Predictive energy equations for spinal muscular atrophy type I children

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ABSTRACT

Background: Knowledge on resting energy expenditure (REE) in spinal muscular atrophy type I (SMAI) is still limited. The lack of a population-specific REE equation has led to poor nutritional support and impairment of nutritional status.

Objective: To identify the best predictors of measured REE (mREE) among simple bedside parameters, to include these predictors in population-specific equations, and to compare such models with the common predictive equations.

Methods: Demographic, clinical, anthropometric, and treatment variables were examined as potential predictors of mREE by indirect calorimetry (IC) in 122 SMAI children consecutively enrolled in an ongoing longitudinal observational study. Parameters predicting REE were identified, and prespecified linear regression models adjusted for nusinersen treatment (discrete: 0 = no; 1 = yes) were used to develop predictive equations, separately in spontaneously breathing and mechanically ventilated patients.

Results: In naïve patients, the median (25th, 75th percentile) mREE was 480 (412, 575) compared with 394 (281, 554) kcal/d in spontaneously breathing and mechanically ventilated patients, respectively ($P = 0.009$). In nusinersen-treated patients, the median (25th, 75th percentile) mREE was 609 (592, 702) compared with 639 (479, 723) kcal/d in spontaneously breathing and mechanically ventilated patients, respectively ($P = 0.949$). Both in spontaneously breathing and mechanically ventilated patients, the best prediction of REE was obtained from 3 models, all using as predictors: 1 body size related measurement and nusinersen treatment status. Nusinersen treatment was correlated with higher REE both in spontaneously breathing and mechanically ventilated patients. The population-specific equations showed a lower interindividual variability of the bias than the other equation tested, however, they showed a high root mean squared error.

Conclusions: We demonstrated that ventilatory status, nusinersen treatment, demographic, and anthropometric characteristics determine energy requirements in SMAI. Our SMAI-specific equations include variables available in clinical practice and were generally more accurate than previously published equations. At the individual level, however, IC is strongly recommended for assessing energy requirements. Further research is needed to externally validate these predictive equations. *Am J Clin Nutr* 2020;00:1–14.

Keywords: spinal muscular atrophy type I, resting energy expenditure, predictive equations, nutritional status, nusinersen

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Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Data described in the article, code book, and analytic code will be made available upon request pending approval.

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Abbreviations used: BW, body weight; FFM, fat-free mass; FM, fat mass; IC, indirect calorimetry; IVT, invasive ventilation-tracheostomy; mREE, measured resting energy expenditure; NIV, noninvasive mechanical ventilation; pREE, predictive resting energy expenditure; R^2_{adj}, adjusted R-squared; REE, resting energy expenditure; RMSE, root mean squared error; SDS, Z-score; SL, supine length; SMAI, spinal muscular atrophy type I; SMAII, spinal muscular atrophy type II; SMAGNG, General Nutrition Guidelines for Spinal Muscular Atrophy; SMN, survival motor neuron; TL, tibia length; VCO_2, carbon dioxide production; VO_2, oxygen consumption.

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Introduction

Spinal muscular atrophy (SMA) is a rare autosomal recessive neurodegenerative disease characterized by the degeneration of spinal cord motor neurons, atrophy of skeletal muscles, and generalized weakness (1). SMA is caused by deletion, conversion, or mutation of the survival motor neuron 1 (SMN1) gene (2). SMA type I (SMAI), together with the prenatal type 0, is the most severe phenotype of the 5 forms of SMA. Children with SMAI show hypotonia and muscle weakness at birth or within the first months of life, never acquire the independent sitting position, and show progressive difficulty in breathing and swallowing (3), requiring early mechanical ventilation and artificial feeding (4). Both over- and undernutrition are reported in SMA (5, 6), suggesting a multifactorial impairment that can produce very different nutritional phenotypes. Until recently, multidisciplinary supportive care was the only option to manage the respiratory, nutritional, and orthopedic comorbidities, but between 2016 and 2017 nusinersen treatment was approved by the FDA and the European Medicines Agency. Nusinersen is an antisense oligonucleotide designed to modulate pre-mRNA splicing of the SMN2 gene, for treatment of all SMA types. Although nusinersen is not a definitive cure, clinical trials have demonstrated significant improvements in survival and motor function, particularly in patients treated promptly (7, 8).

There is a significant gap in knowledge regarding energy requirement estimations in SMA; therefore, it is not usually possible to prescribe the optimal energy intake for SMA patients according to their specific energy requirements. The dietary clinical management in SMAI patients is also hampered by their abnormalities in body composition. As previously demonstrated (9, 10), SMAI patients can appear severely underweight compared with healthy children's growth charts, due to the disproportion in fat mass (FM) and fat-free mass (FFM) (10). This imbalance leads to the misinterpretation of nutritional status and the imprecise determination of resting energy expenditure (REE).

The gold standard method for the determination of REE is indirect calorimetry (IC) (11); however, IC devices are rarely available in clinics, and nutritional care professionals often have to rely on predictive equations to estimate REE. WHO (12) and Schofield (13) equations have been studied to a limited extent in treatment-naïve SMA patients, all showing overestimation of energy requirements compared with REE obtained by IC (4, 14, 15). The International Standards of Care for SMA recommended 9–11 kcal/height (cm) regardless of age, sex, and clinical status (16), without external validation studies confirming this energy recommendation. Essentially, there are currently no predictive equations specifically developed for the estimation of REE in SMAI patients.

The primary aim of this study was to develop a predictive energy equation for SMAI children. We therefore investigated the most relevant predictors of measured resting energy expenditure (mREE) among various demographic, anthropometric, and clinical variables, including nusinersen treatment and type of feeding and breathing. The secondary aim was to establish the overall precision of our predictive energy equation in comparison with other commonly used equations.

Methods

Sample and study design

Since April 2015, a longitudinal observational study in SMA children has been conducted at the International Center for the Assessment of Nutritional Status (ICANS), University of Milan. On 18 January, 2019, 158 patients with a clinical and genetic diagnosis of SMAI were consecutively enrolled; patients were included in the present study according to the following inclusion criteria: Caucasian children with a body weight of ≥5 kg, age lower than 10 y, absence of acute infections, no inclusion in ongoing experimental pharmacological trials, and clinical management according to the guidelines set out in the Consensus Statement for Standard of Care in SMA (17–19). Patients under nusinersen treatment had received ≥4 loading doses. Patients with hemodynamic or respiratory instability or ventilated with an inspiratory oxygen fraction (FIO_2) >0.6 or positive end-expiratory pressure (PEEP) >10 cm H_2O were also excluded in order to avoid measurement errors due to gas leaks and hypercatabolic status.

The participant flow chart is available as online supporting material (**Supplementary Figure 1**).

Patients

Patients were recruited from 5 clinical referral centers for SMA in Italy (Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan; SAPRE UONPIA, Fondazione IRCSS Cà Granda, Policlinico di Milano, Milan; Department of Neurosciences, Neuromuscular, and Neurodegenerative Disorders Unit, Laboratory of Molecular Medicine, Bambino Gesu' Children's Research Hospital, IRCCS, Rome; Italian Department of Neurosciences and Rehabilitation, Institute "G. Gaslini," Genoa; and Department of Women's and Children's Health, University of Padua, Padua). On the same morning, IC, anthropometric measurements, and clinical examination were performed for each patient at the ICANS center. The study protocol received Institutional Review Board approvals (Ethics Committee of the University of Milan n.7/16 and Carlo Besta Neurological Institute Foundation n.37/2016) and completely complied with the Helsinki Declaration. The parents, on behalf of their children, gave their informed and written consent to the study.

Study variables

The dependent variable was the measured REE (mREE, kcal/d) by IC. The independent variables were categorized into 3 groups: demographic, anthropometric, and clinical. The demographic variables included age at study date and sex. The anthropometric variables included body weight (BW, kg), supine length (SL, m), tibia length (TL, cm), and BMI (BW/SL^2, kg/m^2). The clinical variables included type of breathing: spontaneous compared with mechanical ventilation (noninvasive mechanical ventilation [NIV] or invasive ventilation-tracheostomy [IVT]), type of feeding (oral compared with nasogastric tube or gastrostomy), and the presence of nusinersen treatment (yes: treated, ≥4 infusions; no: untreated). The clinical variables were

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collected by a pediatric neurologist (GB) 1 d before nutritional and REE evaluation.

REE was also estimated using predictive equations (pREE). The clinical data were prospectively collected and reported in electronic medical records.

Measured REE

An open-circuit ventilated-hood system IC (VMAX Sensor Medics 29) designed to measure VO_2 (oxygen consumption) and VCO_2 (carbon dioxide production) from ventilation gases in both spontaneously breathing and ventilated patients was used to measure mREE. IC was calibrated daily before starting the tests, using a 2-point calibration method based on 2 separate mixtures of known gas content. The flow rate was calibrated with a 3-liter syringe, according to the IC manufacturer's instructions.

Each measurement was done by 2 trained dietitians early or late morning (between 09:00 and 13:00) after a 6-h fast for patients under 1-y old, after a 12-h fast for patients older than 1 y, or after stopping continuous enteral feeding in tube-fed children for 4 h to eliminate nutrient thermogenesis. Children laid awake completely at rest supine on a bed in a thermally neutral environment (24°C) and were destressed by infant music or video cartoons.

In spontaneously and NIV-supported breathing patients, gas exchange was measured by a transparent ventilated canopy. To avoid gas leakages, the subject's head was carefully wrapped with a plastic sleeve. Following the protocol validated by Siirala et al. (20) in NIV-supported breathing patients, the expiration valve of the ventilation mask was placed near the canopy's aperture from which the mixed gases were suctioned into the IC. In addition, the plastic sleeve of the canopy was tucked carefully under the pillow and wrapped around the inspiration tubing and along the body of the child to minimize any leakage into the measurement circuit.

In IVT patients, expired gas was collected from the expiratory outlet of the ventilator by flexible tubing connected to the IC.

A 15-min resting period was maintained before starting the measurements in order to balance the mixing canopy of the instrument with alveolar gas from the patient. Any breath values with a >10% difference, reflecting an airway leak, were not included in the calculation. Before the study, each patient was suctioned to clear secretions from the trachea. This procedure was approved by the IC manufacturer and had been previously applied in REE assessment in mechanically ventilated patients in several studies (21, 22).

Respiratory gas samples were taken for ≥20 min and the data collected during the first 5 min were discarded, as recommended by Isbell et al. (23). This allowed the subjects to acclimatize themselves to the canopy and instrument noise. An air flow value of 12 L/min was maintained for a weight range of 5–10 kg and of 15 L/min when the child's weight was over 10 kg.

A 5-min steady state was defined as the first 5 consecutive stable 1-min readings with a coefficient of variation <5% for VCO_2 and VO_2 (21, 24).

To calculate mREE, oxygen consumption and carbon dioxide production were substituted into the modified Weir equation (25):

$$\text{mREE (kcal/day)} = [3.941\ VO_2\ (\text{mL/min}) + 1.106\ VCO_2\ (\text{mL/min})] \times 1.44 \quad (1)$$

Patients ventilated (NIV or IVT) for <16 h a day performed consecutive REE measurement both with and without the NIV support. This approach enabled us to measure the effect of ventilation support on REE.

The association between demographic, clinical, and anthropometric variables with mREE was evaluated to test whether these factors had a significant influence on energy expenditure.

Predicted REE

The mREE was then compared with the following published REE prediction equations: *1*) WHO (12), *2*) Schofield (13), *3*) General Guidelines for SMA Children (16), and *4*) Culley and Middleton (26). The algorithm of each equation for the prediction of REE is reported in **Table 1**.

Anthropometric variables

All anthropometric measurements were collected by 2 well-trained dietitians and had been standardized by applying conventional criteria (27) and recognized measuring procedures, as described previously (28). Specifically, BW was measured using a wheelchair scale to the nearest 100 g: the child and wheelchair were weighed together, then the wheelchair was weighed alone, and the difference in the 2 measurements gave the weight of the subject. Infants with a BW of 5–7 kg were weighed in the arms of a family member or observer, after which only the adult was weighed, and the difference of the weights was obtained.

SL was measured in segments using a straight edge (Seca 210) from the top of the head to the greater trochanter of the hip, from the hip to the femoral epicondyle of the knee, and from the knee to the distal point of the calcaneus. To identify the top of the head, a vertical headboard was used, and the tape was positioned on a line parallel to the sagittal plane, passing through the greater trochanter of the hip (9).

BMI was calculated by the following formula: BW (kg)/SL^2 (m^2). Sex-specific weight, length, and BMI-Z-scores were derived using the 2006 WHO Growth Standards (29). According to WHO Z-score (SDS) cut-off points, BMI-for-age values below –1.644 (5th percentile) were considered underweight, between –1.644 and +1.036 normal weight, between +1.036 and +1.644 overweight, and above +1.644 obese.

TL, approximated to the nearest 0.5 cm, was taken along the child's left side by a nonelastic tape and with the child lying supine on the exam table, as with the SL measurement. TL was measured from the proximal end of the medial border of the tibia to the distal tip of the medial malleolus (28).

Clinical variables

A medical history was collected to define the presence, type, and duration of ventilatory support [spontaneous compared with mechanical ventilation (NIV or IVT)] and feeding (oral compared with nasogastric tube or gastrostomy). In patients

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TABLE 1 Predictive equations for calculating resting energy expenditure (kcal/d)

	Girls	Boys
WHO (12)		
0–3 y	REE = 60.9 × BW – 54	REE = 61 × BW – 51
3–10 y	REE = 22.7 × BW + 495	REE = 22.4 × BW + 499
Schofield (BW) (13)		
0–3 y	REE = 59.48 × BW – 30.33	REE = 58.29 × BW – 31.05
3–10 y	REE = 22.7 × BW + 505	REE = 20.3 × BW + 486
Schofield (BW&SL) (13)		
0–3 y	REE = 0.167 × BW + 15.174 × SL – 617.6	REE = 16.25 × BW + 10.232 × SL – 413.5
3–10 y	REE = 19.6 × BW + 130.3 × SL + 414.9	REE = 16.97 × BW + 161.8 × SL + 371.2
General Guidelines for SMA Children (16, 18)		
All ages	REE = 9–11 kcal/ SL	REE = 9–11 kcal/ SL
Culley & Middleton[1] (26)		
All ages	REE = 11.1 kcal/ SL	REE = 11.1 kcal/ SL

[1]Nonambulatory patients.
BW, body weight (kg); REE, resting energy expenditure; SL, supine length (cm); SMA, spinal muscular atrophy.

treated with nusinersen, the number of intrathecal infusions was also collected.

Statistical analysis

Most continuous variables were not Gaussian distributed, and all are reported as median (25th, 75th percentile). Discrete variables are reported as the number and proportion of subjects with the characteristic of interest.

We evaluated the contribution of age, BW, SL, and TL to REE, separately in spontaneously breathing and mechanically ventilated patients, using linear regression models adjusted for nusinersen treatment (discrete: 0 = no; 1 = yes). Standard diagnostic plots were used to evaluate model fit (30). Not unexpectedly, age, BW, SL, and TL were collinear, so we did not need to develop multivariable models. The adjusted coefficient of determination (R^2_{adj}) and the root mean squared error of the estimate (RMSE) were used as measures of model fit. The 95% CIs of the regression coefficients, R^2_{adj}, and RMSE were calculated using bootstrap analysis on 1000 random samples of 83 spontaneously breathing patients and 39 mechanically ventilated patients. Bootstrap analysis offers an efficient way of correcting for over optimism and is currently considered the best method for internal crossvalidations (31).

Bias was calculated as (estimated REE – mREE) and percentage bias as [(estimated REE – mREE)/mREE] ∗100 (32).

Bland–Altman plots of percentage bias [(pREE – mREE)/average] compared with average bias [(pREE + mREE)/2] were used to investigate the agreement between currently available REE predictive equations and mREE by IC.

The Wilcoxon rank sum test was used to compare mREE in subpopulations determined by ventilation and nusinersen status.

Statistical analysis was performed using Stata 15.1 (Stata Corporation).

Results

Demographic, clinical, and anthropometric variables

In total, 122 SMAI children (73 girls and 49 boys) were included in the study. The median (25th, 75th percentile) age was 13 (5, 25) mo. Thirty-four percent of the children ($n = 42$) were on mechanical ventilation (22% with NIV and 12% with IVT) and 31% were artificially fed (23% with percutaneous endoscopic gastroscopy and 8% with a nasogastric tube). In the whole sample, the median SDS of weight and BMI were –1.46 and –2.35, respectively, corresponding to the 7th and 0.4th percentiles of the WHO distribution. The median SDS of length was 0.37, corresponding to the 64th percentile of the WHO distribution.

Table 2 shows the demographic, clinical, and anthropometric variables stratified by nusinersen and ventilatory status. In both naïve and nusinersen-treated patients, we did not observe significant differences in age and age-normalized variables between spontaneously breathing and mechanically ventilated patients.

Table 3 shows the measured and predicted values of REE as absolute values (kcal/d) and normalized for kg of BW (kcal · d^{-1} · kg^{-1}) in naïve and nusinersen-treated patients according to ventilatory status.

In naïve patients, the median (25th, 75th percentile) mREE was 480 (412, 575) compared with 394 (281, 554) kcal/d in spontaneously breathing and mechanically ventilated patients, respectively ($P = 0.009$). The median (25th, 75th percentile) mREE was 63 (54, 71) compared with 51 (19, 61) kcal/d per kg of BW in spontaneously breathing and mechanically ventilated patients, respectively ($P < 0.001$).

By contrast, in nusinersen-treated patients, the median (25th, 75th percentile) mREE was 609 (592, 702) compared with 639 (479, 723) kcal/d in spontaneously breathing and mechanically ventilated patients, respectively ($P = 0.949$). The median (25th, 75th percentile) mREE was 66 (58, 76) compared with 67 (56, 76) kcal/d per kg of BW in spontaneously breathing and mechanically ventilated patients, respectively ($P = 0.925$).

Influence of demographic, anthropometric, and clinical variables on mREE values

To test whether age, BW, SL, TL, ventilatory status, and nusinersen treatment had a significant impact on energy expenditure, we plotted in **Figure 1** the relations between these variables and

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TABLE 2 Demographic, clinical, and anthropometric variables in spinal muscular atrophy type I children

	Naïve			Nusinersen		
	Spontaneous breathing $N = 73$	Mechanical ventilation $N = 26$	Total $N = 99$	Spontaneous breathing $N = 10$	Mechanical ventilation $N = 13$	Total $N = 23$
Demographic variables						
Age, mo	7 (5, 15)	24 (5, 46)	8 (5, 25)	19 (16, 25)	19 (16, 41)	20 (17, 28)
Sex						
Girls	44 (60.3%)	17 (65.4%)	61 (61.6%)	4 (4.0%)	8 (61.5%)	12 (52.2%)
Boys	29 (39.7%)	9 (4.6%)	38 (38.4%)	6 (6.0%)	5 (38.5%)	11 (47.8%)
Clinical variables						
Nusinersen						
Number of infusions	0 (0, 0)	0 (0, 0)	0 (0, 0)	6 (5, 8)	6 (6, 7)	6 (5, 7)
Mechanical ventilation						
Noninvasive ventilation	0 (0.0%)	12 (46.2%)	12 (12.1%)	0 (0.0%)	12 (92.3%)	12 (52.2%)
Tracheostomy	0 (0.0%)	14 (53.8%)	14 (14.2%)	0 (0.0%)	1 (7.7%)	1 (4.3%)
Feeding						
By mouth	63 (86.3%)	7 (27.0%)	70 (70.7%)	7 (70.0%)	7 (53.8%)	14 (60.9%)
Nasogastric tube	10 (13.7%)	13 (50.0%)	23 (23.2%)	3 (30.0%)	2 (15.4%)	5 (21.7%)
Percutaneous endoscopic gastrostomy	0 (0.0%)	6 (23.0%)	6 (6.1%)	0 (0.0%)	4 (30.8%)	4 (17.4%)
Total artificial feeding	10 (13.7%)	19 (73.0%)	29 (29.3%)	3 (30.0%)	6 (46.2%)	9 (39.1%)
Anthropometric variables						
Weight, kg	7.2 (6.3, 8.7)	8.9 (6.5, 14.7)	7.4 (6.4, 9.5)	9.6 (8.3, 10.1)	8.8 (7.7, 9.5)	9.3 (7.8, 9.9)
Weight-for-age, SDS	− 1.12 (−2.12, −0.27)	− 1.57 (−2.72, −0.14)	− 1.26 (−2.15, −0.30)	− 1.51 (−2.64, −0.87)	− 2.07 (−2.80, −1.78)	− 2.01 (−2.79, −1.30)
Length, m	0.71 (0.66, 0.81)	0.88 (71.8, 104.3)	0.72 (0.66, 0.83)	0.83 (0.77, 0.88)	0.84 (0.81, 0.95)	0.84 (0.77, 0.91)
Length-for-age, SDS	0.55 (−0.54, 1.86)	0.37 (−0.12, 1.04)	0.53 (−0.91, 1.49)	− 1.15 (−1.85, 0.91)	− 0.08 (−1.01, 0.21)	− 0.12 (−1.71, 0.52)
Tibia length, cm	12 (11, 14)	15 (12, 20)	12 (11, 15)	14 (14, 15)	14 (13, 17)	14 (13, 17)
BMI, kg/m^2	13.7 (12.1, 15.1)	12.9 (11.9, 14.1)	13.9 (12.3, 15.4)	14.3 (13.0, 15.7)	12.3 (11.6, 13.1)	13.0 (11.8, 14.1)
BMI-for-age, SDS	− 2.27 (−3.52, −1.09)	− 2.35 (−3.45, −0.73)	− 2.23 (−3.26, −0.95)	− 1.21 (−2.95, −0.58)	− 2.82 (−3.99, −2.44)	− 2.60 (−3.38, −1.40)
BMI classes, WHO						
Underweight	47 (64.4%)	15 (57.7%)	62 (62.7%)	3 (30.0%)	12 (92.3%)	15 (65.3%)
Normal weight	24 (32.8%)	10 (38.5%)	34 (34.3%)	6 (60.0%)	0 (0.0%)	6 (26.1%)
Overweight	1 (1.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Obese	1 (1.4%)	1 (3.8%)	2 (2.0%)	1 (10.0%)	1 (7.7%)	2 (8.6%)

Data are presented as median (25th, 75th percentile) for continuous measures, and *n* (%) for categorical measures.
SDS, WHO Growth Standards Z-score.

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TABLE 3 Measured and predictive resting energy expenditure values of spinal muscular atrophy type I children

	Naïve				Nusinersen			
	Spontaneous breathing $N = 73$	Mechanical ventilation $N = 26$	P value	Total $N = 99$	Spontaneous breathing $N = 10$	Mechanical ventilation $N = 13$	P value	Total $N = 23$
Measured resting energy expenditure								
mREE, kcal/d	480 (412, 575)	394 (281, 554)	0.009	466 (384, 568)	609 (592, 702)	639 (479, 723)	0.949	622 (540, 726)
mREE, kcal/d/kg	63 (54, 71)	51 (19, 61)	<0.001	61 (51, 70)	66 (58, 76)	67 (56, 76)	0.925	67 (57, 76)
Predictive resting energy expenditure								
Schofield (BW), kcal/d	395 (339, 482)	491 (347, 821)	0.103	410 (338, 579)	535 (462, 559)	482 (422, 677)	0.519	511 (426, 597)
Schofield (BW and SL), kcal/d	445 (370, 583)	686 (424, 828)	0.011	466 (376, 704)	617 (525, 668)	603 (559, 699)	0.535	617 (552, 689)
WHO, kcal/d	385 (333, 486)	487 (342, 828)	0.092	400 (336, 578)	533 (454, 563)	486 (419, 710)	0.478	516 (422, 597)
SMAGNG, kcal/d	639 (591, 725)	788 (646, 938)	0.006	650 (594, 787)	752 (693, 792)	761 (728, 851)	0.627	752 (693, 815)
Culley & Middleton,[1] kcal/d	788 (729, 894)	971 (796, 1157)	0.006	821 (733, 971)	927 (855, 977)	938 (898, 1049)	0.627	927 (855, 1005)
New population-specific equations								
M1, kcal/d	465 (457, 496)			465 (457, 496)	598 (591, 622)			598 (591, 622)
M2, kcal/d	469 (438, 521)			469 (438, 521)	628 (583, 644)			628 (583, 644)
M3, kcal/d	465 (431, 525)			465 (431, 525)	619 (578, 648)			619 (578, 648)
M4, kcal/d	471 (435, 520)			471 (435, 520)	618 (605, 642)			618 (605, 642)
M5, kcal/d		401 (378, 436)		401 (378, 436)		590 (586, 616)		590 (586, 616)
M6, kcal/d		391 (372, 436)		391 (372, 436)		595 (586, 600)		595 (586, 600)
M7, kcal/d		406 (370, 445)		406 (370, 445)		604 (596, 627)		604 (596, 627)
M8, kcal/d		393 (352, 459)		393 (352, 459)		579 (566, 620)		579 (566, 620)

[1]Nonambulatory patients.

Data are presented as median (25th, 75th percentile).

BW, body weight (kg); M1, linear regression model employing age and nusinersen treatment in spontaneous breathing; M2, linear regression model employing weight and nusinersen treatment in spontaneous breathing; M3, linear regression model employing supine length and nusinersen treatment in spontaneous breathing; M4, linear regression model employing tibia length and nusinersen treatment in spontaneous breathing; M5, linear regression model employing age and nusinersen treatment in mechanical ventilation; M6, linear regression model employing weight and nusinersen treatment in mechanical ventilation; M7, linear regression model employing supine length and nusinersen treatment in mechanical ventilation; M8, linear regression model employing tibia length and nusinersen treatment in mechanical ventilation; SL, supine length (cm); SMA, spinal muscular atrophy; SMAGNG, General Guidelines for SMA children.

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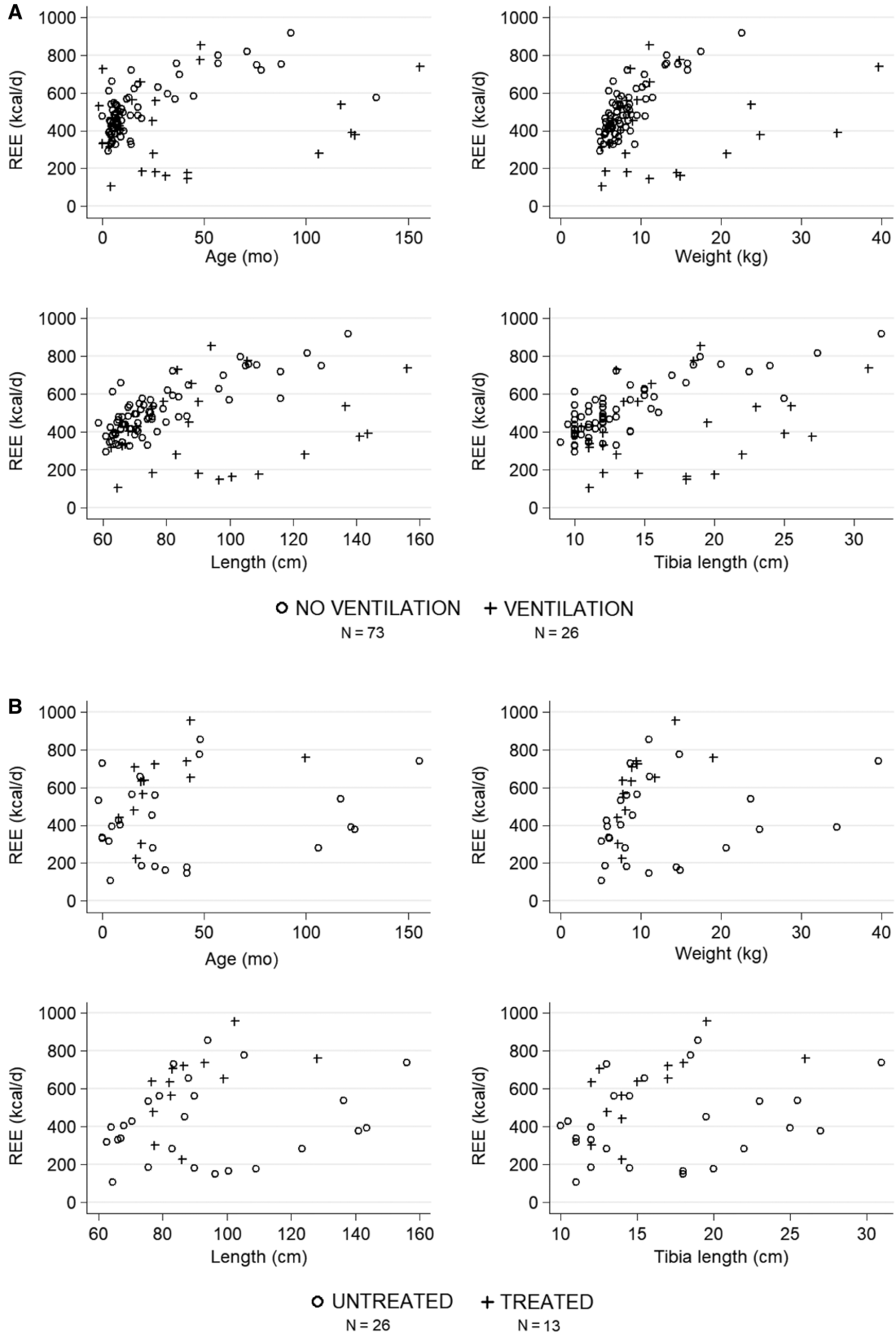


FIGURE 1 Relation between age, weight, body, and tibia length and measured resting energy expenditure (mREE) according to the ventilatory status (yes compared with no) and nusinersen treatment (yes compared with no). A) Plots the relation between age, weight, supine and tibia length, and mREE according to the ventilatory status (yes compared with no). B) Plots the relation between age, weight, supine and tibia length, and mREE according to the nusinersen treatment (yes compared with no). Children with mechanical ventilation (noninvasive mechanical ventilation or invasive ventilation-tracheostomy) have been considered ventilated. Children with ≥4 infusions have been considered treated. REE, resting energy expenditure.

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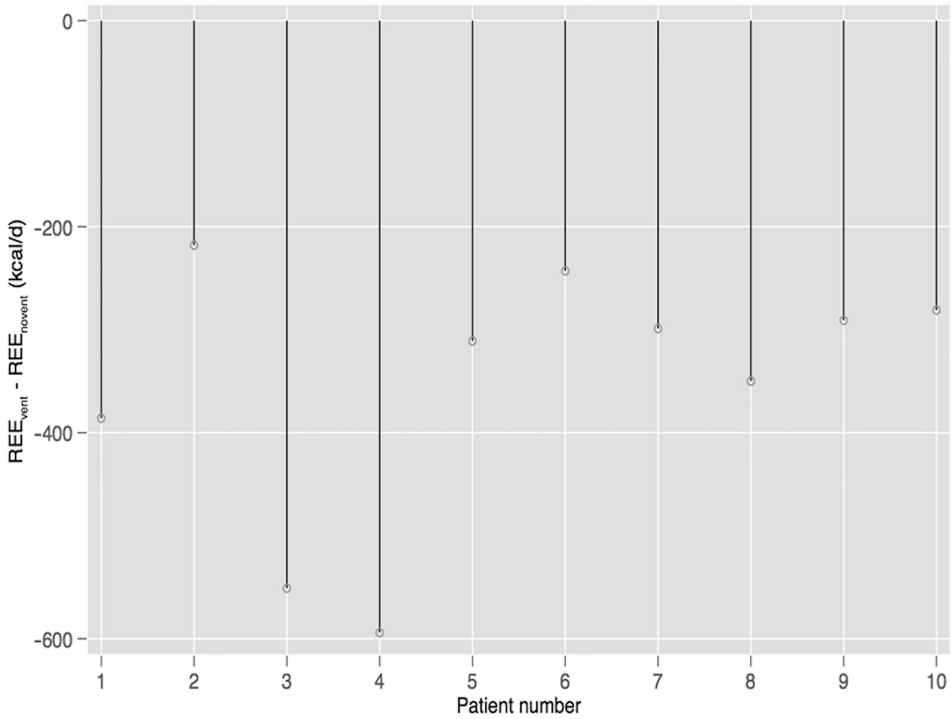


FIGURE 2 Difference between measured resting energy expenditure (kcal/d) with and without mechanical ventilation during the same session in 10 subgroup children. REE_{vent}, measured resting energy expenditure with mechanical ventilation; REE_{novent}, measured resting energy expenditure in spontaneous breathing.

mREE according to the ventilatory status (yes compared with no) and nusinersen treatment (yes compared with no).

Ventilated patients had a lower REE in relation to all independent variables considered, whereas patients treated with nusinersen had a higher REE than the untreated ones. The magnitude of ventilation status effect on mREE was also evaluated in a subsample of 10 children, by measuring REE with and without the artificial ventilator during the same session. **Figure 2** plots the difference between the estimated REE with and without the artificial ventilator during the same session for each child. The median difference between the estimated and measured REE in the 10 children was –305 kcal/d, with a within-children difference ranging from –594 to –218 kcal/d.

Development of population-specific REE equations

Table 4 gives the regression models used to develop population-specific equations for spontaneously breathing and mechanically ventilated SMAI patients.

Spontaneously breathing patients

The best prediction of REE was obtained from models M2, M3, and M4.

Model M2 employs BW and nusinersen treatment as predictors and explains 63% (bootstrapped 95% CI: 48, 79%) of REE variance with an RMSE of 86 (bootstrapped 95% CI: 72, 101) kcal/d. The corresponding equation is:

$$\text{REE (kcal/d)} = 35^{*}\text{BW (kg)} + 75^{*}\text{nusinersen treatment (1 = yes)} + 219 \quad (2)$$

Model M3 employs SL and nusinersen treatment as predictors and explains 63% (bootstrapped 95% CI: 47, 79%) of REE variance with an RMSE of 85 (bootstrapped 95% CI: 69, 101) kcal/d. The corresponding equation is:

$$\text{REE (kcal/d)} = 6^{*}\text{SL (cm)} + 75^{*}\text{nusinersen treatment (1 = yes)} + 10 \quad (3)$$

Model M4 employs TL and nusinersen treatment as predictors and explains 62% (bootstrapped 95% CI: 48, 76%) of REE variance with an RMSE of 88 (bootstrapped 95% CI: 74, 102) kcal/d. The corresponding equation is:

$$\text{REE (kcal/d)} = 24^{*}\text{TL (cm)} + 97^{*}\text{nusinersen treatment (1 = yes)} + 179 \quad (4)$$

Models M2, M3, and M4 gave identical measures of model fit due to the fact that weight and SL are virtually surrogate measures (Spearman's rho = 0.85, $P < 0.0001$).

Mechanically ventilated patients

The best prediction of REE was obtained from model M8 and, subsequently, from model M5, M6, and M7.

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TABLE 4 Population-specific regression equations for the prediction of resting energy expenditure in children with spinal muscular atrophy type I

	Spontaneous breathing				Mechanical ventilation			
	M1 Age, mo	M2 Weight, kg	M3 Length, cm	M4 Tibia length, cm	M5 Age, mo	M6 Weight, kg	M7 Length, cm	M8 Tibia length, cm
Age, mo	44*** (23, 65)				15 (−2, 32)			
Nusinersen, yes vs. no	90* (13, 168)	75* (2, 149)	75 (−5, 155)	97** (30, 165)	195** (63, 326)	205** (75, 334)	205** (73, 336)	200** (75, 324)
Weight, kg		35*** (29, 40)				8 (−1, 16)		
Supine length, cm			6*** (5, 8)				2* (0, 4)	
Tibia length, cm				24*** (19, 29)				14** (4, 23)
Intercept	438 (408, 468)	219 (170, 267)	10 (−76, 95)	179 (113, 245)	371 (279, 463)	323 (206, 439)	206 (7, 405)	190 (25, 355)
RMSE	101 (81, 120)	86 (72, 101)	85 (69, 101)	88 (74, 102)	204 (166, 241)	201 (163, 239)	203 (165, 241)	197 (159, 234)
R^2_{adj}	0.50 (0.29, 0.71)	0.63 (0.48, 0.79)	0.63 (0.47, 0.79)	0.62 (0.48, 0.76)	0.16 (0.00, 0.39)	0.18 (0.00, 0.42)	0.18 (0.00, 0.42)	0.22 (0.00, 0.45)
Observations	83	83	83	83	39	39	39	39

95% bootstrapped CIs in brackets.
*P <0.05, **P <0.01, ***P <0.001.
M1, linear regression model employing age and nusinersen treatment in spontaneous breathing; M2, linear regression model employing weight and nusinersen treatment in spontaneous breathing; M3, linear regression model employing supine length and nusinersen treatment in spontaneous breathing; M4, linear regression model employing tibia length and nusinersen treatment in spontaneous breathing; M5, linear regression model employing age and nusinersen treatment in mechanical ventilation; M6, linear regression model employing weight and nusinersen treatment in mechanical ventilation; M7, linear regression model employing supine length and nusinersen treatment in mechanical ventilation; M8, linear regression model employing tibia length and nusinersen treatment in mechanical ventilation; RMSE, root mean squared error; R^2_{adj}, adjusted R-squared; SMA, spinal muscular atrophy.

Model M8 employs TL and nusinersen treatment as predictors and explains 22% (bootstrapped 95% CI: 0, 45%) of REE variance with an RMSE of 197 (bootstrapped 95% CI: 159, 234) kcal/d. The corresponding equation is:

$$\text{REE (kcal/d)} = 14^{*}\text{TL(kg)} + 200^{*}\text{nusinersen treatment (1 = yes)} + 190 \quad (5)$$

An REE calculator (https://jscalc.io/calc/Q91zp6clkwI9PVBn) can be used as a further aid.

Accuracy of tested and new population-specific equations to predict REE

Table 5 reports the bias and percentage bias of the tested and the new population-specific equations stratified for nusinersen and ventilatory status.

In both naïve and nusinersen-treated patients, the Culley and Middleton equation for nonambulatory patients had the highest median (25th, 75th percentile) percentage bias [77% (56–112%) compared with 44% (33–68%), respectively] followed by the General Nutrition Guidelines for Spinal Muscular Atrophy (SMAGNG) equation [43% (27–72%) compared with 16% (8–37%), respectively], even when we considered ventilation status. Both equations are based on SL: their use in SMA patients leads to considerable overestimation of REE. SL contribution on REE ranged from 9 to 11.1 kcal/cm in the Culley and Middleton and SMAGNG equations (16, 26), whereas in our equations it was only 6 (95% CI: 5, 8) kcal/cm in spontaneously breathing patients and 2 (95% CI: 0, 4) kcal/cm in mechanically ventilated patients, as shown in Table 4. The Schofield BW and SL equations (13) had the lowest median percentage bias in nusinersen-treated patients (both in spontaneously breathing and mechanically ventilated patients) and in naïve spontaneously breathing patients. Overall, the WHO equation performed better than the other equations, with low median percentage bias in all subpopulation groups.

Figure 3 shows Bland and Altman plots for each REE predictive equation compared with measured REE stratified for nusinersen and ventilatory status. Differences were not normally distributed for any equation (Shapiro–Wilk normality test), so limits of agreement were not computed. These plots add to the results from Table 5, revealing a proportional bias affecting even equations with a low median bias.

Discussion

To our knowledge, this is the first study to develop population-specific predictive energy equations for naïve and nusinersen-treated SMAI children breathing spontaneously or on mechanical ventilation with a higher accuracy than the existing equations. It is common practice in healthy subjects and neurological patients (12, 13, 26) to only include demographic and anthropometric variables (e.g., sex, weight, length) in REE predictive equations. Based on the results of this study, the addition of nusinersen treatment produced a better fitting model of mREE in SMAI.

One of the most important findings is the critical role of ventilatory status on mREE in SMAI children. We investigated its contribution in 2 different ways: firstly, by plotting the relations between demographic, clinical, and anthropometric variables and mREE according to the ventilatory status (yes

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TABLE 5 Bias and percentage bias of tested and new population-specific equations

	Naïve			Nusinersen		
	Spontaneous breathing $N = 73$	Mechanical ventilation $N = 26$	Total $N = 99$	Spontaneous breathing $N = 10$	Mechanical ventilation $N = 13$	Total $N = 23$
Predicted resting energy expenditure						
Bias Schofield BW, kcal/d	− 53 (−114, 11)	33 (−47, 471)	− 40 (−103, 27)	− 98 (−177, −26)	− 62 (−152, 71)	− 95 (−172, 8)
Bias Schofield BW, %	− 12 (−24, 3)	8 (−14, 151)	− 7 (−23, 6)	− 18 (−27, −4)	− 13 (−25, 11)	− 14 (−26, −1)
Bias Schofield BW and SL, kcal/d	− 18 (−61, 54)	206 (0, 555)	13 (−57, 83)	− 38 (−81, 29)	− 33 (−104, 93)	− 38 (−87, 73)
Bias Schofield BW and SL, %	− 4 (−13, 9)	45 (0, 204)	2 (−12, 20)	− 4 (−13, 5)	− 5 (−13, 16)	− 5 (−13, 12)
Bias WHO, kcal/d	− 65 (−119, 20)	49 (−50, 572)	− 38 (−107, 42)	− 95 (−190, −23)	− 71 (−148, 75)	− 90 (−185, −8)
Bias WHO, %	− 13 (−26, 5)	8 (−11, 144)	− 8 (−25, 8)	− 17 (−28, −3)	− 15 (−25, 17)	− 15 (−27, −1)
Bias SMAGNG, kcal/d	185 (135, 241)	299 (188, 684)	198 (142, 280)	87 (63, 130)	140 (54, 277)	104 (56, 214)
Bias SMAGNG, %	37 (26, 55)	79 (45, 259)	43 (27, 72)	14 (9, 23)	24 (8, 46)	16 (8, 37)
Bias Culley & Middleton,[1] kcal/d	343 (283, 394)	477 (353, 846)	352 (302, 447)	250 (248, 305)	322 (231, 474)	276 (246, 376)
Bias Culley & Middleton,[1] %	70 (56, 91)	121 (79, 343)	77 (56, 112)	41 (34, 51)	322 (231, 474)	44 (33, 68)
New population-specific Equations						
Bias M1, kcal/d	4 (−67, 55)		4 (−67, 55)	− 9 (−46, 44)		− 9 (−46, 44)
Bias M1, %	1 (−13, 14)		1 (−13, 14)	− 1 (−7, 5)		− 2 (−8, 5)
Bias M2, kcal/d	9 (−55, 50)		9 (−55, 50)	− 13 (−68, 55)		− 13 (−68, 55)
Bias M2, %	2 (−10, 10)		2 (−10, 10)	− 2 (−9, 9)		− 2 (−8, 9)
Bias M3, kcal/d	0 (−49, 62)		0 (−49, 62)	− 28 (−66, 20)		− 28 (−66, 20)
Bias M3, %	0 (−9, 12)		0 (−9, 12)	− 5 (−11, 4)		− 5 (−11, 4)
Bias M4, kcal/d	10 (−52, 43)		10 (−52, 43)	− 4 (−60, 35)		− 4 (−60, 35)
Bias M4, %	2 (−10, 10)		2 (−10, 10)	− 1 (−9, 6)		0 (−9, 6)
Bias M5, kcal/d		8 (−162, 194)	8 (−162, 194)		− 45 (−122, 105)	− 45 (−122, 105)
Bias M5, %		3 (−27, 69)	3 (−27, 69)		− 7 (−17, 22)	− 7 (−17, 22)
Bias M6, kcal/d		4 (−142, 191)	5 (−142, 191)		− 39 (−111, 110)	− 39 (−111, 110)
Bias M6, %		2 (−25, 65)	2 (−25, 65)		− 6 (−16, 23)	− 6 (−16, 23)
Bias M7, kcal/d		1 (−152, 183)	1 (−152, 183)		− 44 (−108, 52)	− 45 (−108, 52)
Bias M7, %		1 (−26, 65)	1 (−26, 65)		− 6 (−15, 10)	− 7 (−15, 10)
Bias M8, kcal/d		2 (−120, 175)	2 (−120, 175)		− 33 (−103, 87)	− 33 (−103, 87)
Bias M8, %		1 (−21, 67)	0 (−21, 67)		− 5 (−14, 18)	− 5 (−14, 18)

Data are presented as median (25th, 75th percentile).

[1]Non-ambulatory patients.

BW: body weight (kg); M1: linear regression model employing age and nusinersen treatment in spontaneous breathing; M2, linear regression model employing weight and nusinersen treatment in spontaneous breathing; M3, linear regression model employing supine length and nusinersen treatment in spontaneous breathing; M4, linear regression model employing tibia length and nusinersen treatment in spontaneous breathing; M5, linear regression model employing age and nusinersen treatment in mechanical ventilation; M6, linear regression model employing weight and nusinersen treatment in mechanical ventilation; M7, linear regression model employing supine length and nusinersen treatment in mechanical ventilation; M8, linear regression model employing tibia length and nusinersen treatment in mechanical ventilation; SL, supine length (cm); SMA, spinal muscular atrophy; SMAGNG, General Nutrition Guidelines for Spinal Muscular Atrophy.

compared with no); secondly, by measuring REE with and without mechanical ventilation during the same session in children not completely dependent on ventilatory support. With the first approach we demonstrated that artificial ventilation always significantly reduces mREE regardless of the other variables considered. With the second approach, we proved that the use of ventilation reduced energy needs by >50%. The magnitude of the effect of the ventilatory status on energy requirements can be explained by the very specific thoracic-abdominal patterns of respiration in SMA (particularly in SMAI) (33–36). Lo Mauro et al. performed a kinematic analysis of thoracic-abdominal movements of SMA patients both during spontaneous breathingand mechanical ventilation, showing that SMA patients had a paradoxical ventilation pattern during spontaneous respiration that disappeared during mechanical ventilation. This was seemingly due to the normalization of kinematic volume changes during alveolar ventilation, significantly reducing the energy expenditure for respiratory work (33, 37).

Our previous observation that SMAI children have significantly higher REE per kg of FFM than SMA type II (SMAII) children (10) supports the hypothesis that greater impairment of intercostal muscles in SMAI requires greater energy expenditure to perform respiratory work (33–36).

Few studies have evaluated the impact of mechanical ventilation on REE and no studies in SMA patients are available. Gonzalez-Bermejo et al. (38) investigated the impact of mechanical ventilation on REE in adult patients affected by Duchenne muscular dystrophy, a severe type of muscular dystrophy characterized by progressive muscle degeneration and increased difficulty in breathing in the last phase of disease, as occur in SMAI patients just at the onset of disease. They found that the mean difference between REE in spontaneous and mechanical ventilation was 19% (38). We have found a much greater REE reduction but it should also be taken into consideration that the respiratory rate declines from birth to early adolescence. The median respiratory rate decreases by >40%

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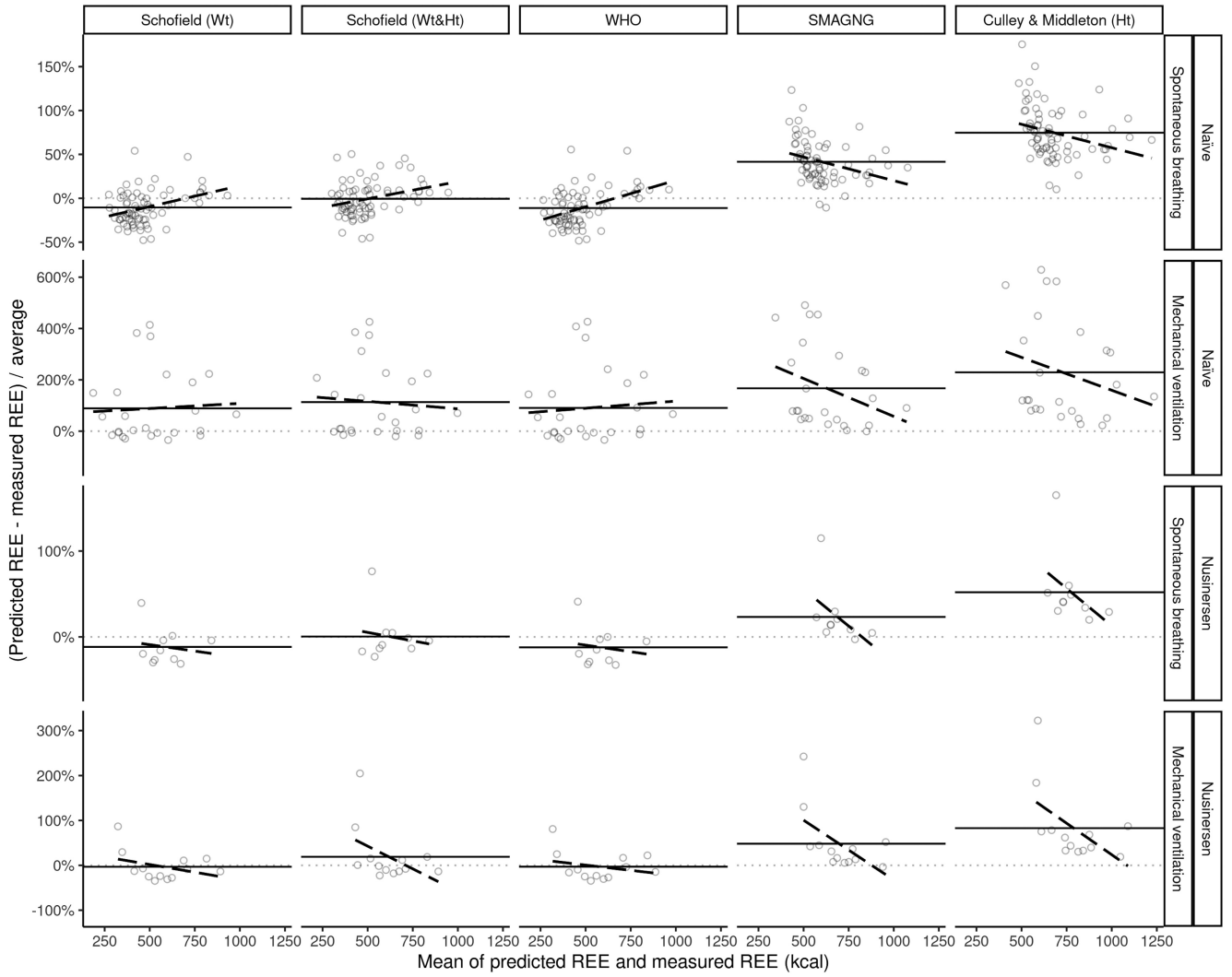


FIGURE 3 Relative Bland–Altman plots of currently available predictive equations compared with measured resting energy expenditure. Wt, weight; Ht, height; REE, resting energy expenditure; SMAGNG, General Nutrition Guidelines for Spinal Muscular Atrophy; Wt, weight. Schofield (Wt) in naïve patients in spontaneous breathing: $N = 73$. Schofield (Wt) in naïve patients in mechanical ventilation: $N = 25$. Schofield (Wt) in patients treated with nusinersen in spontaneous breathing: $N = 10$. Schofield (Wt) in patients treated with nusinersen in mechanical ventilation: $N = 13$. Schofield (Wt&t) in naïve patients in spontaneous breathing: $N = 73$. Schofield (Wt&t) in naïve patients in mechanical ventilation: $N = 25$. Schofield (Wt&t) in patients treated with nusinersen in spontaneous breathing: $N = 10$. Schofield (Wt&t) in patients treated with nusinersen in mechanical ventilation: $N = 13$. WHO in naïve patients in spontaneous breathing: $N = 73$. WHO in naïve patients in mechanical ventilation: $N = 25$. WHO in patients treated with nusinersen in spontaneous breathing: $N = 10$. WHO in patients treated with nusinersen in mechanical ventilation: $N = 13$. SMAGNG in naïve patients in spontaneous breathing: $N = 73$. SMAGNG in naïve patients in mechanical ventilation: $N = 25$. SMAGNG in patients treated with nusinersen in spontaneous breathing: $N = 10$. SMAGNG in patients treated with nusinersen in mechanical ventilation: $N = 13$. Culley & Middleton (Ht) in naïve patients in spontaneous breathing: $N = 73$. Culley & Middleton (Ht) in naïve patients in mechanical ventilation: $N = 25$. Culley & Middleton (Ht) in patients treated with nusinersen in spontaneous breathing: $N = 10$. Culley & Middleton (Ht) in patients treated with nusinersen in mechanical ventilation: $N = 13$. Ht, height; REE, resting energy expenditure; SMAGNG, General Nutrition Guidelines for Spinal Muscular Atrophy; Wt, weight.

changing from 44 breaths/min at birth to 20 breaths/min at adult age (39). Our sample may have a greater energy expenditure for respiratory work than that observed in Duchenne muscular dystrophy adult patients because of its median (25th, 75th percentile) age [13 (5, 25 mo)].

Interestingly, when we analyzed naïve and nusinersen-treated patients separately, we observed that, in naïve patients, mechanical ventilation significantly reduced total mREE and normalized REE for BW. By contrast, mechanical ventilation did not affect REE in nusinersen-treated patients. Other studies are needed to better understand the role of respiratory work on energy expenditure in SMA patients. These considerations led us to develop 2 sets of predictive equations, 1 for spontaneous breathing and 1 for mechanical ventilation, including treatment of nusinersen as a predictor of REE.

To the best of our knowledge, this is the first study that describes the effect of nusinersen treatment on energy metabolism. We demonstrated that nusinersen treatment always significantly increases mREE irrespective of the other considered variables, as shown in the different models, suggesting a potential positive

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effect of nusinersen treatment on FFM. Future longitudinal studies on the effect of nusinersen on energy metabolism are needed to confirm this hypothesis.

Age, BW, SL, and TL were also significantly correlated with mREE in this study. Even though FFM should be a stronger predictor of mREE, it is of limited clinical utility to dietitians and physicians, as few clinics have access to gold standard methods for the assessment of body composition. For this reason, in the predictive models we included BW or SL, which are recommended for a 6-monthly assessment according to the standard of care (16, 18), and are easily obtained in clinical settings, making them a suitable alternative for FFM.

Unsurprisingly, the nutritional status in our overall sample was significantly impaired, with BW Z-score and BMI Z-score mean values indicating malnutrition. On the other hand, the SL Z-score was in line with or over the median values of the reference group. These data confirm results from previous studies (5, 10, 40, 41) and support the hypothesis that, compared with healthy children (10), SMAI children have high FM and low FFM as a consequence of their underlying neurological condition, and not due to insufficient energy intake.

Our nusinersen-treated patients showed an SL Z-score lower than naïve patients, confirming previous results on decreased growth (height/length) among nusinersen-treated infants compared with sham controls (42).

Because of the well-known difficulties in obtaining accurate and repeatable measurements of SL in neuromuscular patients due to scoliosis and contractures (43), we also considered TL, which is a surrogate parameter of SL (44–46). In spontaneously breathing SMAI patients, the use of SL produces a better fitting model of mREE than TL. On the other hand, the use of TL produces a more suitable model of mREE in mechanically ventilated SMAI patients. However, scoliosis and contractures in SMAI patients occur more frequently at a later age than the children enrolled in this study, so these results should be verified in older children.

The present study compared the predicted REE from other published predictive equations (12, 13, 16, 26) with measured mREE from IC. We found that none of the predictive equations were sufficiently accurate to estimate the REE in these patients. Regarding median bias in spontaneously breathing patients, the WHO and Schofield equations (12, 13) performed best in estimating REE, but the proportional bias was too large to ensure proper management of nutritional support at the individual level. In nusinersen-treated spontaneously breathing patients, Schofield (BW and SL) performed particularly well, showing that this subpopulation is the closest to the general population.

Only 3 previous studies have compared mREE in SMA children with published REE predictive equations proposed for healthy children, but they were all conducted before the approval of nusinersen treatment. Cutillo et al. (47) investigated the differences between predicted (Schofield BW and SL equation, Schofield BW and WHO equations) and observed measures for REE in 18 Caucasian children affected by SMAII. They evaluated the largest deviation from the measured value using an overall average value of difference between the predictive and the measured REE – all the equations had a bias large enough to be potentially dangerous in the management of nutritional support. Similar results were also obtained in 7 SMA patients by Barja et al. (15). These results also confirmed our findings in SMAI and in SMAII where the Schofield equation overestimated REE by >20% (10).

Finally, the predictive equation for mental and motor disabilities in children (26) and the equation proposed by the SMAGNG (16), overestimated the contribution of SL on REE in our children by 3–9 kcal/cm, showing a higher bias than the equations for healthy children. The bias in Culley and Middleton may be attributable to the specific body composition and motor function features of SMAI children, who unlike other patients with motor dysfunction disabilities, have not only low FFM but also severe hypotonia (26).

When we compared our new predictive equations with others previously published (12, 16, 26), we found a better validity of the new equations in SMA children than any of the other equations. This was of course expected, because an internally developed equation nearly always performs better than an externally derived one. Thus, our SMAI-specific equations need external crossvalidation before they can be employed in clinical practice.

The greatest strength of this study is both the relatively large sample size of treated and naïve SMA patients, and the quality of data; it included patients from an ongoing longitudinal study on nutritional aspects in SMA children which enabled us to prospectively collect the parameters with standardized procedures by the same dietitians (28). In addition, REE was measured under strictly controlled conditions and by a single center. Despite our original findings (10), the SMAI population is heterogeneous and patients may have a large metabolic interindividual variability; this increases the difficulty of finding 1 predictive equation that can be accurate for all patient types.

In conclusion, we highlighted that ventilatory status and nusinersen treatment, as well as demographic and anthropometric characteristics, determine energy requirements in SMAI patients. In particular, we demonstrated that nusinersen treatment is correlated with higher REE both in spontaneously breathing and mechanically ventilated patients.

Our new equations were more accurate than any of the other previously published equations; however, they explain 62–63% and 18–22% of REE variance in spontaneously breathing and mechanically ventilated children, respectively, leading us to the conclusion that IC is strongly recommended for assessing energy requirements in SMAI children. Nonetheless, IC devices are rarely available in clinics; our SMAI-specific equations, that include variables readily available in clinical practice, may allow dietitians and physicians to optimize the management of nutritional support, also taking into consideration ventilatory status and nusinersen treatment. Further research is needed to perform external validation of these equations.

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AveXis, Inc., Roche, PTC, and Sarepta Therapeutics. All the other authors declare no conflicts of interest.

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