patients. Secondary outcome was the correlation between respiratory (FVC%P) and motor function (HFMS and/or RULM). The FVC%P trajectories pre and post scoliosis surgery and the annual variation of FVC absolute, PEF%P and PEF absolute were also analysed.

The population characteristics are presented as mean (SD), median (range or interquartile range) for skewed data and frequency (percentage) for categorical data.

For FVC%P, FVC absolute and PEF%P we estimated the mean annual change using mixed effects regression models, accounting for the longitudinal data and age at baseline. Results are presented as mean annual change, or difference in mean annual change between subgroups, with 95% confidence intervals. As the change in these outcomes was not linear over the full age range, we used linear splines to estimate and compare the relationships before and after 8 (SMA type 3) and 13 years of age. Using Kaplan Meier and Cox regression analyses we estimated the median age when FVC%P fell below 60%, 40% and 20%, scoliosis surgery occured and gastrostomy was placed.

Correlation between respiratory (FVC%P) and motor function (HMFS and/or RULM) was performed for both SMA type 2 and 3 patients by Spearman rank correlation. We reported the correlation between FVC%P and each motor functional score at first available visit, as the correlation factor was not different to that obtained when correlating FVC%P. and motor function throughout the study period.

All analyses were conducted in Stata v15 with significance level of $p < 0.05$.

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Data Availability

The data that support the findings of this study are owned by the iSMAC academic consortium and available from the corresponding author on reasonable request.

RESULTS

Study population

Data were available for 437 patients. There were 348 (80%) SMA type 2, at first visit 278 were sitters, 32 non-sitters, in 38 sitting status was not available. Fourteen patients who were sitters at first visit lost their ability to sit independently during the follow-up. Eighty-nine (20%) were non-ambulant SMA type 3 (Figure 1). In both SMA type 2 subgroups, most patients had 3 copies of *SMN2*: they accounted for the 89% and 67% of the available data in sitters and non-sitters respectively. Patients with 2 copies of *SMN2* accounted for 9% and 33% of the available data in sitters and non-sitters.

Mean age at first visit was 6.9 (±4.4) years for SMA type 2 and 11.1 (±4) years for SMA type 3. Median follow up was 1.2 years, IQR (0, 3.3) years range (0, 12.5) years.

Median BMI at first visit was 15.8 (14.0-19.1) kg/m^2 in SMA type 2 and 18.1 (16.6-22.0) kg/m^2 in type 3. BMI and FVC absolute at first visit positively correlated in both SMA type 2 ($r=0.5$, $p<0.05$) and type 3 ($r=0.6$, $p<0.01$). Throughout the study period 9 SMA type 2 and none of the SMA type 3 required NG tube. Only SMA type 2 patients required gastrostomy (62/278), 25% of them by 12 years of age (Table 1 and eFigure 1).

Respiratory progression and respiratory support

Data on FVC%P was available for 260 patients. Over the eight-year observation, the annual rate of decline of FVC%P between 5 and 18 years was 3.6% in SMA type 2, CI 95% (-4.2, -

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2.9), and 3.5% in SMA type 3, CI 95% (-5.6, -1.4). However, the trajectory of FVC%P progressed differently in the two SMA subgroups in the age range 5 to 13 years, followed by a similar plateau phase after the age of 13 years.

Indeed, in SMA type 2, FVC%P (n=200) declined by 4.2% per year, 95% CI (-4.8, -3.7) from 5 to 13 years of age, followed by a significantly slower ($p<0.001$) decline of 1.0% per year, 95% CI (-2.1, 0.2). When subdividing SMA type 2 into sitters and non-sitters SMA type 2 sitters (n=165), had an annual decline of FVC%P of 4.1%, 95% CI (-4.7, -3.5) from 5 to 13 years followed by a slower ($p<0.001$) progression of 1.3%, 95% CI (-2.5, -0.04). A similar decline ($p=0.15$ vs sitters, adjusted for age) was observed in SMA type 2 non-sitters (n=17). Their FVC%P from 5 to 13 years declined annually by 6.0%, 95% CI (-8.0, -4.0), followed by a slower progression.

Non-ambulant SMA type 3 (n=59) had a three-phase respiratory progression characterised by a mild increase of FVC%P from 5 to 8 years followed by a steeper decline from 8 to 13 years and a levelling thereafter. In detail, in the age range 5- 8 years FVC%P increased annually by 11.8%, 95% CI (4.5, 19.1), from age 8 to 13 years FVC%P declined by 6.3%, 95% CI (-8.7, -3.8) and after 13 years declined significantly slower ($p=0.01$) by 0.9%, 95%CI (-3.1, 1.4) (Figure 2). The mild improvement in pulmonary function observed in the age range 5 to 8 years is interesting and is reminiscent with improvement noticed in other outcome measures, although firm conclusions cannot be drawn due to the small sample size in that age window.

After 13 years of age, FVC%P stabilised and its annual decline became similar in SMA type 2 sitters, non-sitters and non-ambulant SMA type 3. However, the estimated FVC%P was higher in SMA type 3 (65.8%, 95% CI (68.2-83.4)) than in SMA type 2 sitters (41.0%, 95% CI (35.2-46.9)) ($p<0.001$) and non-sitters (32.1%, 95% CI (14.1-50.1)) ($p<0.001$). No differences were found between SMA type 2 sitters and non-sitters ($p=0.36$).

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Three significant lung function thresholds were evaluated in relation to the increased risk of sleep disordered breathing (FVC%P<60% and FVC%P<40%) and the development of diurnal respiratory failure (FVC%P<20%). One hundred and eleven SMA type 2 and 51 type 3 had FVC%P>60%. The median (50%) age at FVC%P<60% was 12.8 years in SMA type 2 while in less than 25% SMA type 3 FVC%P fell below 60% (p<0.001). One hundred and fifty SMA type 2 and 58 SMA type 3 had FVC%P>40% at their first visit. At the age of 13.4 years 25% SMA type 2 had FVC%P<40% while in SMA type 3 FVC%P fell below 40% in less than 25% (p<0.01). Less than 25% of the 189 SMA type 2 and none of the 60 SMA type 3 in our cohort reached FVC%P<20% (Figure 3).

Absolute FVC in SMA type 2 increased by 0.03 L/year, 95% CI (0.02, 0.05) with a stability between 10 to 14 years. There was no difference between SMA type 2 sitters and non-sitters (p=0.54). In SMA type 3 absolute FVC steadily increased from age 5 to 18 years by 0.10 L per year, 95% CI (0.04, 0.16) (eFigure 2).

Absolute PEF and PEF%P trajectories were only available in SMA type 2 (n=63). PEF%P annually declined from 5 years of age by 4.1%, 95% CI (-6.2, -1.9). Absolute PEF increased by 7.3 L/min per year, 95% CI (2.6-12.1) (eFigure 3). The progression of absolute PEF stabilized between 10 to 14 years, similar to absolute FVC.

One hundred and thirty-six of 298 (46%) SMA type 2 patients whose data at latest visit were available, required NIV. Of those 98/256 (38%) were sitters, 28/46 (61%) were non-sitters, and 10 with sitting ability missing. Eight of 71 (11%) SMA type 3 required NIV. For those who had started NIV, median (range) age was 5.0 (1.8-16.6) years in SMA type 2 while 15.1 (13.8-16.3) years in SMA type 3. FVC%P at start of NIV was 44% (IQR 28.5-57) in SMA type 2 (n=55). Thirteen (24%) had FVC%P>60%, 19 (35%) had FVC%P 40% to 60%, 14 (25%) had FVC%P 20% to 40%, 9 (16%) had FVC%P<20%. See Table 2 for details on NIV establishment and requirement per day.

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Correlation between respiratory and motor function

HFMS positively correlated with FVC%P in patients with SMA type 2 (n= 76), r=0.67 p<0.001 and non-ambulant type 3 (n=28), r=0.68, p<0.001. RULM positively correlated with FVC%P in SMA type 2 (n=32), r=0.61 p<0.001 and in SMA type 3 (n= 21), r=0.61, p<0.01(Figure 5).

HFMS score was available at NIV establishment in 39 patients SMA type 2. Thirty-one (79%) had HFMS below 10 and 24 (62%) had HFMS below 6. HFMS score at NIV establishment in SMA type 3 and RULM in SMA type 2 and 3 were available in only a few patients and were not analysed.

Respiratory function and scoliosis

One hundred and eighty of 215 (84%) SMA type 2 and 39 of 49 (80%) non-ambulant SMA type 3, whose information was available at latest visit, had scoliosis. Seventy of 145 SMA type 2 (48%) and 11 of 35 (31%) SMA type 3 patients underwent scoliosis surgery. Details on the different surgical techniques ranging from the use of growing rods in the younger children to full fixation in the older population are shown in Table 1. Median age (IQR) at surgery was 11 (8-14.4) years in SMA type 2. Sixty-five were sitters and had surgery at median age (IQR) 11 (8-13.2) years, 11 were non-sitters and had surgery at median (IQR) age 9.8 (8.2-16.1) years. Median age (IQR) at surgery in SMA type 3 was 11.7 (10.8-15.9) years (n= 16), similar to SMA type 2 (p=0.12).

A worsening trend of FVC%P was observed in the whole population after spinal surgery, going from -2.7 % to -3.6 % per year although this change was not significant (p=0.22). SMA type 2 non-sitters had the largest difference in respiratory function after surgery, going from +2.4% to -5.2% per year. This difference was not significant (p=0.19). ~~likely due to small sample size of the cohort~~. In SMA type 2 sitters FVC%P slope went from -2.8% to -3.4% per

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year (p=0.49). In SMA type 3 it went from -1.3% to -4.2% (p=0.48) (Figure 4). Similarly, FVC absolute yearly slope was not different pre- and post- surgery in SMA type 2 (overall and subtypes) and type 3.

DISCUSSION

In the last decade, the availability of new treatments has prompted the need for a precise understanding of the natural history of ambulant and non-ambulant patients with SMA ~~patients~~, from the most severe to the milder subtypes. Most of the emphasis has been devoted to the careful analysis of the progression of motor function, as this was often the main outcome measure in clinical trials. Recently, the description of the natural history of motor function in SMA type 2 and 3 has identified that in the early years after diagnosis an improvement in SMA type 2 can occur, followed by subsequent decline [26]. This information is essential when planning clinical trials and assessing the efficacy of intervention in a broad population. However, very few studies have focused on respiratory function, and none on the correlation between respiratory and motor function in a real-world broad population of intermediate SMA.

Recent long-term data from the patients with SMA type 2 and 3 enrolled in the Nusinersen clinical trials showed remarkable results on motor function (improvement of HFMSE and RULM) [16] but with incomplete data on respiratory outcomes. As Nusinersen has become commercially available for all types of SMA in some countries, real-world data on motor and respiratory function are becoming available.

In this scenario, the phenotyping of motor and respiratory function in SMA subtypes and age range is crucial to establish the actual efficacy of Nusinersen and other new treatments.

Our work adds novel long-term respiratory data from a large international cohort (n=437) of SMA type 2 and non-ambulant type 3 patients followed over eight years. Similar to motor function [26, 27], the decline of FVC%P in SMA type 2 and type 3 followed different

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trajectories across age ranges. In both subtypes FVC%P declined more steeply from 5 to 13 years (~4% per year in SMA type 2 and ~3% per year in type 3) followed by a slower annual progression after 13 years of age (1% in SMA type 2 and 0.9% in type 3). However, in type 3 the FVC%P decline was more obvious after the age of 8 years (rather than 5, as observed in type 2), with a similar pattern to the slopes of the 6 minute walk test. The rate of decline did significantly change after 13 years in both SMA types. The FVC%P declined to a stable level after 13 years and remained higher in type 3 (~ 66%) than in type 2 (41% sitters, 32% non-sitters). It is of interest that although non-sitters generally have a more severe phenotype, there was no significant difference in the rate of decline between sitters and non-sitters.

The annual decline of FVC%P had been reported as being 2.9% in 79 SMA type 2 and type 3 children and young adult over 36 months. SMA type 2 declined faster than type 3, however, the relatively small sample size did not allow further conclusions [13]. In a separate retrospective study on 31 SMA type 2 and 3 patients (age range 3-21 years) the median decline of the FVC%P was 7.9% in SMA type 2 and 2.8% in type 3 [14]. The results cannot be easily compared, both for the different sizes of the two populations studied and because the previous study, as opposed to ours, also included ambulant type 3. Our considerably larger population and the longer observation period allowed the identification of age-specific trajectories of pulmonary function selectively for SMA type 2 and 3. We explored the potential use of the Peak Expiratory Flow (PEF) as surrogate of expiratory muscle function in SMA type 2. In other neuromuscular disorders such as Duchenne muscular dystrophy PEF captured respiratory decline earlier than FVC% [28]. In patients with SMA, our novel findings showed that PEF%P declined consistently with FVC%P, confirming its potential utility as a measure of pulmonary function in SMA.

According to the most recent standard of care, FVC%P below 60% and below 40% are associated with the increased risk of respectively REM-related and NREM-related sleep

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disordered breathing [4, 29]. In SMA type 2 FVC%P fell below 60% at a median age of 12.8 years and at the age of 13.4 years 25% SMA type 2 had FVC%P<40%. In our cohort, 39% SMA type 2 had started NIV at a median FVC%P of 44 % (28.5-57) at a median age of 5 (1.8-16.6) years. Interestingly, despite over 75% of SMA type 3 in our cohort maintaining a FVC%P>60% at 18 years, 9% of SMA type 3 patients required NIV at a median age of 15.1 (13.8-16.3) years. NIV was started more frequently to treat acute respiratory decompensation during chest infections. Given the relatively incomplete information on the main reason to start NIV, it was not possible to retrospectively assess whether, for example, chest infections occurred more frequently in patients not using cough assistance. Similarly, details on the frequency NIV support was used as needed during acute decompensations only as opposed to chronic use were not available. Our results confirm that a reduced FVC%P (~40%) and an increased number of respiratory infections is strongly associated with NIV requirement as recently reported in a cross-sectional study of paediatric SMA type 1, 2 and 3 [30]. The revised standard-of-care guidelines promote the early adoption of cough assist devices and a pro-active early respiratory workup to identify the need for NIV establishment. Our study did not contain information on whether the adoption of such pulmonary measures reduced the number of respiratory infections, an important consideration for future studies. We acknowledge, however, that the more pro-active use of cough assistance and NIV in the recent years, could act as confounding factor in the analysis of long-term respiratory function. Although functional motor data were limited because some of the tools used, such as the RULM, only became available recently, our data suggest that FVC%P positively correlates with HFMS and RULM. In an attempt of translate this into clinically meaningful thresholds, we found that at time of starting NIV, 31 out of 39 SMA type 2 had HFMS score ≤ 10 and 24 had HFMS ≤ 6.

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Scoliosis was a common feature of both SMA type 2 (84%) and non-ambulant SMA type 3 (80%) in keeping with previous data [31]. Median (IQR) age at surgery was 11 (8-13.3) years in SMA type 2 and 11.7 (10.8-15.9) years in SMA type 3. We evaluated whether the surgical correction of scoliosis could influence the respiratory progression. A few studies have cross-sectionally evaluated the pulmonary function pre- and post- scoliosis with controversial results [32-34]. We have compared the annual decline of FVC%P and absolute FVC. Their trajectories post-surgery were steeper than pre-surgery, even though the difference was not significant (p=0.22). Possibly, the steep decline of pulmonary function occurring in the year post surgery contributes to this negative results[35]; in addition, different surgical techniques were used in this group of patients, ranging from different types of growing rods, to full spinal fusion, contributing to the heterogeneity of the outcome. As respiratory and motor function correlate, we confirm the data of a recent report on 17 SMA type 2 and 3 patients suggesting that motor function (HFMSE) significantly and permanently worsened after surgery [36].

Patients' nutritional status expressed as BMI (kg/m^2) and respiratory function expressed as FVC (L) did correlate in both SMA type 2 and 3. This finding suggests that the regular body growth and a wider ribcage allow the expansion of the lungs and are positively associated with higher lung volumes. In patients with SMA ~~patients~~ an adequate nutritional intake should be monitored and promoted[37].

To the best of our knowledge, this is the largest observational study on long-term respiratory function in SMA type 2 and non-ambulant type 3 reported to date. It provides novel data on respiratory function measures in addition to FVC%P along with data about the correlation with motor function and the requirement for NIV. The breakdown of severity within SMA type 3 (i.e. type 3 A, 3 B) was beyond the purposes of the current work as we decided to exclude ambulant SMA type 3. The identification of thresholds of pulmonary function

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associated to clinically meaningful events such as sleep disordered breathing, use of NIV or recurrent respiratory infections was limited by the retrospective nature of our study and missing data. While we acknowledge that the retrospective design was the main limitation of our study, our registry is systematically promoted in each of the 3 participating networks that have been contributing to real world data collection since 2010.

This data should be confirmed in larger prospective studies which may allow to establish more precisely thresholds of motor function scores associated with different levels of respiratory function. The upcoming set-up of a unique customised platform within iSMAc [20] will allow a more robust data collection for prospective longitudinal study of respiratory function in intermediate SMA types and the impact of new treatments.

CONCLUSIONS

Our work adds novel long-term respiratory data from a large international cohort (n=437) of patients SMA type 2 and non-ambulant type 3 followed over eight years. Similar to what has been described in motor function [26, 27], the decline of FVC%P. in SMA type 2 and type 3 followed different trajectories across age ranges. FVC%P. annual decline was steeper from 5 to 13 years (~4% in SMA type 2 and ~3% in SMA type 3) followed by a slower progression after age 13 years (1% in SMA type 2, 0.9% in type 3). However, in SMA type 3 the decline was more obvious after age 8 years (rather than age 5 years as SMA type 2). Although non-sitters generally had a more severe phenotype, there was no significant difference in their rate of decline compared to sitters. In both SMA types 2 and 3, the motor (HFMS and RULM) and respiratory functions correlated positively. The data provided by this study will be important when interpreting the long-term real world respiratory outcome of patients who are now being treated with disease modifying therapies.

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Acknowledgements:

The SMA REACH UK working group: UK - Great Ormond Street Hospital; University College London; Birmingham Heartlands Hospital; Leeds Children Hospital; Evelina Children's Hospital, London; The Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry; Sheffield Teaching Hospital.

The support of the SMA Trust and of MDUK to the activities of the Dubowitz Neuromuscular Centre is gratefully acknowledged.

The National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London.

The support of Biogen to the iSMAC registry is gratefully acknowledged. Biogen had no role in the study design or interpretation

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TABLES

Table 1. Baseline characteristics of the study population

N=437	**SMA 2 (N=348)**	**SMA 3 (N=89)**	**p**
Gender (Male, %)	163 (47%)	46 (52%)	0.99
Mean age 1st visit (±sd), years	6.9 (±4.4)	11.1 (±4.0)	< 0.001
Mean age last visit (±sd), years	9.2 (±4.9)	12.4 (±4.1)	< 0.001
Median visits (min, max)	3 (1, 21)	2 (1, 11)	< 0.01
Median follow-up (min, max), years	1.4 (0, 12.5)	0.5 (0, 6.7)	
SMA 2 sitters at 1st visit	278		
Mean age 1st visit (±sd), years	7.0 (±4.4)		
Median follow-up (min, max), years	1.7 (0, 12.5)		
SMA 2 non-sitters at 1st visit	32		
Mean age 1st visit (±sd), years	7.6 (±5.0)		
Median follow-up (min, max), years	2.0 (0, 11.3)		
SMN 2 copies			
- 1	1	0	
- 2	21	0	
- 3	148	28	
- 4	1	12	
Scoliosis (N, %)	180/215 (84%)	39/49 (80%)	
Scoliosis surgery (N, %)	70/145 (48%)	11/35 (31%)	
- Growing rods	25	0	
- Spinal Fusion	31	10	
- Magnetic growing rods	1	0	
- VEPTR$^{\infty}$	13	1	
BMI (kg/m^2) at first visit (N)	n=147	n=41	
Median BMI (IQR)	15.8 (IQR 14.0-19.1)	18.1 (IQR 16.6-22.0)	
Swallowing impairment (N, %)	85/280 (30%)	1/69 (1%)	
Naso-gastric tube	9/278 (3%)	0/69 (0%)	

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Gastrostomy tube (N, %)	62/278 (22%)	0/69 (0%)

[∞] Vertical Expandable Prosthetic Titanium Rod

Table 2. Non-invasive (NIV) and invasive (tracheostomy) ventilation requirement and use of cough assistance in study population

N=437	**SMA 2 (N=348)**	**Non-ambulant SMA 3 (N= 89)**
NIV (N, %)	136/298 (46%)	8/71 (11%)
Reason for NIV start		
- Recurrent respiratory infections	15	1
- Hypoventilation	10	1
- Sleep apnoea	7	0
FVC%P. at start of NIV, Median (IQR)	44 % (28.5-57)	N/A
NIV use		
- Overnight only	57	7
- Overnight + daytime	9	0
- As needed	11	0
Cough assistance (N, %)	78/152 (51%)	6/37 (16%)
Tracheostomy (N, %)	4/306 ~~350~~ (1%)	0/83~~90~~ (0%)

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FIGURES

Figure 1. CONSORT flowchart of patients included in the final analysis according to inclusion and exclusion criteria

Data were available for 673 patients in the whole cohort. Were excluded patients older than 18 years of age, patients enrolled in interventional clinical trial and SMA type 3 ambulant at the first recorded visit. The breakdown of patients (n=437) included in the analysis refers to first visit.

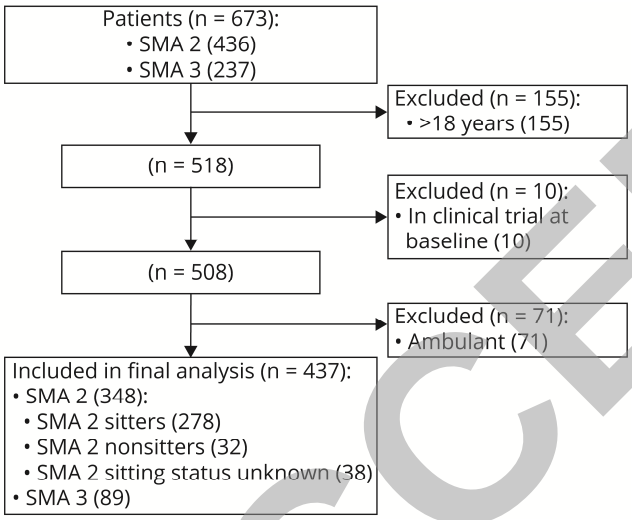

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Figure 2. Rate of decline of FVC% predicted in SMA type 2, SMA type 2 sitters and SMA type 3

a. SMA type 2 (632 observations from 200 patients). The slope of FVC%P. age 5 to 13 years was -4.2, 95%CI (-4.8, -3.7), p < 0.01 and post age 13 years was -1.0, 95%CI (-2.1, 0.2), p=0.1. The two slopes were significantly different (p < 0.001).

b. SMA type 2 sitters (565 observation from 165 patients). The slope of FVC%P. age 5 to 13 years was -4.1 % per year, 95%CI (-4.7, -3.5), p< 0.001 and post age 13 years was -1.3, 95%CI (-2.5, -0.04), p = 0.04. The two slopes were significantly different (p < 0.001).

c. SMA type 3 non-ambulant (151 observations from 59 patients). FVC%P. mildly improved from age 5 to 8 years by +11.8, 95%CI (4.5, 19.1), p = 0.002 before declining from age 8 to 13 years by 6.3 95%CI (-8.7, -3.8), p < 0.001. Post age 13 years FVC%P. slope declined by 0.9, 95%CI (-3.1, 1.4), p = 0.46. The slopes 5 to 8 years and 8 to 13 years were significantly different (p < 0.001 and p < 0.01).

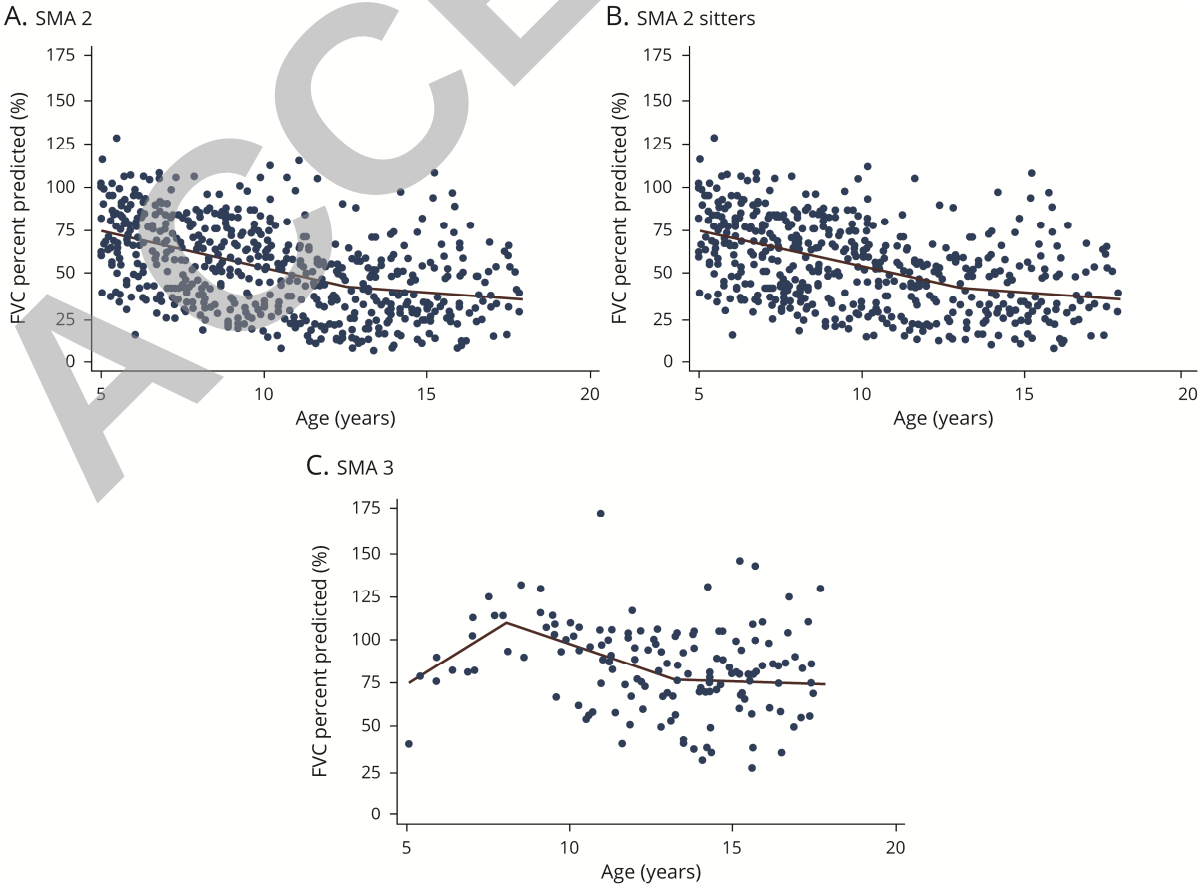

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Figure 3. Age at FVC% predicted fell below 60%, 40% and 20% in SMA type 2 and 3

a. At the age of 9.5 years 25% SMA type 2 had FVC%P below 60%. Median (50%) age at FVC%P<60% was 12.8 years for SMA type 2. Less than 25% patients SMA type 3 had FVC%P below 60% ($p<0.001$).
b. At the age of 13.4 years 25% SMA type 2 and less than 20% patients SMA type 3 had FVC%P below 40% pred. ($p < 0.01$).
c. Less than 25% SMA type 2 and none of the SMA type 3 had FVC%P below 20%.

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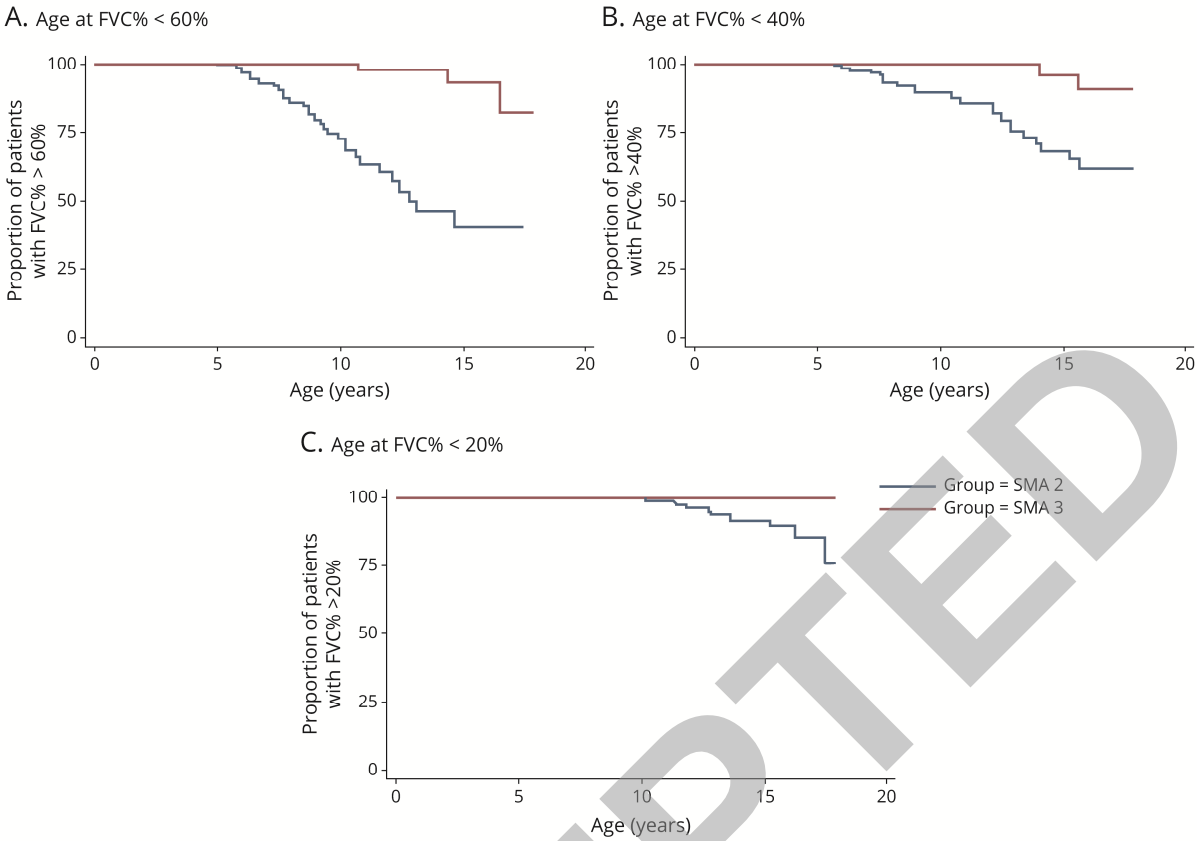

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Figure 4. Slope of FVC% predicted before and after spinal surgery in SMA type 2 and 3

a. Overall population. FVC%P declined yearly by 2.7% before scoliosis surgery and declined by 3.6% afterwards (p=0.22).

b. SMA 2 non-sitters. FVC%P increased by 2.4% per year before scoliosis surgery and declined by 5.2% afterwards (p=0.19).

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c. SMA 2 sitters. FVC%P declined yearly by 2.8% per year before scoliosis surgery and declined by 3.4% afterwards (p=0.49).

d. SMA 3 non-ambulant. FVC%P declined by 1.3% per year before scoliosis surgery and declined by 4.2% afterwards (p=0.48).

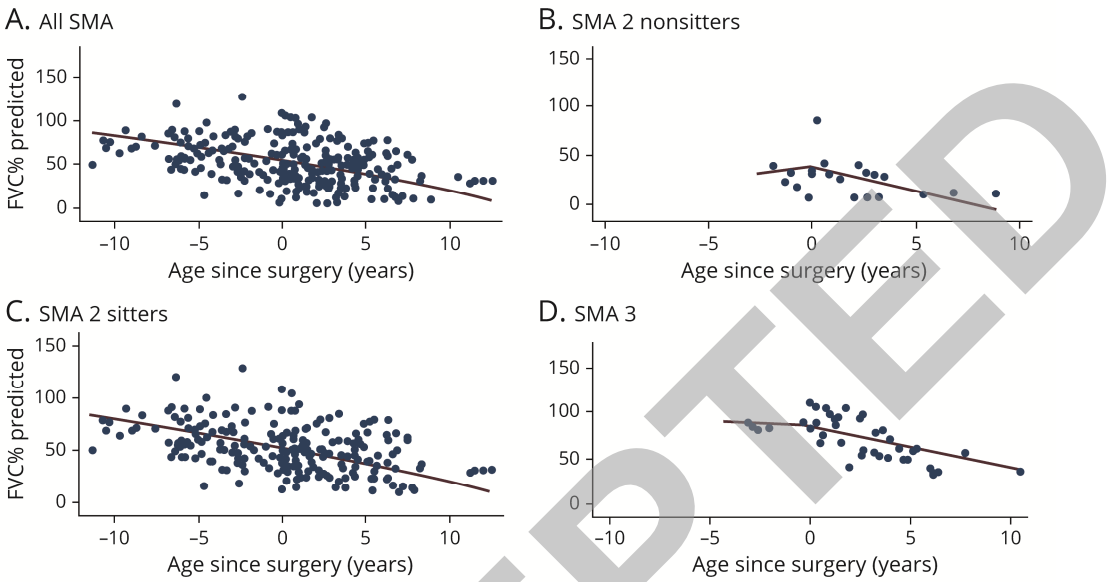

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Figure 5. Correlation between respiratory and motor function in SMA type 2 and type 3 at first available visit.

a. Correlation between FVC%P. and Hammersmith functional motor scale (HFMS) in SMA type 2, r=0.67 p<0.001) and SMA type 3 non-ambulant (r = 0.68, p < 0.001)

b. Correlation between FVC%P. and Revised Upper Limb Module (RULM) in SMA type 2 (r=0.61 p<0.001) and SMA type 3 non-ambulant (r = 0.61, p < 0.01).

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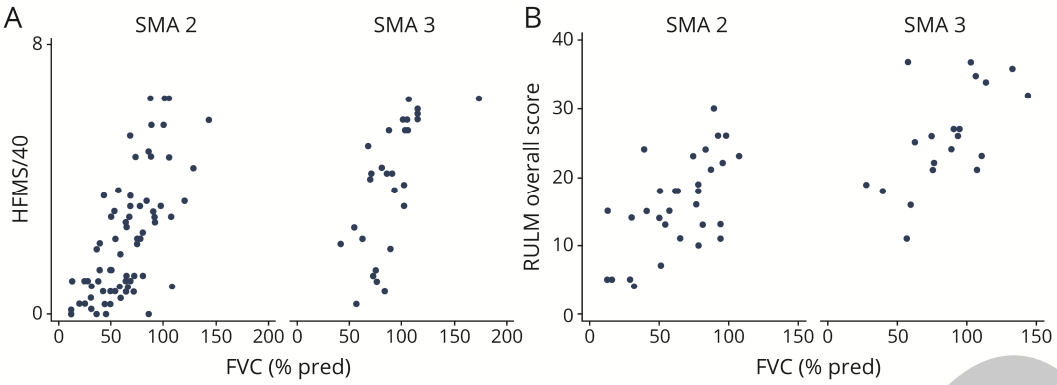

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APPENDIX 1: Authors

Name	Location	Contribution
Federica Trucco, MD	Dubowitz Neuromuscular Centre, UCL GOS Institute of Child Health London DINOGMI, University of Genoa,	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content

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Mariacristina Scoto MD, PhD	Dubowitz Neuromuscular Centre, UCL GOS Institute of Child Health, London	Interpreted the data; revised the manuscript for intellectual content
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Marika Pane MD PhD	Paediatric Neurology and Centro Clinico Nemo, Catholic	Revised the manuscript for intellectual content

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Min Ong MD	Sheffield Children's Hospital, UK	Revised the manuscript for intellectual content
Chiara Marini-Bettolo MD PhD	John Walton Muscular Dystrophy Research Centre, Newcastle	Major role in the acquisition of data

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Basil T. Darras MD	Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA	Revised the manuscript for intellectual content
John Day MD, PhD	Stanford University, Medical Centre, Palo Alto, CA	Revised the manuscript for intellectual content
Elizabeth A Kichula, MD	Divisions of Pediatric Neurology The Children's Hospital of Philadelphia, Philadelphia, PA	Revised the manuscript for intellectual content
Oscar H. Mayer MD	Divisions of Pediatric Pulmonology, Children's Hospital of Philadelphia, and The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA	Revised the manuscript for intellectual content
Aledie Navas Nazario, MD	Division of Pulmonary Medicine, Department of Pediatrics, Nemours Children's Hospital, Orlando, Florida, USA	Revised the manuscript for intellectual content
Richard S. Finkel MD	Division of Neurology, Department of Pediatrics, Nemours Children's Hospital, Orlando, Florida, USA	Interpreted the data; revised the manuscript for intellectual content
Eugenio Mercuri MD, PhD	Paediatric Neurology and Centro Clinico Nemo, Catholic University and Policlinico Gemelli, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Rome, Italy	Interpreted the data; revised the manuscript for intellectual content
Francesco Muntoni, MD	Dubowitz Neuromuscular Centre, UCL, GOS Institute of Child Health, London NIHR Biomedical Research	Design and conceptualized study; revised the manuscript for intellectual content

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	Centre, London	

APPENDIX 2 – Co-investigators

Name	Location	Role	Contribution
Roberto De Sanctis PT	Paediatric Neurology and Centro Clinico Nemo, Catholic University and Policlinico Gemelli, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Rome, Italy	Centre part of Italian SMA Network	Data collection
Alice Pirola PT	Paediatric Neurology and Centro Clinico Nemo, Milan, Italy	Centre part of Italian SMA Network	Data collection
Antonella Longo MD	Unit of Neuromuscular and Neurodegenerative Disorders, Post-Graduate Bambino Gesù Children's Research Hospital, IRCCS, Rome, Italy.	Centre part of Italian SMA Network	Data collection
Maria Sframeli MD PhD	Nemo Sud Clinical Centre, Messina, Italy	Centre part of Italian SMA Network	Data collection
Marina Pedemonte MD PhD	IRCCS Istituto Giannina Gaslini, Genova, Italy	Centre part of Italian SMA Network	Data collection
Lindsey Pallant PT	Leeds Children Hospital	Centre part of UK SMA-REACH Network	Data collection
Elizabeth Wraige MD	Evelina Children's Hospital, London	Centre part of UK SMA-REACH Network	Data collection
Sarah Turner PT	The Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry;	Centre part of UK SMA-REACH Network	Data collection
Kay White PT	Sheffield Children's Hospital, UK	Centre part of UK SMA-REACH Network	Data collection

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Robert Muni-Lofra PT	John Walton Muscular Dystrophy Research Centre, Newcastle University, UK	Centre part of UK SMA-REACH Network	Data collection
Allan M Glanzman PT	Division of Physical Therapy, Children's Hospital of Philadelphia, Philadelphia, PA	Centre part of US PNCR Network	Data collection
Matthew Civitello, PT	Nemours Children's Hospital, Orlando, FL	Centre part of US PNCR Network	Data collection
Angela Berardinelli MD PhD	C.Mondino Neurological Institute	External partner to Italian SMA network	Data collection
Giovanni Baranello MD PhD	C. Besta Neurological Institute, Milano	External partner to Italian SMA network	Data collection
Stefan Spinty MD	Alder Hey Children's Hospital, Liverpool	External partner to UK SMA network	Data collection
Anirban Majumbdar MD	Bristol, Royal Hospital for Children	External partner to UK SMA network	Data collection
Imelda Huges MD	Royal Manchester Children's Hospital	External partner to UK SMA network	Data collection
Deepa Krishnakumar MD	Child Development Centre Addenbrooke's Hospital Cambridge, UK	External partner to UK SMA network	Data collection
Gabriel Chow MD	Nottingham University Hospitals	External partner to UK SMA network	Data collection
Neil Thomas MD	University Hospital Southampton	External partner to UK SMA network	Data collection
Sithara Ramdas MD	Oxford Children's Hospital	External partner to UK SMA network	Data collection
Salma Samsuddin	Dubowitz Neuromuscular Centre, UCL, GOS Institute of Child Health, London	Data coordinator for SMA REACH	Data coordinator for SMA REACH
Julia Balashkina	Nemours Children's Hospital, Orlando, Florida	Data coordinator for PNCR	Data coordinator for PNCR
Bill Martens	University of Rochester, Rochester, New York	Data coordinator for PNCR	Data coordinator for PNCR

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Neurology published online October 16, 2020
DOI 10.1212/WNL.0000000000011051

This information is current as of October 16, 2020

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