Increased resting energy expenditure compared with predictive theoretical equations in amyotrophic lateral sclerosis

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Pierre Jésus[1,2,3], Philippe Fayemendy[1,2,3], Benoit Marin[2,3,4], Marie Nicol[2,3,5], Huguette Sourisseau[1], Yves Boirie[6,7], Stéphane Walrand[7], Najate Achamrah[8,9], Moïse Coëffier[8,9], Pierre-Marie Preux[2,3,4], Géraldine Lautrette[5], Philippe Couratier[2,3,5], Jean-Claude Desport[1,2,3].

[1] Nutrition Unit, University Hospital of Limoges, Limoges, France.

[2] INSERM, U1094, Tropical Neuroepidemiology, Limoges, France.

[3] Univ. Limoges, UMR_S 1094, Tropical Neuroepidemiology, Institute of Neuroepidemiology and Tropical Neurology, CNRS FR 3503 GEIST, Limoges, France.

[4] Center of Epidemiology, Biostatistics and Research Methodology (CEBIMER), University Hospital of Limoges, Limoges, France.

[5] ALS center, University Hospital of Limoges, Limoges, France.

[6] Université Clermont Auvergne, CHU Clermont-Ferrand, Service de Nutrition Clinique, CRNH Auvergne, Clermont-Ferrand, France

[7] Université Clermont Auvergne, INRA, UNH, Unité de Nutrition Humaine, CRNH Auvergne, Clermont-Ferrand, France

[8] Nutrition Department, Clinical Investigation Centre CIC-1404, University Hospital, Rouen, France.

[9] INSERM UMR 1073, « Nutrition, Inflammation and Gut-Brain axis dysfunction », Normandie University, UNIROUEN, Rouen, France.

Corresponding author: Dr. Pierre Jésus, Nutrition Unit, University Hospital, 2 Avenue Martin Luther King, 87042 Limoges cedex. pierre.jesus@chu-limoges.fr; Phone: + 33 5 55 05 66 21; Fax: + 33 5 55 05 63 54

Short running head: Increased resting energy expenditure in ALS

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Highlights:

- In ALS patients measured REE is higher than calculated REE.
- Increase of metabolic rate is present whatever the REE predictive equations used.
- HB 1919 formula is still relevant as a reference value to search a REE variation.
- Mifflin formula seems also interesting to screen patient with evolving risk.
- Threshold of REE variation of 20% is better than 10% to screen patient with evolving risk.

Abstract

Introduction: About 50-60% of Amyotrophic Lateral Sclerosis (ALS) is characterized by an increase of metabolic rate. Harris and Benedict's (HB) 1919 formula is the equation mainly used to calculate REE (cREE) compared to measured REE (mREE) by indirect calorimetry (IC), but others are also applied in current practice. The present study aimed i) to assess mREE in ALS patients compared to 12 cREE formulas and ii) to study the relevant threshold of REE variation to screen patients with the higher evolving risk.

Method: Nutritional assessments and body composition (by bioimpedance analysis) were performed in ALS patients. mREE was measured by IC and cREE was calculated using HB 1919 and 1984, World Schofield, De Lorenzo, Johnstone, Mifflin, WHO/FAO, Owen, Fleisch, Wang, Rosenbaum and Nelson formulas. Functional and Respiratory evolution and survival by Log-rank test according to two thresholds of REE variation 10% and 20% were studied.

Results: 315 ALS patients were included. Median mREE was 1503 kcal/24h (1290 – 1698) and was higher than all predictive equations ($p < 0.0001$). Depending on the predictive equation, REE variation over 10% and 20% was found in 35.2% to 76.3% and in 14.6% to 53.3% of ALS patients, respectively. Patients with REE variation over 20% with HB 1919 and HB 1984 had a lower survival. Moreover, with this same threshold with Mifflin formula patients had a higher functional and respiratory evolution and a lower survival.

Conclusion: The increase of metabolic rate is present according to the different cREE formulas used compared to IC. In clinical practice REE formulas, such as HB 1919, HB 1984 or Mifflin, can be used as a reference value compared to IC to screen ALS patients with REE variation over 20% who have a higher evolving risk.

Keywords: Amyotrophic lateral sclerosis, metabolic rate, resting energy expenditure, predictive equation, evolution, survival.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare and severe neurodegenerative disease with an age at diagnosis of 65-70 years and a median survival of 25 to 30 months after diagnosis in Europe [1]. Its incidence is stable at around 2/ 100 000 person years in Western populations [1]. For 9-55% of patients according to the studies, malnutrition is present, which is an independent factor for survival [2–4]. One cause of malnutrition is an abnormal increase of resting energy expenditure (REE) [4–9]. The reference method to assess REE is to measure it (mREE) by indirect calorimetry (IC) [6,7,10–13]. When this method is not available, predictive formulas are used to derive theoretical REE (cREE) principally Harris and Benedict 1919 (HB 1919) [6,7,10–14].

The increase of metabolic rate in ALS is defined by more than +10% of REE variation between mREE and cREE [4–7,14]. Using HB 1919 for cREE, this REE variation over 10% was found in 48.0% to 68.0% of ALS patients [4–7,14]. Funalot et al. reported that all of 11 patients with familial form with SOD1 mutation had an increase of metabolic rate [10]. In ALS patients with this increase of metabolic rate, the level of REE variation was +10 to 20% [4–7]. The REE variation during ALS is a prognostic factor for the survival in patients with a REE variation over +20% [15,16]. However, Vaisman et al. found + 3.6% REE variation in ALS patients, with no difference compared to healthy controls [12]. All these data were derived using only HB 1919 equations [17]. Thus, authors are not in agreement about this increase of metabolic rate in ALS and the validity of the HB 1919 formula. Assessment of REE variation in ALS using REE formulas other than HB 1919 is therefore necessary. The aim of our study was i) to assess the level of REE and REE variation in ALS patients, with 12 predictive formulas, commonly used in healthy patients (HB 1919, HB 1984, World Schofield (WSchofield), De Lorenzo, Johnstone, Mifflin St. Jeor (Mifflin)) [18] and used in ALS studies (HB 1919, world health organization / food and agriculture organization of the United

95 Nations (WHO/FAO), Owen, Fleisch, Wang, Rosenbaum, Mifflin and Nelson) [6,7,19–21]
96 and ii) to study the relevant threshold of REE variation to screen patients with the higher
97 evolving risk.
98

Methods

ALS patients were diagnosed according to Airlie House criteria (definite, probable, or laboratory-supported probable and possible) [22], followed in the ALS expert center in Limoges (France) and all treated with riluzole. IC was performed less than 12 months after diagnosis. The respiratory quotient (RQ) during IC was between 0.7 and 0.87 [23]. The general data were sex and date of IC. The data were collected prospectively and extracted from the CleanWEB™ database of the Limoges ALS expert center. The databases were validated by the French Commission Nationale de l'Informatique et des Libertés (CNIL; reference: DP/DMS/DI074591, No. 1244525). ALS patients gave their informed consent for the data collection.

The nutritional assessment of ALS patients was performed within four months after the diagnosis in the Nutrition Unit of the University Hospital of Limoges. Patients were weighed in underwear using a SECA® electronic balance recording to 0.1 kg (Vogel & Halke, Hamburg, Germany) in an upright position or on a SECA® weighing chair if they could not stand upright. Their height was measured using a SECA® gauge recording to 0.2 cm (Vogel & Halke, Hamburg, Germany) in an upright position or using the Chumlea formulas for people over 60 years old who could not be held vertically [24]. BMI was calculated as weight (kg) / height x height (m^2). Malnutrition was defined according to French criteria by a BMI < 18.5 for patients under 70 years, and a BMI < 21.0 for those over 70 [25]. Normal status was defined as a BMI between 18.5 and 24.9 for patients under 70 and between 21.0 and 26.9 for patients over 70. Overweight was defined as a BMI between 25.0 and 29.9 under 70 and between 27.0 and 29.9 over 70. Obesity was defined as a BMI ≥ 30. Body composition, fat free mass (FFM in kg) and fat mass (FM in kg) were calculated by bioelectrical impedance analysis (BIA) with the validated formula of Desport et al. for ALS patients (FFM = (0.436 *

W) + (0.349 * mean H^2/Z50) - (0.695 * mean triceps skinfold [TSF]) + 9.245 with FFM in kg, W in kg, H in cm, Z in Ohm, and TSF in mm) with the Analycor® device (Eugédia, Chambly, France) [27]. TSF necessary for the formula of Desport et al. was obtained from the average of three measurements on each side with a Harpenden caliper (Baty International, Burgess Hill, UK) according to the usual modalities [26].

IC was performed during 30 min with the Quark RMR® with canopy (Cosmed, Rome, Italy) for ALS patients after calibration of the instrument (± 0.02% on absolute concentration of expired CO2 and inspired O2) [23]. IC was performed in the morning after 12 hours of fasting at home without treatment, drink, tobacco or chewing gum during this period of fasting. IC was realized in a supine position and at rest. The patient did not have physical activity before the IC nor sleep during the exam, nor hyperventilate. During IC, the respiratory quotient (RQ) between 0.7 and 0.87 were needed [28]. The REE was also calculated (cREE in kcal / 24h) according to 12 predictive formulas (HB 1919, HB 1984, WSchofield, De Lorenzo, Johnstone, Mifflin, WHO/FAO, Owen, Fleisch, Wang, Rosenbaum and Nelson) (Table 1) [18,19,21]. Results in kJ (WSchofield, De Lorenzo, Johnstone and Nelson) were converted to kcal by multiplying by 0.2388. The REE variation (in %) for each predictive formula used was calculated according to the formula: (mREE [kcal / 24h] - cREE [kcal / 24h]) / cREE (kcal / 24h) * 100. Increase of metabolic rate was defined by REE variation over 10% of the theoretical value for each predictive formula used [6,7,10]. A major increase of metabolic rate was defined by a REE variation over 20% of the theoretical value for each predictive formula used [15,16].

The amyotrophic lateral sclerosis functional rating scale (ALSFRS) (on 40 points before 2009) and ALSFRS-revised (ALSFRS-R on 48 points after 2009) were collected. To homogenize the results, ALSFRS was converted into a score on 48 points [29]. ALSFRS-R

slope (in points/month) from diagnosis to the last assessment was calculated according to the formula: (ALSFRS-R score at the last assessment – ALSFRS-R score at diagnosis) / (time from diagnosis to the last assessment [month]). Forced vital capacity (FVC, % of the theoretical value), was collected using a Hans Rudolph® pneumotachograph, integrated into a body plethysmography system 1085 (CPF Medical Graphics, St Paul, Minnesota, USA). FVC slope (in %/month) from diagnosis to the last assessment was also calculated according to the formula: (FVC at the last assessment – FVC at diagnosis) / (time from diagnosis to the last assessment [month]).

Statistical analysis was performed using GraphPad Prism 6.0 (GraphPad Software Inc, La Jolla, CA, USA). Quantitative variables were expressed with the median (interquartile range [IQR]). The qualitative variables were expressed in number and percentage. Normality was studied using the Shapiro-Wilk test. Comparisons of quantitative variables were made using non-parametric Mann-Whitney test. Comparisons of the qualitative variables were made using the Chi2. Comparative analyses were conducted, mREE and cREE with HB 1919 was compared to all cREE with other formulas, REE variation and percentage of patients with REE variation over 10% and 20% with HB 1919 versus other formulas. FVC slope and ALSFRS-R slope were compared between patients with or without REE variation over 10% and over 20% according to each REE formula used. For survival analysis, the event was the date of death or of tracheostomy. Univariate survival analysis between patients with or without REE variation over 10% and over 20% (according to each REE formula used), was performed using the Log-rank test. The threshold of significance for all statistical analyses was $p < 0.05$. We complied with the STROBE statement to be in agreement for observational - cross sectional studies [30].

Results

The nutritional characteristics of ALS patients are presented in Table 2.

From November 1996 to November 2014, 405 ALS patients had IC, 90 were excluded (flowchart: Figure 1). The 315 patients included had a median age at IC of 66.6 years (56.9–4.1) with a sex ratio of 1.0. ALS patients. Median BMI was 24.2 kg / m^2 (22.0 – 27.6). There was missing data on BIA measurement which could not be realized for 28 patients.

Figure 2 shows mREE, REE variations and percentages of patients with REE variation over 10%.

mREE was 1503 kcal /24h (1290-1698), higher than cREE with the formulas ($p < 0.0001$ whatever the equation used). Increase of metabolic rate with REE variation over 10% was found in 35.2% to 76.3% of cases (Table 3). These percentages were lower for WSchofield, WHO/FAO, Owen and Fleisch versus HB 1919 ($p = 0.03$, $p < 0.0001$, $p < 0.0001$, and $p = 0.007$, respectively) and higher for Johnstone, Mifflin, Wang and Nelson versus HB 1919 ($p = 0.03$, $p < 0.0001$, $p = 0.003$ and $p < 0.0001$, respectively). Nelson equations provided the highest REE variation compared to HB 1919. A REE variation over 20% was found in 14.6% to 53.3% of patients (Table 3).

Patients with the same metabolic status as HB 1919 using the other predictive formulas is presented in figure 3. Concerning the patient with a REE variation under 10% more than 80% of patients kept the same metabolic status with HB1984, WSchofield, De Lorenzo, WHO/FAO, Owen, Fleisch and Rosenbaum formulas with respect to HB 1919. Concerning the patient with a REE variation over 20% more than 80% of patients kept the same metabolic status with HB1984, De Lorenzo, Johnstone, Mifflin, and Nelson formulas with respect to HB 1919.

The respiratory and functional evolution and the survival of patients with or without REE

variation over 10% and 20% are presented in Table 4 and 5. With a threshold of REE variation of 10%, only with HB 1919 formula respiratory evolution was worst in patients over 10% (Table 4). No other pejorative evolution was found in these patients according to the different formulas studied. With a threshold of REE variation of 20%, using HB 1919, HB 1984 and Mifflin formulas patients over 20% had a lower survival compared to the other patients ($p = 0.01$, $p = 0.02$ and $p = 0.003$, respectively) (Table 5). Moreover, with the Mifflin formula, patients over 20% had a more severe respiratory and functional evolution ($p = 0.02$ and $p = 0.03$, respectively).

Discussion

This study assessed the increase of metabolic rate in ALS patients with 12 equations to evaluate cREE compared to mREE by IC. The results strongly suggest that the increase of metabolic rate is a reality in ALS patients. REE variation was in accordance with the main previous studies [6,7,11,13–16]. REE variation over 10% was very prominent, with a prevalence of 55.2% with HB 1919 reference equation and this phenomenon was confirmed with all the formulas used (35.2% to 76.3% of cases). A major REE variation over 20% was found in 14.6% to 53.3% of patients in our study according to the predictive formulas used. Indeed, this increase of metabolic rate during ALS is a prognostic factor for the functional status and the survival, mainly in patients with a REE variation over +20% assessed with HB 1919 formula [15,16]. We found that a threshold of +20% for the REE variation especially with HB 1919, HB 1984 and Mifflin formulas seemed more interesting to screen patients with a higher evolving risk (functional and respiratory evolution and survival). As with HB 1919, the increase of metabolic rate with HB 1984 was also a prognostic factor for survival over 20% of REE variation. Indeed, classification of patients according to REE variation with HB 1984 was close to HB1919 in our study. Nevertheless, there were differences according to other formulas used versus HB 1919. Indeed, Mifflin equations yielded one the highest REE variation compared to IC and to HB 1919. Our results could suggest that Mifflin is less appropriate than other formulas to be used to calculate cREE in ALS patients. However, with this formula as a reference, we found a more severe respiratory and functional evolution and a lower survival in patients with REE variation over 20%. Indeed, 93.1% of patients kept this same metabolic status (REE variation over 20%) with Mifflin according to HB 1919. With Nelson formula which use body composition to predict REE we found the highest REE variation compared to IC. This is in relation with a lower REE prediction with this formula as in the study of Ioannides et al. although they used another method of body composition

measurement (plethysmography) [21]. But the variation of REE with Nelson formula compared to IC did not seem interesting for the evolving risk of ALS patients. The finding was the same with the other formulas which used body composition (Johnstone, Wang and Rosenbaum), although body composition was assessed in our study by BIA with a validated formula for ALS patients [27]. Indeed, the decrease of predicted REE with formula using body composition could be related with this decrease of FFM in ALS. These formulas including body composition were created in healthy people and with different methods of body composition measurement (Dual X-ray absorptiometry, double labelled water…) which could bias the results of prediction of REE. Moreover, the FFM decrease during the ALS but the mREE by IC and the REE variation is stable during the disease as found by Bouteloup et al. [7]. It suggests other mechanisms causing an increase of the metabolic rate during this disease. Concerning the presence of this modification of metabolic rate in ALS patient, based on studies using HB 1919 formula, increase of metabolic rate was not associated with neurological form (bubar form, ALSFRS-R), riluzole treatment, tobacco, fasciculation, respiratory insufficiency, or the familial form which could explain this increase in energy metabolism [14,15]. Further studies are needed to investigate the causes of this metabolic change in ALS and which may involve several neurological mechanisms (alteration of central nervous system, neuro-inflammation, nerve hyperexcitability or re-innervation) [31–34]. Cortical hyperexcitability could be related to this metabolic dysfunction with an increase of glucose metabolism which is the main energy substrate in neuron. Indeed, an increase of glucose metabolism was found in brain of ALS patients and could lead to an increase of metabolic rate in these patients [35,36]. Globally, the REE predictive formulas should not be used to calculate the energy needs of ALS patients but only used as a reference to calculate and assess the level of REE variation compared to IC. Indeed, predictive formulas would allow to assess REE for the healthy condition of the patient and IC would allowed to assess

REE for the pathological condition (ALS) of the patient. IC is thus, a very useful tool for the measurement of REE in ALS, but is still not available.

Our study presents several limitations. First, we did not measure REE during the follow up of the patients to assess its evolution according to body composition evolution and the evolution of REE variation according to the different formulas used. We did not use a control population of heathy people. Indeed, the study of Vaisman et al. did not find difference of REE variation between healthy control and ALS patient [12]. In addition, they found a higher mREE in control than in ALS patients. However, there was a notable bias in this study because FFM was significantly higher in the control group, suggesting that after normalization for FFM, ALS patients could have a higher metabolic level than the controls. However, the strength of our work is the study of metabolic rate of ALS patients with a reference method (IC) compared to several (n=12) different predictive REE formulas. Moreover, we studied a large ALS patients' cohort with functional, respiratory and survival analysis according to their metabolic rate.

Conclusion

In ALS mREE by IC is higher than cREE whatever the equation used. A major REE variation over 20% between mREE and cREE is found in 14.6% to 53.3% of patients according to the formulas used. In our study with this threshold of 20%, the HB 1919, HB 1984 and Mifflin formulas seem the more pertinent formula as a reference compared to IC to screen ALS patient with a higher evolving risk. Using HB 1919 and HB 1919 formula as a reference, patients with a REE variation over 20% had a lower survival. However, with Mifflin as a reference, a more severe respiratory and functional evolution and a lower survival were found in patients with REE variation over 20%. Our Study confirm the importance to assess the metabolic rate in ALS with IC and relevant predictive formula as HB 1919, HB 1984 and Mifflin formulas.

References

[1] Marin B, Logroscino G, Boumédiene F, Labrunie A, Couratier P, Babron M-C, et al. Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. Eur J Epidemiol 2016;31:229–45.

[2] Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. Neurology 1999;53:1059–63.

[3] Marin B, Desport JC, Kajeu P, Jesus P, Nicolaud B, Nicol M, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. J Neurol Neurosurg Psychiatry 2011;82:628–34.

[4] Genton L, Viatte V, Janssens J-P, Héritier A-C, Pichard C. Nutritional state, energy intakes and energy expenditure of amyotrophic lateral sclerosis (ALS) patients. Clin Nutr 2011;30:553–9.

[5] Muscaritoli M, Kushta I, Molfino A, Inghilleri M, Sabatelli M, Rossi Fanelli F. Nutritional and metabolic support in patients with amyotrophic lateral sclerosis. Nutrition 2012;28:959–66.

[6] Desport J-C, Torny F, Lacoste M, Preux P-M, Couratier P. Hypermetabolism in ALS: correlations with clinical and paraclinical parameters. Neurodegener Dis 2005;2:202–7.

[7] Bouteloup C, Desport J-C, Clavelou P, Guy N, Derumeaux-Burel H, Ferrier A, et al. Hypermetabolism in ALS patients: an early and persistent phenomenon. J Neurol 2009;256:1236–42.

[8] Marin B, Jésus P, Preux P-M, Couratier P, Desport JC. Troubles nutritionnels lors de la sclérose latérale amyotrophique (SLA). Nutr Clin Metab 2011;25:205–216.

[9] Ngo ST, Steyn FJ, McCombe PA. Body mass index and dietary intervention: implications for prognosis of amyotrophic lateral sclerosis. J Neurol Sci 2014;340:5–12.

[10] Funalot B, Desport J-C, Sturtz F, Camu W, Couratier P. High metabolic level in patients

312 with familial amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2009;10:113–7.
313 [11] Kasarskis EJ, Berryman S, Vanderleest JG, Schneider AR, McClain CJ. Nutritional
314 status of patients with amyotrophic lateral sclerosis: relation to the proximity of death.
315 Am J Clin Nutr 1996;63:130–7.
316 [12] Vaisman N, Lusaus M, Nefussy B, Niv E, Comaneshter D, Hallack R, et al. Do patients
317 with amyotrophic lateral sclerosis (ALS) have increased energy needs? J Neurol Sci
318 2009;279:26–9.
319 [13] Sherman MS, Pillai A, Jackson A, Heiman-Patterson T. Standard equations are not
320 accurate in assessing resting energy expenditure in patients with amyotrophic lateral
321 sclerosis. J Parenter Enter Nutr 2004;28:442–6.
322 [14] Desport JC, Preux PM, Magy L, Boirie Y, Vallat JM, Beaufrère B, et al. Factors
323 correlated with hypermetabolism in patients with amyotrophic lateral sclerosis. Am J
324 Clin Nutr 2001;74:328–34.
325 [15] Jésus P, Fayemendy P, Nicol M, Lautrette G, Sourisseau H, Preux P-M, et al.
326 Hypermetabolism is a deleterious prognostic factor in patients with amyotrophic lateral
327 sclerosis. Eur J Neurol 2018;25(1):97-104.
328 [16] Steyn FJ, Ioannides ZA, Eijk RPA van, Heggie S, Thorpe KA, Ceslis A, et al.
329 Hypermetabolism in ALS is associated with greater functional decline and shorter
330 survival. J Neurol Neurosurg Psychiatry 2018;89(10):1016-1023.
331 [17] Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. Proc Natl
332 Acad Sci U S A 1918;4:370–3.
333 [18] Jésus P, Achamrah N, Grigioni S, Charles J, Rimbert A, Folope V, et al. Validity of
334 predictive equations for resting energy expenditure according to the body mass index in
335 a population of 1726 patients followed in a Nutrition Unit. Clin Nutr 2015;34:529–35.
336 [19] Kasarskis EJ, Mendiondo MS, Matthews DE, Mitsumoto H, Tandan R, Simmons Z, et

al. Estimating daily energy expenditure in individuals with amyotrophic lateral sclerosis. Am J Clin Nutr 2014;99:792–803.

[20] Siirala W, Olkkola KT, Noponen T, Vuori A, Aantaa R. Predictive equations over-estimate the resting energy expenditure in amyotrophic lateral sclerosis patients who are dependent on invasive ventilation support. Nutr Metab 2010;7:70.

[21] Ioannides ZA, Steyn FJ, Mi JD, Henderson RD, McCombe PA, Ngo ST. Predictions of resting energy expenditure in amyotrophic lateral sclerosis are greatly impacted by reductions in fat free mass. Cogent Med 2017;4:1343000.

[22] Brooks BR, Miller RG, Swash M, Munsat TL, World federation of neurology research group on motor neuron diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Mot Neuron Disord Off Publ World Fed Neurol Res Group Mot Neuron Dis 2000;1:293–9.

[23] Ferrannini E. The theoretical bases of indirect calorimetry: A review. Metabolism 1988;37:287–301.

[24] Chumlea WC, Roche AF, Steinbaugh ML. Estimating stature from knee height for persons 60 to 90 years of age. J Am Geriatr Soc 1985;33:116–20.

[25] Haute Autorité de Santé (HAS). Stratégie de prise en charge en cas de dénutrition protéino-énergétique chez la personne âgée. Nutr Clin Metab 2007;21:120–33.

[26] Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr 1981;34:2540–5.

[27] Desport JC, Preux PM, Bouteloup-Demange C, Clavelou P, Beaufrère B, Bonnet C, et al. Validation of bioelectrical impedance analysis in patients with amyotrophic lateral sclerosis. Am J Clin Nutr 2003;77:1179–85.

[28] Fullmer S, Benson-Davies S, Earthman CP, Frankenfield DC, Gradwell E, Lee PSP, et al. Evidence analysis library review of best practices for performing indirect calorimetry

in healthy and non-critically ill individuals. J Acad Nutr Diet 2015;115:1417-1446.e2.

[29] Marin B, Arcuti S, Jesus P, Logroscino G, Copetti M, Fontana A, et al. Population-based evidence that survival in amyotrophic lateral sclerosis Is related to weight loss at diagnosis. Neurodegener Dis 2016;16:225–34.

[30] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–9.

[31] Loeffler J-P, Picchiarelli G, Dupuis L, Gonzalez De Aguilar J-L. The role of skeletal muscle in amyotrophic lateral sclerosis. Brain Pathol 2016;26:227–36.

[32] Vercruysse P, Sinniger J, El Oussini H, Scekic-Zahirovic J, Dieterlé S, Dengler R, et al. Alterations in the hypothalamic melanocortin pathway in amyotrophic lateral sclerosis. Brain 2016;139:1106–22..

[33] Santa-Cruz LD, Guerrero-Castillo S, Uribe-Carvajal S, Tapia R. Mitochondrial dysfunction during the early stages of excitotoxic spinal motor neuron degeneration in vivo. ACS Chem Neurosci 2016;7(7):886-96.

[34] Ioannides ZA, Ngo ST, Henderson RD, McCombe PA, Steyn FJ. Altered metabolic homeostasis in amyotrophic lateral sclerosis: mechanisms of energy imbalance and contribution to disease progression. Neurodegener Dis 2016:382–97.

[35] Cistaro A, Valentini MC, Chiò A, Nobili F, Calvo A, Moglia C, et al. Brain hypermetabolism in amyotrophic lateral sclerosis: a FDG PET study in ALS of spinal and bulbar onset. Eur J Nucl Med Mol Imaging 2011;39:251–9.

[36] Buhour M-S, Doidy F, Mondou A, Pélerin A, Carluer L, Eustache F, et al. Voxel-based mapping of grey matter volume and glucose metabolism profiles in amyotrophic lateral sclerosis. EJNMMI Res 2017;7:21.

Figure 1: Flowchart of ALS patients included in the study.

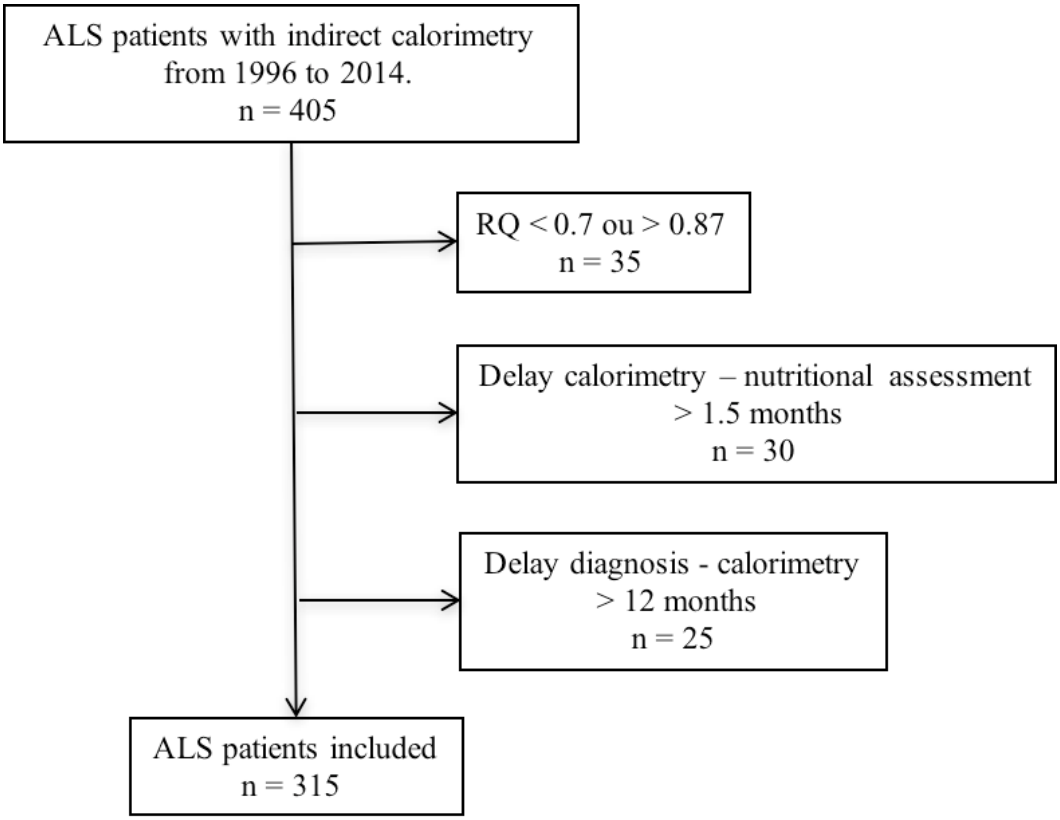
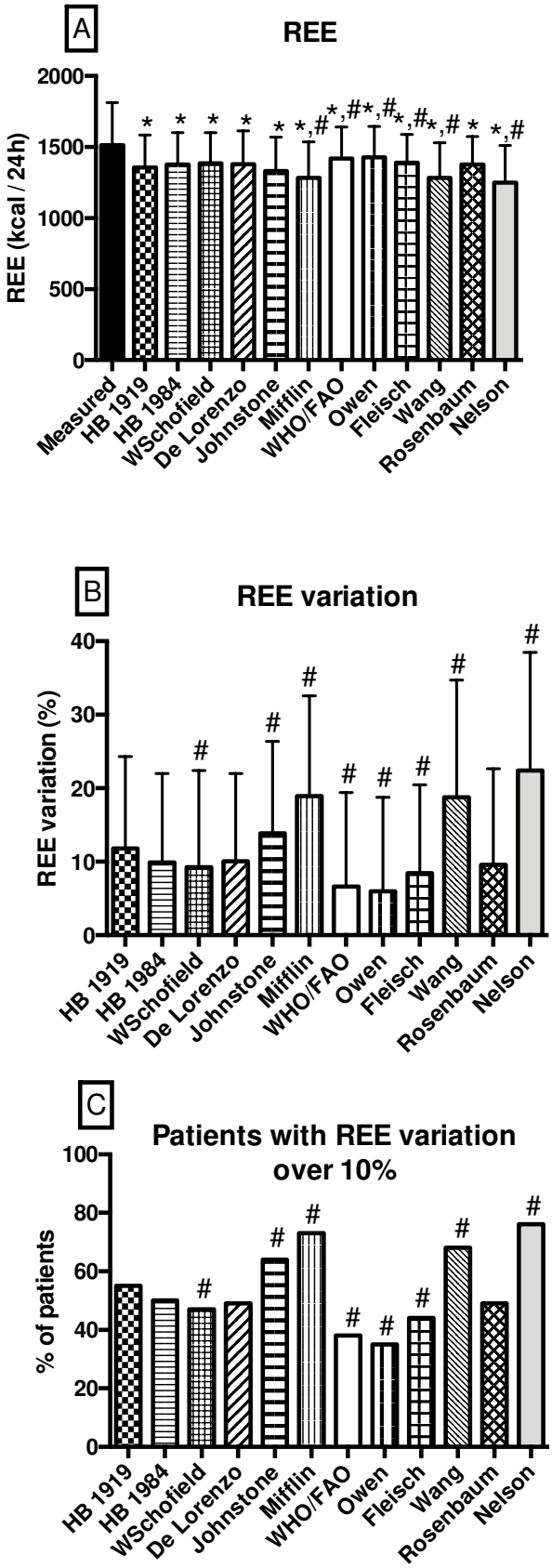


Figure 2: Resting energy expenditure (REE), REE variation and percentage of patients with REE variation over 10% in ALS patients (n=315) according to the 12 predictive formulas used.

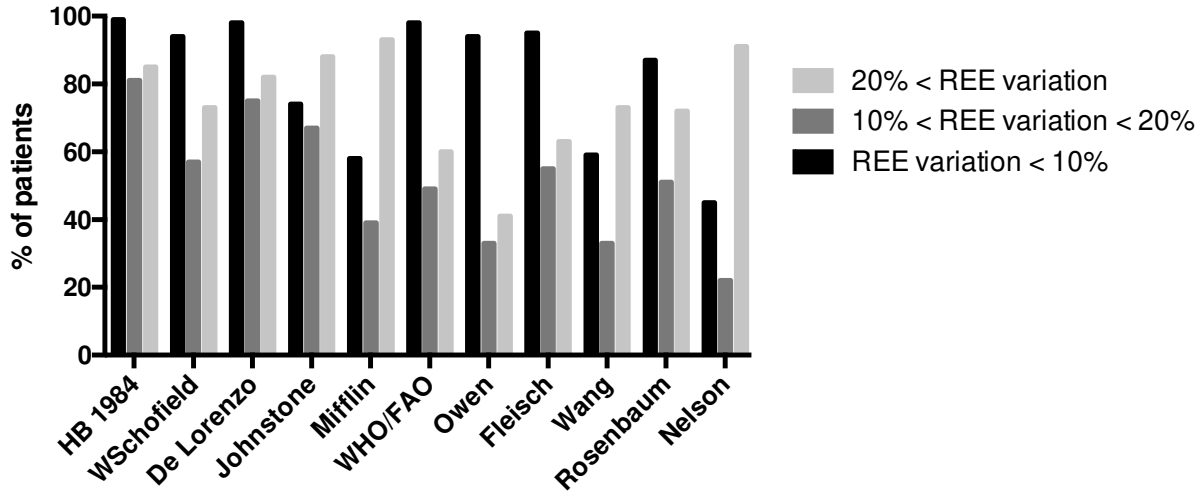


ALS: amyotrophic lateral sclerosis; HB: Harris & Benedict; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; cREE: calculated resting energy expenditure; mREE: measured resting energy expenditure; WHO/FAO: World health organization / food and agriculture organization of the United Nations, WSchofield: World Schofield.

*: mREE vs. cREE, $p<0.05$

[#] : HB 1919 vs. other formulas, $p < 0.05$

Figure 3: Patients with the same metabolic status as Harris and Benedict 1919 using the other predictive formulas.



HB: Harris & Benedict; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; WHO/FAO: World health organization / food and agriculture organization of the United Nations, WSchofield: World Schofield.

Table 1: Resting energy expenditure formulas used.

Harris & Benedict 1919	- Male: (Weight (kg) * 13.7516) + (Height (cm) * 5.0033) - (Age (years) * 6.755) + 66.473 - Female: (Weight (kg) * 9.5634) + (Height (cm) * 1.8496) - (Age (years) * 4.6756) + 655.0955
Harris & Benedict 1984	- Male: (Weight (kg) * 13.397) + (Height (cm) * 4.799) - (Age (years) * 5.677) + 88.362 - Female: (Weight (kg) * 9.247) + (Height (cm) * 3.098) - (Age (years) * 4.33) + 477.593
World Schofield	- Male of 18 - 30 years: (0.063 * Weight (kg)) + 2.896 - Male of 30 - 60 years: (0.048 * Weight (kg)) + 3.653 - Male > 60 years: (0.049 * Weight (kg)) + 2.459 - Female of 18 - 30 years: (0.062 * Weight (kg)) + 2.036 - Female of 30 - 60 years: (0.034 * Weight (kg)) + 3.538 - Female > 60 years: (0.038 * Weight (kg)) + 2.755
De Lorenzo	- Male: (53.284 * Weight (kg)) + (20.957 * Height (cm)) – (23.859 * Age (years)) + 487 - Female: (46.322 * Weight (kg)) + (15.744 * Height (cm)) - (16.66 * Age (years)) + 944
Johnstone	(90.2 * FFM (kg)) + (31.6 * FM (kg)) – (12.2 * Age (years)) + 1613
Mifflin St. Jeor	- Male: (9.99 * Weight (kg)) + (6.2 * Height (cm)) - (4.92 * Age (years)) + 5 - Female: (9.99 * Weight (kg)) + (6.2 * Height (cm)) - (4.92 * Age (years)) - 161

WHO/FAO	- Male of 18 - 30 years: (15.4 * Weight (kg)) – (27 * Height (cm)) + 717 - Male of 31 - 60 years: (11.3 * Weight (kg)) + (16 * Height (cm)) + 901 - Male of > 60 years: (8.8 * Weight (kg)) + (1128 * Height (cm)) - 1071 - Female of 18 - 30 years: (13.3 * Weight (kg)) + (334 * Height (cm)) + 35 - Female of 31 - 60 years: (8.7 * Weight (kg)) – (25 * Height (cm)) + 865 - Female of > 60 years: (9.2 * Weight (kg)) + (637 * Height (cm)) - 302
Owen	- Male: 879 + 10.2 * Weight (kg) - Female: 795 + 7.18 * Weight (kg)
Fleisch	- Male: 24 * BSA * (38 - 0.073 * (Age (years) - 20)) - Female: 24 * BSA * (35.5 - 0.064 * (Age (years) - 20))
Wang	24.6 * FFM (kg) +175
Rosenbaum	(17.2 * FFM (kg)) + (10.5 * FM (kg)) + 375
Nelson	(108 * FFM (kg)) + (16.9 * FM (kg))

BSA: body surface area = 0.007184 * (Height (cm)$^{0.725}$) * (Weight (kg)$^{0.425}$); FFM: fat-free mass; FM: fat mass; WHO/FAO: world health organization / food and agriculture organization of the United Nations.

Table 2: Characteristics of ALS patients (n = 315).

	Median (IQR) n (%)	Missing data
Age (years)	66.6 (56.9 – 74.1)	0
Men (%)	161 (51.1)	0
Weight (kg)	65.0 (57.3 – 74.7)	0
Height (cm)	163.0 (155.0 – 171.0)	0
BMI (kg / m^2)	24.2 (22.0 – 27.6)	0
Nutritional status		0
- Malnutrition	30 (9.5)	
- Normal	168 (53.3)	
- Overweight	73 (23.2)	
- Obesity	44 (14.0)	

FFM (kg)	44.4 (36.9 – 51.9)	28
FM (kg)	20.7 (15.2 – 25.4)	28
ALSFRS-R (points)	40 (35 – 43)	24
FVC (%)	90.0 (69.0 – 106.0)	76

ALS: amyotrophic lateral sclerosis; ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised; BMI: body mass index; FFM: free fat mass; FM: fat mass; FVC: forced vital capacity; IQR: interquartile range; n: number.

Table 3: Patient with increase of metabolic rate according to the predictive formula used and compared to Harris & Benedict 1919.

	Total (10% < REE variation) n (%)	10% < REE variation ≤ 20% n (%)	20% < REE variation n (%)
HB 1919	174 (55.2)	101 (32.1)	73 (23.1)
HB 1984	157 (49.8)	94 (29.8)	63 (20.0)
WSchofield	147 (46.7)[#]	85 (27.0)	62 (19.7)
De Lorenzo	155 (49.2)	92 (29.2)	63 (20.0)
Johnstone	184 (64.1)[#]	101 (35.2)	83 (28.9)
Mifflin	229 (72.7)[#]	78 (24.8)[#]	151 (47.9)[#]
WHO/FAO	121 (38.4)[#]	74 (23.5)[#]	47 (14.9)[#]
Owen	111 (35.2)[#]	65 (20.6)[#]	46 (14.6)[#]

Fleisch	140 (44.4)[#]	89 (28.2)	51 (16.2)[#]
Wang	194 (67.6)[#]	71 (24.7)[#]	123 (42.9)[#]
Rosenbaum	141 (49.1)	76 (26.5)	65 (22.6)
Nelson	219 (76.3)[#]	66 (23.0)[#]	153 (53.3)[#]

HB: Harris & Benedict; MD: missing data; Mifflin: Mifflin St. Jeor; n: number; REE: resting energy expenditure; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield.

[#]: $p < 0.05$ compared to HB 1919

Table 4: Respiratory and functional evolution and survival according to a threshold of REE variation of 10% with the different predictive formula used.

	FVC slope (%/month) (n = 171)			ALSFRS-R slope (points/month) (n = 264)			Survival (n = 315)	
	REE variation ≤10% Median (IQR)	REE variation >10% Median (IQR)	p	REE variation ≤10% Median (IQR)	REE variation >10% Median (IQR)	p	REE variation >10% vs. ≤10% HR (95%CI)	p
HB 1919	-2.2 (-4.2 – -1.1)	-3.2 (-6.2 – -1.5)	**0.03**	-1.1 (-1.9 – -0.6)	-1.3 (-2.0 – -0.6)	0.61	1.13 (0.89 – 1.43)	0.31
HB 1984	-2.3 (-4.3 – -1.1)	-3.1 (-6.2 – -1.5)	0.11	-1.2 (-2.0 – -0.6)	-1.2 (-2.0 – -0.6)	0.97	1.11 (0.88 – 1.40)	0.40
WSchofield	-2.5 (-4.7 – -1.1)	-2.7 (-6.2 – -1.5)	0.20	-1.2 (-2.1 – -0.7)	-1.2 (-1.9 – -0.5)	0.39	1.04 (0.81 – 1.31)	0.77
De Lorenzo	-2.4 (-4.5 – -1.1)	-3.0 (-6.1 – -1.4)	0.23	-1.2 (-2.0 – -0.6)	-1.2 (-2.0 – -0.6)	1.00	1.16 (0.92 – 1.47)	0.20
Johnstone	-2.3 (-4.2 – -0.8)	-3.0 (-5.8 – -1.4)	0.12	-1.2 (-2.0 – -0.6)	-1.3 (-2.0 – -0.6)	0.91	1.06 (0.82 – 1.36)	0.68
Mifflin	-2.3 (-4.2 – -1.0)	-3.0 (-6.1 – -1.2)	0.09	-1.1 (-1.9 – -0.6)	-1.2 (-2.0 – -0.6)	0.67	1.29 (1.00 – 1.65)	0.06

WHO/FAO	-2.7 (-5.1 – -1.1)	-2.7 (-6.1 – -1.7)	0.30	-1.2 (-2.1 – -0.6)	-1.3 (-1.9 – -0.6)	0.98	1.03 (0.81 – 1.31)	0.84
Owen	-2.5 (-5.5 – -1.1)	-3.1 (-5.6 – -1.4)	0.52	-1.1 (-2.0 – -0.6)	-1.3 (-1.9 – -0.6)	0.88	0.87 (0.68 – 1.10)	0.25
Fleisch	-2.7 (-5.3 – -1.1)	-2.7 (-5.8 – -1.5)	0.45	-1.2 (-2.0 – -0.6)	-1.2 (-1.9 – -0.6)	0.81	1.01 (0.80 – 1.23)	0.94
Wang	-2.7 (-6.5 – -1.0)	-2.6 (-5.2 – -1.3)	0.90	-1.4 (-2.1 – -0.7)	-1.1 (-1.9 – -0.6)	0.11	0.81 (0.61 – 1.05)	0.11
Rosenbaum	-2.8 (-5.3 – -1.1)	-2.5 (-5.3 – -1.2)	0.94	-1.3 (-2.0 – -0.7)	-1.2 (-1.9 – -0.6)	0.35	0.76 (0.60 – 0.97)	**0.03**
Nelson	-2.3 (-4.6 – -0.9)	-2.8 (-5.4 – -1.3)	0.38	-1.4 (-2.1 – -0.7)	-1.2 (-2.0 – -0.6)	0.40	0.82 (0.60 – 1.10)	0.17

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised; CI: confidence interval; FVC: forced vital capacity; HB: Harris & Benedict; HR: hazard ratio; IQR: interquartile range; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield

In bold: $p < 0.05$

Table 5: Respiratory and functional evolution and survival according to a threshold of REE variation of 20% with the different predictive formula used.

	FVC slope (%/month) (n = 171)			ALSFRS-R slope (points/month) (n = 264)			Survival (n = 315)	
	REE variation ≤20% Median (IQR)	REE variation >20% Median (IQR)	p	REE variation ≤20% Median (IQR)	REE variation >20% Median (IQR)	p	REE variation >20% vs. ≤20% HR (95%CI)	p
HB 1919	-2.7 (-5.3 – -1.1)	-2.7 (-6.1 – -1.4)	0.40	-1.1 (-2.0 – -0.6)	-1.4 (-2.8 – -0.7)	0.28	1.42 (1.10 – 1.99)	**0.01**
HB 1984	-2.7 (-5.2 – -1.1)	-2.7 (-6.2 – -1.3)	0.40	-1.1 (-1.9 – -0.6)	-1.5 (-2.3 – -0.7)	0.10	1.38 (1.06 – 1.92)	**0.02**
WSchofield	-2.7 (-5.3 – -1.1)	-2.6 (-6.4 – -1.3)	0.61	-1.2 (-1.9 – -0.6)	-1.4 (-2.2 – -0.7)	0.22	1.27 (0.95 – 1.76)	0.10
De Lorenzo	-2.7 (-5.2 – -1.2)	-2.7 (-5.2 – -1.2)	1.00	-1.1 (-1.9 – -0.6)	-1.5 (-2.4 – -0.8)	**0.047**	1.30 (0.98 – 1.81)	0.07
Johnstone	-2.6 (-5.0 – -1.1)	-2.7 (-5.7 – -1.4)	0.48	-1.2 (-1.9 – -0.7)	-1.4 (-2.0 – -0.6)	0.78	1.02 (0.78 – 1.32)	0.90
Mifflin	-2.3 (-4.4 – -1.1)	-3.5 (-6.5 – -1.5)	**0.03**	-1.0 (-1.7 – -0.6)	-1.4 (-2.2 – -0.6)	**0.02**	1.42 (1.14 – 1.83)	**0.003**

WHO/FAO	-2.7 (-5.5 – -1.2)	-2.5 (-5.7 – -1.0)	0.97	-1.1 (-1.9 – -0.6)	-1.5 (-2.4 – -0.6)	0.17	1.13 (0.83 – 1.57)	0.44
Owen	-2.6 (-5.5 – -1.1)	-3.2 (-6.0 – -1.5)	0.56	-1.1 (-2.0 – -0.6)	-1.4 (-2.1 – -0.9)	0.07	0.91 (0.66 – 1.25)	0.56
Fleisch	-2.7 (-5.5 – -1.2)	-2.5 (-6.0 – -1.1)	0.93	-1.1 (-1.9 – -0.6)	-1.4 (-2.3 – -0.8)	0.11	1.14 (0.82 – 1.59)	0.42
Wang	-2.3 (-4.5 – -1.1)	-3.2 (-5.8 – -1.4)	0.24	-1.1 (-2.0 – -0.6)	-1.3 (-2.0 – -0.6)	0.95	0.91 (0.71 – 1.17)	0.45
Rosenbaum	-2.6 (-5.2 – -1.1)	-2.7 (-6.1 – -1.2)	0.57	-1.2 (-2.0 – -0.6)	-1.4 (-2.0 – -0.7)	0.30	0.96 (0.73 – 1.28)	0.80
Nelson	-2.5 (-6.5 – -1.1)	-2.7 (-5.1 – -1.2)	0.99	-1.3 (-2.1 – -0.7)	-1.2 (-1.9 – -0.6)	0.15	0.91 (0.71 – 1.16)	0.45

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised; CI: confidence interval; FVC: forced vital capacity; HB: Harris & Benedict; HR: hazard ratio; IQR: interquartile range; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield.

In bold: $p < 0.05$