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## **Resting energy expenditure equations in amyotrophic lateral sclerosis, creation of an ALS-specific equation**

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1 **Resting energy expenditure equations in Amyotrophic Lateral Sclerosis, creation of an**  
2 **ALS-specific equation.**

3  
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21

22 **Abstract**

23 Introduction: Resting energy expenditure (REE) formulas for healthy people (HP) are used to  
24 calculate REE (cREE) in amyotrophic lateral sclerosis (ALS) patients. In 50-60% of ALS  
25 cases an increase of measured REE (mREE) in indirect calorimetry (IC) compared to cREE is  
26 found. The aims here were (i) to assess the accuracy of cREE assessed using 11 formulas as  
27 compared to mREE and (ii) to create (if necessary) a specific cREE formula for ALS patients.

28 Method: 315 Patients followed in the ALS expert center of Limoges between 1996 and 2014  
29 were included. mREE assessed with IC and cREE calculated with 11 predictive formulas  
30 (Harris Benedict (HB) 1919, HB 1984, WSchofield, De Lorenzo, Johnstone, Mifflin,  
31 WHO/FAO, Owen, Fleisch, Wang and Rosenbaum) were determined at the time of diagnosis.  
32 Fat free mass (FFM) and fat mass (FM) were measured with impedancemetry. A Bland and  
33 Altman analysis was carried out. The percentage of accurate prediction  $\pm 10\%$  of mREE, and  
34 intraclass correlation coefficients (ICC) were calculated. Using a derivation sample, a new  
35 REE formula was created using multiple linear regression according to sex, age, FFM and  
36 FM. Accuracy of this formula was assessed in a validation sample.

37 Results: ICC ranged between 0.60 and 0.71 (moderate agreement), and percentage of accurate  
38 prediction between 27.3% and 57.5%. Underestimation was found from 31.7% to 71.4% of  
39 cases. According to these unsatisfactory results we created an ALS-specific formula in a  
40 derivation sample (130 patients). ICC and percentage of accurate prediction increased in a  
41 validation sample (143 patients) to 0.85 (very good agreement) and 65.0% respectively, with  
42 17.5% underestimation.

43 Conclusion: REE formulas for HP underestimate REE in ALS patients compared to mREE.  
44 Our new ALS-specific formula produced better results than formulas for HP. This formula  
45 can be used to estimate REE in ALS patients if IC is not accessible.

46

47 **Keywords:** Amyotrophic lateral sclerosis, resting energy expenditure, predictive formula,  
48 indirect calorimetry, new formula.

49

50 **Highlight:**

51 REE formulas predict REE with accuracy in less than 58% of cases in ALS.

52 REE formulas underestimate REE in 32 to 71% of cases in ALS.

53 ALS-specific formula improves percentage of accurate prediction of REE in ALS.

54 ALS-specific formula decreases underestimation of REE in ALS.

55 ALS-specific formula can be used if indirect calorimetry is not accessible.

56

57 **Abbreviations**

58 ALS: amyotrophic lateral sclerosis

59 ALSFRS: amyotrophic lateral sclerosis functional rating scale

60 ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised

61 BIA: bioelectric impedance analysis

62 BMI: body mass index

63 CI: confidence interval

64 WHO/FAO: world health organization / food and agriculture organization of the United  
65 Nations.

66 FM: fat mass

67 FFM: free fat mass

68 HB: Harris and Benedict

69 IC: indirect calorimetry

70 IQR: interquartile range

71 Mifflin: Mifflin St. Jeor

72 PA: phase angle

73 cREE: calculated resting energy expenditure

74 mREE: measured resting energy expenditure

75 RQ: respiratory quotient

76 SD: standard deviation

77 TEE: total energy expenditure

78 TSF: triceps skin fold

79 WSchofield: World Schofield

80

81

## 82 **Introduction**

83 Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease affecting motor  
84 neurons, age at diagnosis is 65-70 years (1–4) and its incidence is stable at around 2/ 100 000  
85 person years in Western populations (5). The prognosis is severe, with a median survival in  
86 Europe of 25 to 30 months from onset (4).

87 ALS patients are at risk of malnutrition in the short and medium term (9-55% according to the  
88 literature) (1,6,7). Causes may include increased resting energy expenditure (REE) (7–12)  
89 which if not compensated by diet, may cause weight loss. REE may be measured (mREE)  
90 with indirect calorimetry (IC) (9,10,13–16),but because of the low availability of this high-  
91 cost apparatus, and the length of time necessary for each measurement ( $\geq 20$  min), predictive  
92 formulas have been developed to provide calculated REE (cREE). The most widely used is  
93 Harris and Benedict 1919 (HB1919) (9,10,13,14,16). The Mifflin St. Jeor (Mifflin) formula is  
94 also used (17,18). The difference between mREE and cREE allows for the definition of  
95 energy metabolism disorder. A difference between mREE and cREE of more than 10%  
96 defines hypermetabolism, which is found in 50-60% of ALS patients (7–10,19). REE may  
97 increase from +10 to +20% in these patients. For Sherman et al., HB 1919 is not valid when  
98 used to predict REE in ALS patients (16). Kasarskis et al. and Shimizu et al. recently created  
99 total energy expenditure (TEE) formulas for ALS patients using HB1919 and Mifflin  
100 formulas for REE prediction. These REE formulas were constructed for healthy people (20).  
101 Currently, no REE formulas are validated for ALS patients.

102 The objectives here were, in ALS patients: (i) to assess the accuracy of cREE calculated with  
103 11 predictive formulas, commonly used in healthy patients (HB 1919, HB 1984, World  
104 Schofield (WSchofield), De Lorenzo, Johnstone, Mifflin) (20) and used in ALS studies (HB  
105 1919, world health organization / food and agriculture organization of the United Nations  
106 (WHO/FAO), Owen, Fleisch, Wang, Rosenbaum, Mifflin) (9,10,17,21) as compared to

107 mREE assessed using IC, and; (ii) to create, if necessary a REE formula adapted to ALS  
108 patients and suitable for use in clinical practice without IC.

109

110 **Methods**

111 ALS patients followed in the ALS expert center in Limoges (France) from November 1996 to  
112 November 2014 with nutritional, neurological and respiratory assessments were included. The  
113 assessments were performed after diagnosis and then regularly until the patient died.  
114 Nutritional assessment included the use of indirect calorimetry to measure REE.

115

116 Inclusion criteria:

117 We included patients with ALS diagnosed according to Airlie House criteria (definite,  
118 probable, or laboratory-supported probable and possible) (22) and treated with riluzole.  
119 Patients could also have had ALS associated with frontotemporal dementia. The respiratory  
120 quotient (RQ) of patients by indirect calorimetry (IC) was required to be between 0.7 and  
121 0.87 (23). IC and the other nutritional assessments had to have been performed within 1.5  
122 months, and IC had to be performed no more than 12 months after diagnosis.

123

124 Data collection:

125 The data were extracted prospectively from the CleanWEB<sup>TM</sup> database of the ALS expert  
126 center, which has been validated by the Commission Nationale de l'Informatique et des  
127 Libertés (CNIL; No. 1244525). Patients gave given informed consent for data collection. The  
128 ClinicalTrial registration number is NCT03378375.

129

130 Nutritional assessments:

131 General data collected were: sex, date of diagnosis, date of calorimetry.

132 Nutritional assessment was carried out in the nutrition unit after diagnosis in the Nutrition  
133 Unit. Patients were weighed (to 0.1 kg) in underwear using a SECA<sup>®</sup> electronic balance  
134 (Vogel & Halke, Hamburg, Germany) in an upright position or on a SECA<sup>®</sup> weighing chair if

135 they could not stand upright. Usual weight 6 months before onset of symptoms was collected  
136 allowing the calculation of the percentage of initial weight loss relative to the usual weight.  
137 Their height (in m) was measured using a SECA<sup>®</sup> gauge recording to 0.2 cm (Vogel & Halke,  
138 Hamburg, Germany) in an upright position or using the Chumlea formulas for people over 60  
139 years who could not be verticalized (24). BMI (in kg / m<sup>2</sup>) was calculated using the formula:  
140  $BMI (kg / m^2) = weight (kg) / height * height (m^2)$ . The triceps skinfold (TSF) was obtained  
141 from the average of three measurements on each side with a Harpenden caliper (Baty  
142 International, Burgess Hill, UK) according to the usual modalities (25). Fat free mass (FFM in  
143 kg) and fat mass (FM in kg) were calculated with the validated formula for ALS patients  
144 using weight, TSF and total body impedance at 50 kHz in bioelectric impedance analysis  
145 (BIA) Analycor<sup>®</sup> (Eugédia, Chambly, France) in supine position after 5 min of rest (26). The  
146 impedancemetry also allowed for measurement of the phase angle (PA) marker of cellular  
147 function (27). Measured REE (mREE in kcal / 24h) by IC was obtained with the Quark  
148 RMR<sup>®</sup> with canopy (Cosmed, Rome, Italy) after a calibration of the instrument ( $\pm 0.02\%$  on  
149 measures of expired volumes of CO<sub>2</sub> and inspired volumes of O<sub>2</sub>) (23). It was performed in  
150 the morning after 12 hours of fasting, in a supine position and at rest. The patient was not  
151 physically active before the IC, and did not sleep during the exam or hyperventilate. The  
152 cREE was calculated (cREE in kcal / 24h) according to eleven predictive formulas (HB 1919,  
153 HB 1984, WSchofield, De Lorenzo, Johnstone, Mifflin, WHO/FAO, Owen, Fleisch, Wang  
154 and Rosenbaum) (Table 1). Formulas with results in kj (WSchofield, De Lorenzo and  
155 Johnstone) were converted into kcal by multiplying by 0.2388. The REE variation (bias in %)  
156 was calculated according to the formula:  $cREE (kcal / 24h) - mREE (kcal / 24h) / mREE (kcal$   
157  $/ 24h) * 100$ . The thresholds of accurate prediction of cREE compared to mREE is of  $\pm 10\%$ .  
158 Overestimation was  $> 10\%$  of measured value and underestimation was  $< 10\%$  of measured  
159 value (20).

160

161 Statistical analysis:

162 Statistical analysis was performed using SAS<sup>®</sup> software v9.3 (SAS Institute, Cary, North  
163 Carolina, USA) and GraphPad Prism 6.0 (GraphPad Software Inc, La Jolla, CA, USA). The  
164 threshold of significance for all statistical analyses was  $p < 0.05$ . We complied with the  
165 STROBE statement (28). Quantitative variables were expressed with the median (interquartile  
166 range [IQR]) or mean  $\pm$  standard deviation (SD). Qualitative variables were expressed in  
167 frequency and percentage. Normality of quantitative variables was studied using the Shapiro-  
168 Wilk test. Quantitative variables were compared using non-parametric Mann-Whitney test,  
169 and qualitative variables were compared using Chi<sup>2</sup>.

170

#### 171 Agreement between mREE and cREE

172 The REE variation (bias in %) was calculated according to the formula:  $cREE \text{ (kcal / 24h)} -$   
173  $mREE \text{ (kcal / 24h)} / mREE \text{ (kcal / 24h)} * 100$ . The threshold of accurate prediction of cREE  
174 compared to mREE was  $\pm 10\%$ . Overestimation is  $> 10\%$  of measured value and  
175 underestimation is  $< 10\%$  of measured value (29). The percentage of prediction between the  
176 95% limit of agreement ( $\pm 2$  SD) and the error risk were computed. The mean percentage  
177 difference between cREE and mREE (bias in kcal / 24h and %) was calculated.

178

#### 179 Formula derivation and validation

180 The entire sample was split at random into a derivation and a validation subsample. The  
181 construction of the formula for REE in ALS patients was based on the following steps using  
182 the derivation sample : (i) detection and elimination of outliers, decision based on the Cook's  
183 D influence statistics (threshold  $4/n$ ); (ii) simple linear regression analysis considering mREE  
184 as the dependent variable and the following independent variables : age, sex, height, weight,

185 FM, FFM and PA assessed using BIA; (iii) multiple linear regression analysis considering as  
186 independent variables those with a p-value <0.20 in the simple regression, the first model was  
187 simplified step by step, confounders were checked at each step; (iv) check of the linear nature  
188 of the relation between dependent and independent variables; (v) evaluation of the normality  
189 (using Shapiro-Wilk test and Kernel and qq plot graphs) and homoscedasticity (White test =  
190 0.42) of the residuals of the final model; (vi) check for any misspecification of the final model  
191 (vii) check for multicollinearity among independent variables included in the final model,  
192 (viii) check for interaction between independent variables.

193 Based on the coefficient of the multiple linear regression, REE was estimated in the validation  
194 sample. Assessment of the agreement between mREE and REE estimated by our equation was  
195 based on the above mentioned strategy.

196

197

198 **Results**

199 Study sample

200 From November 1996 to November 2014, 405 ALS patients had IC. Ninety patients were  
201 excluded: 35 for a RQ < 0.7 or > 0.87; 30 because the time lag between IC and nutritional  
202 assessment was over 1.5 months; and 25 because the delay between diagnosis and IC was  
203 over 12 months. The flowchart of patients included and not included is shown in Figure 1.

204 The 315 included patients had a median age at diagnosis of 65.9 years (56.5 - 73.7), with a  
205 sex ratio of 1.0. The median delay between diagnosis and nutritional assessment was 4.3  
206 months (2.2 – 6.6). The median mREE with IC was of 1503 kcal /24h (1290 - 1698). The  
207 nutritional, and neurological characteristics of the patients included are presented in Table 2.

208

209 cREE accuracy

210 The results of cREE prediction with the 11 REE formulas in the entire sample (n=315) are  
211 presented in Table 3. The analysis found moderate agreement between mREE and cREE, with  
212 an ICC range between 0.60 (-0.07 – 0.84) and 0.71 (0.54 – 0.81).

213 Figure 2 shows the Bland and Altman plots for the 11 formulas. With a threshold of  $\pm 10\%$   
214 difference between mREE and cREE, the proportion of accurate prediction ranged between  
215 27.3% and 57.5%. An underestimation of REE (REE variation < 10%) was found in 31.7% to  
216 71.4% of cases.

217 ALS-specific REE formula derivation and validation

218 Given these results (high percentage of underestimation of REE formula in ALS patients) we  
219 attempted to create a new formula. Some patients were excluded from the derivation and  
220 validation subsamples due to lack of BIA measurement and others were excluded from the  
221 derivation because they had been detected as outliers (hence their inclusion was not  
222 desirable). Both subsamples displayed a high level of comparability only with BMI, which

223 was slightly higher in the derivation sample compared to the validation sample: 24.8 kg/m<sup>2</sup>  
224 (22.3 – 27.7) vs. 23.6 kg/m<sup>2</sup> (21.8 – 26.5), respectively (p = 0.047) (Table 2).

225 After the simple linear regression analysis, age, sex, height, weight, FM, FFM and PA  
226 assessed using BIA were considered to enter the first multiple linear regression model (p-  
227 values <0.0001 for all these variables, except for FM: p = 0.0014). After a step by step  
228 simplification of the model, age, sex, FM and FFM were retained in the final model (p-values  
229 <0.0001 for all these variables, except for age: p = 0.004). The graphical evaluation of the  
230 linear nature of the relation between the dependent and the independent variables was  
231 satisfactory. The residuals of the model were considered as normally distributed (Shapiro  
232 Wilk test p = 0.58, satisfactory Kernel and qq plot graphs) and with a constant error variance  
233 (White test p = 0.42). The model was shown to be correctly specified, there was no  
234 multicollinearity or interaction between dependent variables.

235

236 The formula based on the coefficient of the model from the derivation sample (130 patients)  
237 appeared as follows:

238  $cREE \text{ (kcal/24h)} = 901.34 - (5.82 * \text{age [years]}) + (15.65 * \text{FFM [kg]}) + (8.88 * \text{FM [kg]})$   
239  $+145.21$  if men. The R-square of the model was 76%.

240

241 In the validation sample, our formula was compared to the 11 other REE formulas (Table 4)  
242 and to mREE; results were the same as for the entire sample. The ICC between mREE and  
243 REE estimated using our formula was 0.85 (0.79 – 0.89) (i.e. very good agreement) (Table 3).  
244 Figure 3 shows the Bland and Altman plots for the 11 formulas and our new formula in the  
245 validation sample. With the threshold of  $\pm 10\%$  of mREE, the percentage of accurate  
246 prediction was 65% (-347.7 to 304.4 kcal / 24h) with only 17.5% underestimation. Accurate  
247 prediction was significantly higher with our formula than eight of the other 11

248 formulas used, 45.5%, 49.7%, 49.0%, 51.7%, 34.3%, 26.6%, 30.1% and 43.4% for HB 1919,  
249 HB 1984, WSchofield, De Lorenzo, Johnstone, Mifflin, Wang and Rosenbaum, respectively  
250 ( $p = 0.0009$ ,  $p = 0.0085$ ,  $p = 0.006$ ,  $p = 0.023$ ,  $p < 0.0001$ ,  $p < 0.0001$ ,  $p < 0.0001$  and  $p =$   
251  $0.0002$  respectively). However, though lower than our formulas, accurate prediction was not  
252 significantly different with WHO/FAO, Owen and Fleisch (55.2%,  $p = 0.09$ , 56.6%,  $p = 0.15$   
253 and 55.9%,  $p = 0.12$ , respectively). Underestimation was significantly lower with our formula  
254 (17.5%) than the 11 formulas used 51.0%, 46.2%, 45.5%, 44.8%, 62.9%, 71.3%, 34.3%,  
255 33.6%, 39.9%, 66.6%, and 50.3% for HB 1919, HB 1984, WSchofield, De Lorenzo,  
256 Johnstone, Mifflin, WHO/FAO, Owen, Fleisch, Wang and Rosenbaum, respectively ( $p <$   
257  $0.0001$ ,  $p < 0.0001$ ,  $p < 0.0001$ ,  $p < 0.0001$ ,  $p < 0.0001$ ,  $p < 0.0001$ ,  $p = 0.001$ ,  $p = 0.002$ ,  $p <$   
258  $0.0001$ ,  $p < 0.0001$  and  $p < 0.0001$ , respectively).

259

260 **Discussion**

261 This study is the first to consider the accuracy of 11 REE formulas in a large sample of ALS  
262 patients (n=315), with the creation of an ALS-specific REE formula which was validated in  
263 an independent subsample.

264 Assessment of the level of REE in ALS patients is important as it helps to better match the  
265 diet to the metabolic disorders present in ALS. This allows to better adapt energy intake in  
266 case of hypermetabolism, which is found in 50-60% during this disease according to HB 1919  
267 to predict cREE (9,10). If this adjustment is not made, patients are exposed to weight loss and  
268 accelerated development of undernutrition, which is an important risk factor for death in ALS  
269 (1,3,6). In addition, better food intake could allow increased FM, which is a positively  
270 associated with survival (1). The reference measurement method for REE, indirect  
271 calorimetry, is often unavailable in clinical practice due to lack of equipment. Even if it is  
272 possible, it is still time consuming. For these reasons, reliable predictive formulas are  
273 important. HB 1919 formulas are frequently used to assess energy need in various diseases  
274 including ALS (9,10,16,17,21,30–33). Sherman et al. alone performed, in 2004, a Bland and  
275 Altman analysis to compare HB 1919 formulas with mREE in IC in a small sample of 34  
276 ALS patients with and without ventilation (16). HB 1919 are not adapted to predict REE of  
277 ALS patient. Other studies published focused on mREE and cREE are presented in Table 5.

278 In our study we found a mREE in IC of  $1514 \pm 283$  kcal / 24h in agreement with the literature  
279 (9,10,15,17). Sherman et al. reported slightly lower results in 16 non-ventilated patients (16).

280 This discrepancy may be due to differences in the IC apparatus used. Our study shows that, in  
281 a large population of ALS patients, the 11 predictive formulas used are not adapted to ALS  
282 patients. The main problem with these formulas is underestimation of the energy requirement  
283 in 31.7% to 71.4% of patients, with a real risk of inadequate energy intake, which can lead to  
284 weight loss and undernutrition. Reasons for this maladjustment are probably diverse. The

285 main issue is the absence of validation of these REE formulas in ALS patients with alteration  
286 of the body composition. Indeed, ALS, patients lose FFM and increase their FM (1,9,10). In  
287 addition, the numbers of ALS patients to whom these equations were applied were sometimes  
288 low, and patient characteristics may be very different (13,15,16). Given these difficulties, we  
289 created a new formula that allows for better prediction and less underestimation of REE in  
290 ALS patients. This formula integrates body composition data (FFM and FM) obtained with  
291 impedancemetry according to a validated method which is easy, fast and noninvasive for ALS  
292 patients (26). Moreover, body composition is a better reflection of nutritional status than  
293 weight and height used in several REE predictive formula. REE is therefore related to FFM.  
294 The recent ESPEN guidelines for ALS, propose to use HB 1919 equations to assess energy  
295 needs in the absence of IC (34). But because of the poor agreement of HB 1919 formulas in  
296 ALS, an ALS-specific formula seems necessary. In absence of IC, this new formula could be  
297 used easily in clinical practice to diagnose hypermetabolism at onset of the disease and to  
298 adapt energy needs in ALS during follow up.

299 However, there are several limitations to our study. Although the ALS referral center follows  
300 88.2% of ALS patients in our region, this population is not totally representative of patients  
301 in the region and country (2). There is therefore a selection bias. Moreover, it would be  
302 desirable to validate the new formula in a sample of ALS patients from another center and in  
303 a population-based setting if possible. This new formula found a poor REE prediction for  
304 35% of patients, suggesting that other elements determining REE of ALS patients were not  
305 taken into account ( $R^2$  of the model was 76%). These remain to be discovered (35), as it is  
306 known that neither the intensity of the fasciculations, smoking, nor any inflammatory or  
307 infectious condition is implicated (9,10,35). Cortical hyperexcitability could be related to  
308 metabolic dysfunction in ALS and could increase glucose metabolism in the brains of ALS  
309 patients (36,37). However, there is currently no recognised link between REE in indirect

310 calorimetry and brain hypermetabolism. It is therefore difficult to integrate this parameter into  
311 a REE predictive formula used in daily practice. We did not calculate the sample size a priori  
312 but verified that the power was sufficient given the size of the study. For example, the linear  
313 regression used for formula derivation was at least of 80% even considering an independent  
314 variable that would be weakly correlated to the dependent variable ( $r=0.25$ , e.g.).  
315

316 **Conclusion**

317 When REE formulas for healthy people are used in ALS patients, they provide an accurate  
318 prediction of REE ( $\pm 10\%$  of mREE) in less than 58% of cases, with a high level of  
319 underestimation up to 71% of cases. These formulas are not adapted to predict REE in ALS  
320 patients, and their use can lead to underestimation of energy need with weight loss and  
321 malnutrition, which are important prognosis factors in ALS. The creation of an ALS-specific  
322 REE formula using body composition allows prediction of REE in 65% of cases with only  
323 17.5% underestimation. Agreement between mREE and estimated REE using the formula was  
324 very good (0.85). This formula can therefore be used to predict REE in clinical practice in  
325 ALS patients if indirect calorimetry is not available. Validation in another independent  
326 sample of ALS patients is required.

327

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329

330 **Authors' contributions:**

331 PJ, PC, JCD and BM designed the research; PJ, PF, HS, GL, PC and JCD conducted the  
332 research; PJ, PF, MN, GL, PC and JCD provided essential materials (databases); PJ and BM  
333 performed statistical analysis; PJ, PF, PMP, PC, JCD, BM wrote the paper; PJ and BM had  
334 primary responsibility for the final content. All authors read and approved the final  
335 manuscript.

336

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339

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461 **Figure Legends:**

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

463 ALS: amyotrophic lateral sclerosis; BIA: body impedance analysis; n: number; RQ:  
464 respiratory quotient; REE: resting energy expenditure.

465

466 Figure 2: Bland and Altman graphics between calculated resting energy expenditure with the  
467 11 formulas and measured resting energy expenditure in the entire sample (n=315). Panel A:  
468 Harris and Benedict 1919, panel B: Harris and Benedict 1984, panel C: World Schofield,  
469 panel D: De Lorenzo, panel E: Johnstone, panel F: Mifflin St. Jeor, panel G: WHO/FAO  
470 (world health organization / food and agriculture organization of the United Nations), panel  
471 H: Owen, panel I: Fleisch, panel J: Wang and panel K: Rosenbaum.

472 REE: resting energy expenditure; SD: standard deviation

473

474 Figure 3: Bland and Altman graphics between calculated resting energy expenditure with the  
475 11 formulas and the constructed formula and measured resting energy expenditure in the  
476 validation sample (n=143). Panel A: Harris and Benedict 1919, panel B: Harris and Benedict  
477 1984, panel C: World Schofield, panel D: De Lorenzo, panel E: Johnstone, panel F: Mifflin  
478 St. Jeor, panel G: WHO/FAO (world health organization / food and agriculture organization  
479 of the United Nations), panel H: Owen, panel I: Fleisch, panel J: Wang, panel K: Rosenbaum  
480 and panel L: constructed formula.

481 REE: resting energy expenditure; SD: standard deviation

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

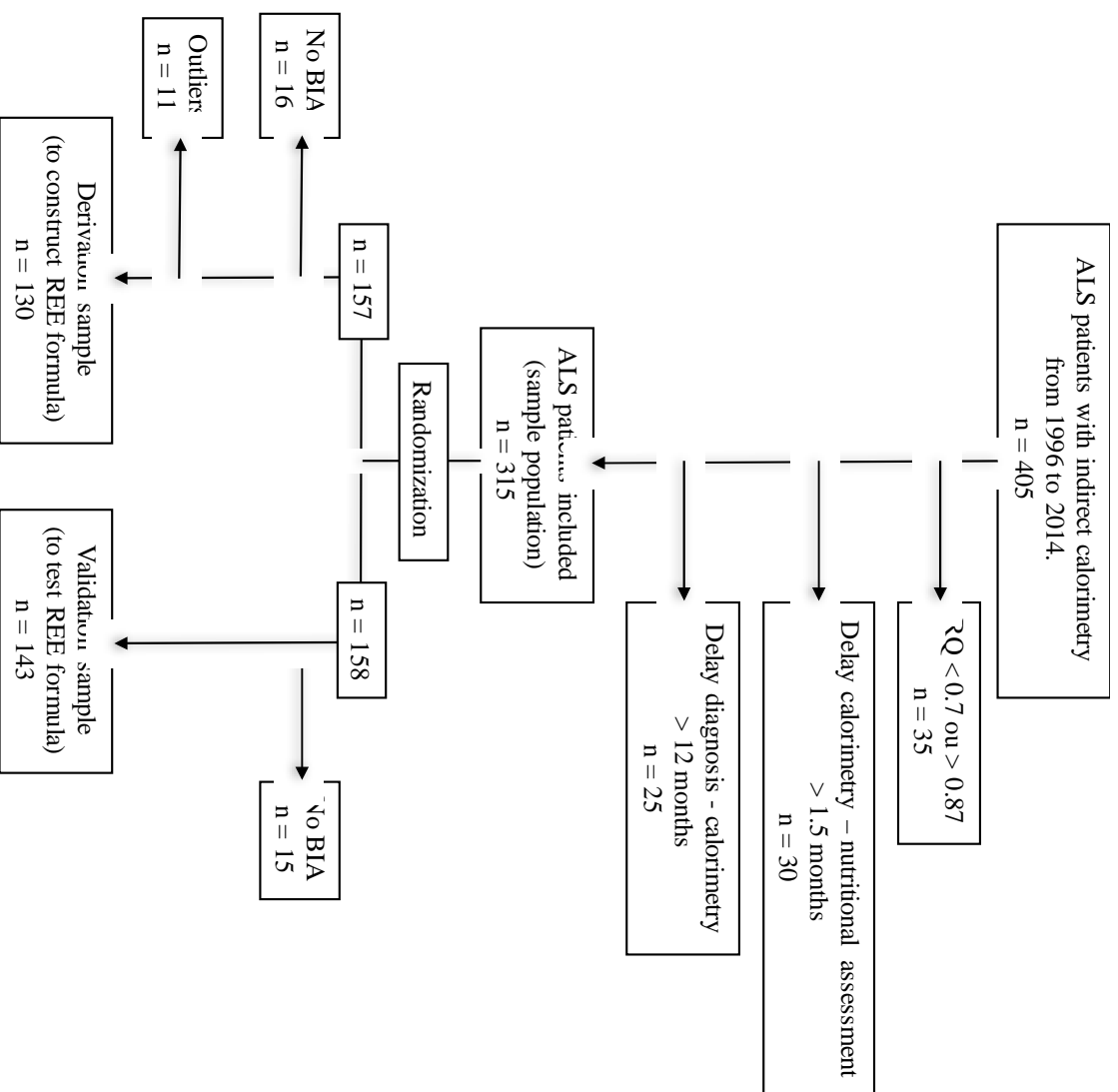


Figure 2: Bland and Altman graphics between calculated resting energy expenditure with the 11 formulas and measured resting energy expenditure in the entire sample (n=315).

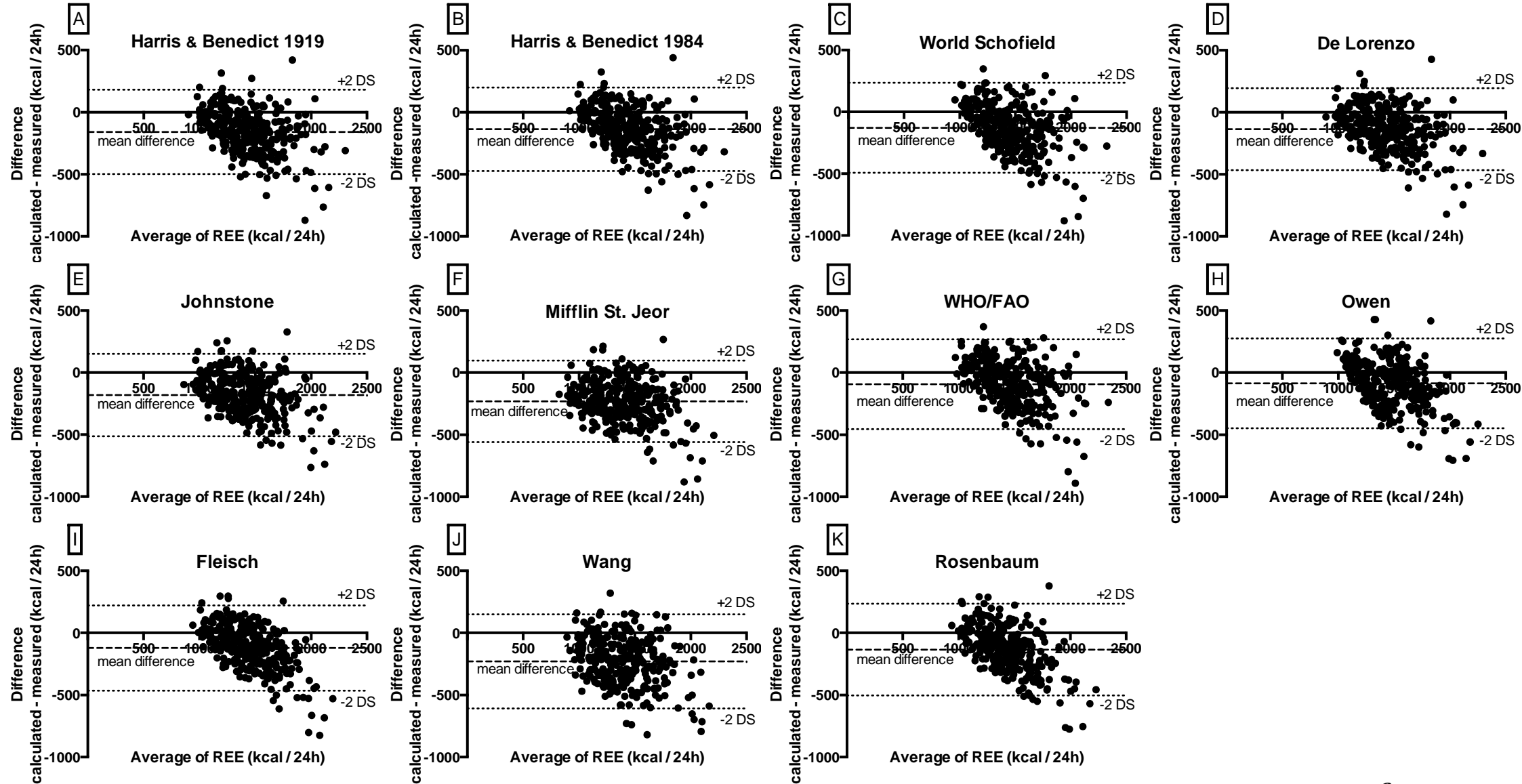


Figure 3: Bland and Altman graphics between calculated resting energy expenditure with the 11 formulas and the constructed formula and measured resting energy expenditure in the validation sample (n=143).

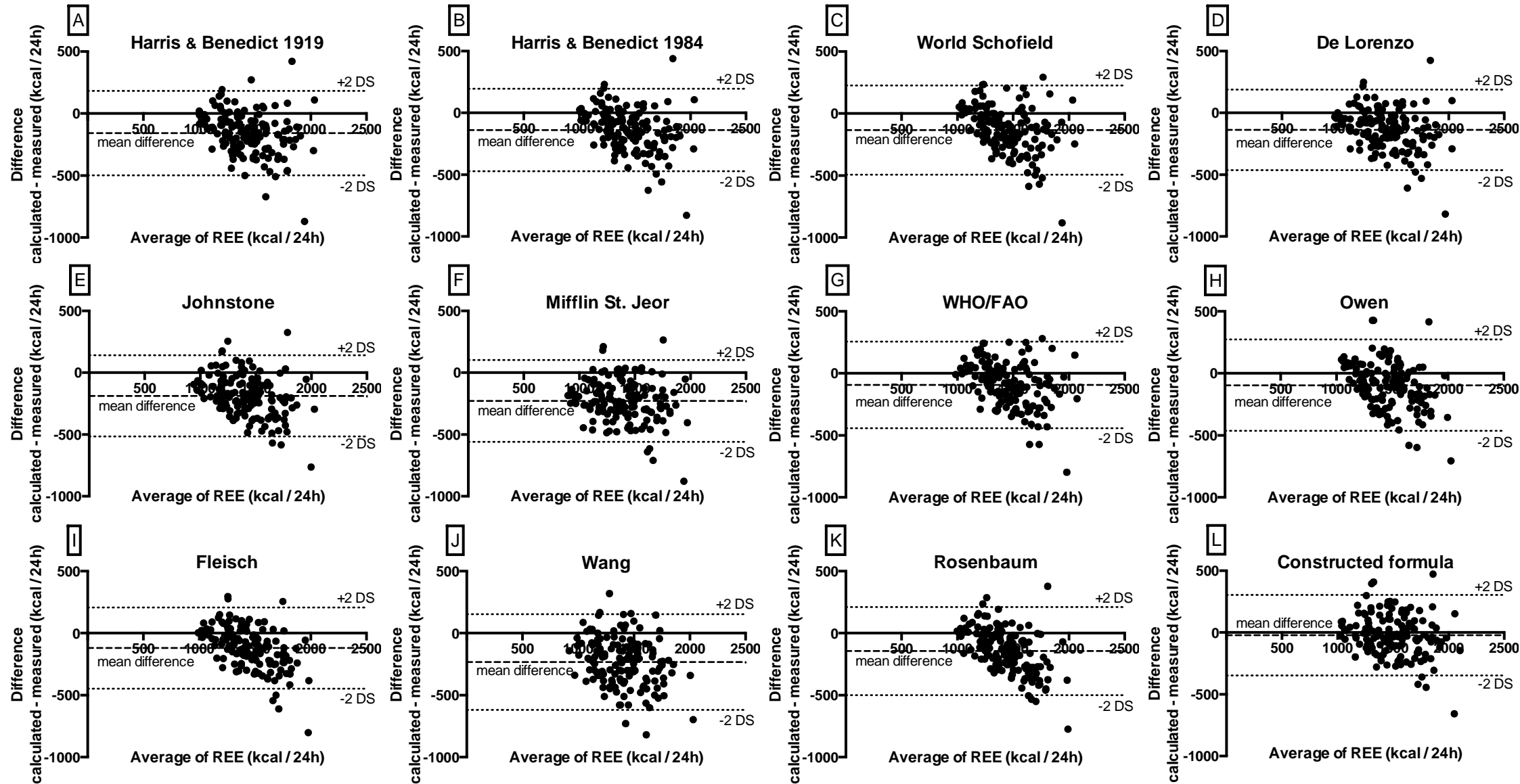


Table 1: Resting energy expenditure formulas tested and new formula constructed.

Harris & Benedict 1919 (38)	- Male: $(\text{Weight (kg)} * 13.7516) + (\text{Height (cm)} * 5.0033) - (\text{Age (years)} * 6.755) + 66.473$ - Female: $(\text{Weight (kg)} * 9.5634) + (\text{Height (cm)} * 1.8496) - (\text{Age (years)} * 4.6756) + 655.0955$
Harris & Benedict 1984 (39)	- Male: $(\text{Weight (kg)} * 13.397) + (\text{Height (cm)} * 4.799) - (\text{Age (years)} * 5.677) + 88.362$ - Female: $(\text{Weight (kg)} * 9.247) + (\text{Height (cm)} * 3.098) - (\text{Age (years)} * 4.33) + 477.593$
World Schofield(20)	- Male of 18 - 30 years: $(0.063 * \text{Weight (kg)}) + 2.896$ - Male of 30 - 60 years: $(0.048 * \text{Weight (kg)}) + 3.653$ - Male > 60 years: $(0.049 * \text{Weight (kg)}) + 2.459$ - Female of 18 - 30 years: $(0.062 * \text{Weight (kg)}) + 2.036$ - Female of 30 - 60 years: $(0.034 * \text{Weight (kg)}) + 3.538$ - Female > 60 years: $(0.038 * \text{Weight (kg)}) + 2.755$
De Lorenzo(20)	- Male: $(53.284 * \text{Weight (kg)}) + (20.957 * \text{Height (cm)}) - (23.859 * \text{Age (years)}) + 487$ - Female: $(46.322 * \text{Weight (kg)}) + (15.744 * \text{Height (cm)}) - (16.66 * \text{Age (years)}) + 944$
Johnstone (40)	$(90.2 * \text{FFM (kg)}) + (31.6 * \text{FM (kg)}) - (12.2 * \text{Age (years)}) + 1613$
Mifflin St. Jeor (41)	- Male: $(9.99 * \text{Weight (kg)}) + (6.2 * \text{Height (cm)}) - (4.92 * \text{Age (years)}) + 5$ - Female: $(9.99 * \text{Weight (kg)}) + (6.2 * \text{Height (cm)}) - (4.92 * \text{Age (years)}) - 161$

WHO/FAO (17)	<p>- Male of 18 - 30 years: <math>(15.4 * \text{Weight (kg)}) - (27 * \text{Height (cm)}) + 717</math></p> <p>- Male of 31 - 60 years: <math>(11.3 * \text{Weight (kg)}) + (16 * \text{Height (cm)}) + 901</math></p> <p>- Male of &gt; 60 years: <math>(8.8 * \text{Weight (kg)}) + (1128 * \text{Height (cm)}) - 1071</math></p> <p>- Female of 18 - 30 years: <math>(13.3 * \text{Weight (kg)}) + (334 * \text{Height (cm)}) + 35</math></p> <p>- Female of 31 - 60 years: <math>(8.7 * \text{Weight (kg)}) - (25 * \text{Height (cm)}) + 865</math></p> <p>- Female of &gt; 60 years: <math>(9.2 * \text{Weight (kg)}) + (637 * \text{Height (cm)}) - 302</math></p>
Owen (17)	<p>- Male: <math>879 + 10.2 * \text{Weight (kg)}</math></p> <p>- Female: <math>795 + 7.18 * \text{Weight (kg)}</math></p>
Fleisch (17)	<p>- Male: <math>24 * \text{BSA} * (38 - 0.073 * (\text{Age (years)} - 20))</math></p> <p>- Female: <math>24 * \text{BSA} * (35.5 - 0.064 * (\text{Age (years)} - 20))</math></p>
Wang (17)	$24.6 * \text{FFM (kg)} + 175$
Rosenbaum (17)	$(17.2 * \text{FFM (kg)}) + (10.5 * \text{FM (kg)}) + 375$
New formula	$901.34 - (5.82 * \text{Age (years)}) + (15.65 * \text{FFM}^\# (\text{kg})) + (8.88 * \text{FM}^\# (\text{kg})) + 145.21$ if men

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

<sup>#</sup> body composition measured in bioelectrical impedancemetry with Desport et al. validated formula (26).

Table 2: Nutritional characteristics of included patients.

Criteria	Entire sample Median (IQR) ; n (%) n = 315	MD	Derivation sample (to construct REE formula) Median (IQR) ; n (%) n = 130	Validation sample (to test REE formula) Median (IQR) ; n (%) n = 143	p
Age at diagnosis (years)	65.9 (56.5 – 73.7)	0	66.1 (56.5 – 73.9)	65.3 (56.4– 72.3)	0.48
Age at calorimetry (years)	66.6 (56.9– 74.1)	0	66.7 (56.9 – 74.3)	66.2 (57.0 – 73.5)	0.47
% male	161 (51.1)	0	65 (50.0)	72 (50.3)	0.95
ALSFRS-R (points)	40 (35 – 43)	24	36 (33 – 40)	34 (31 – 41)	0.23
Weight (kg)	65.0 (57.3 – 74.7)	0	64.3 (57.3 – 74.4)	65.0 (58.0 – 73.6)	0.91
BMI (kg / m <sup>2</sup> )	24.2 (22.0 – 27.6)	0	24.8 (22.3 – 27.7)	23.6 (21.8 – 26.5)	<b>0.047</b>
FFM (kg)	44.4 (36.9 – 51.9)	28	42.7 (36.2 – 51.9)	44.8 (37.1 – 51.5)	0.63
FM (kg)	20.7 (15.2 – 25.4)	28	21.0 (17.0 – 25.5)	19.9 (13.9– 24.6)	0.17
PA (°)	3.0 (2.4 – 3.7)	31	3.0 (2.4 – 3.6)	3.0 (2.4 – 3.7)	0.88
mREE (kcal / 24h)	1503 (1290 – 1698)	0	1455 (1266 – 1683)	1503 (1320 – 1678)	0.39
cREE HB1919 (kcal / 24h)	1327 (1190 – 1497)	0	1293 (1182 – 1480)	1327 (1190 – 1495)	0.58

cREE HB1984 (kcal / 24h)	1355 (1213 – 1511)	0	1338 (1215 – 1500)	1356 (1213 – 1489)	0.69
cREE WSchofield (kcal / 24h)	1350 (1217 – 1510)	0	1380 (1214 – 1500)	1345 (1230 – 1500)	0.95
cREE De Lorenzo (kcal / 24h)	1361 (1203 – 1528)	0	1346 (1191 – 1521)	1364 (1211 – 1503)	0.72
cREE Johnstone (kcal / 24h)	1317 (1158 – 1485)	28	1298 (1145 – 1481)	1326 (1161 – 1462)	0.73
cREE Mifflin (kcal / 24h)	1286 (1085 – 1453)	0	1289 (1055 – 1445)	1273 (1105 – 1438)	0.59
cREE WHO/FAO (kcal / 24h)	1378 (1256 – 1567)	0	1367 (1238 – 1553)	1385 (1275 – 1552)	0.55
cREE Owen (kcal / 24h)	1434 (1221 – 1610)	0	1435 (1221 – 1617)	1422 (1222 – 1577)	0.83
cREE Fleisch (kcal / 24h)	1392 (1242 – 1524)	0	1386 (1222 – 1520)	1386 (1259 – 1505)	0.59
cREE Wang (kcal / 24h)	1268 (1082 – 1451)	28	1226 (1065 – 1451)	1277 (1088 – 1441)	0.63
cREE Rosenbaum (kcal / 24h)	1362 (1232 – 1509)	28	1355 (1230 – 1514)	1369 (1233 – 1472)	0.89

BMI: body mass index; FFM: fat-free mass; FM: fat mass; HB: Harris & Benedict; IQR: interquartile range; Mifflin: Mifflin St. Jeor; PA: phase angle; mREE: measured resting energy expenditure; cREE: calculated resting energy expenditure; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield.

Table 3: Prediction of calculated resting energy expenditure with the 11 formulas compared to measured resting energy expenditure in the entire sample (n=315).

	REE		Bias		95% limits of agreement			ICC (95%CI)	Prediction		
	Mean (kcal/24h)	SD	C-M (kcal/24h)	%	From	to	% between limit		Accurate (± 10%) (%)	Under 10% (%)	Over 10% (%)
Measured REE	1514	298.7	-	-	-	-	-	-	-	-	-
cREE HB1919	1356	229.2	-158.4	-9.4	-498.2	181.5	94.9	0.67 (0.18 – 0.84)	45.1	51.7	3.2
cREE HB1984	1377	223.3	-136.8	-7.9	-473.1	199.6	95.2	0.70 (0.30 – 0.84)	49.8	45.4	4.8
cREE WSchofield	1385	215.3	-129.0	-7.1	-491.6	233.6	95.6	0.67 (0.35 – 0.81)	43.5	43.8	6.7
cREE De Lorenzo	1377	235.8	-136.9	-8.1	-467.0	193.1	95.9	0.71 (0.30 – 0.86)	50.2	45.4	4.4
cREE Johnstone	1332	236.8	-181.0	-11.1	-512.6	150.7	94.4	0.66 (0.06 – 0.85)	36.9	60.3	2.8
cREE Mifflin	1283	252.1	-231.5	-14.8	-560.3	97.4	95.6	0.60 (-0.07 – 0.84)	27.3	71.4	1.3
cREE WHO/FAO	1420	222.9	-94.2	-4.9	-456.0	267.7	96.2	0.71 (0.54 – 0.81)	54.9	33.7	11.4
cREE Owen	1428	218.7	-86.1	-4.3	-447.6	275.3	95.9	0.71 (0.57 – 0.80)	57.5	31.7	10.8
cREE Fleisch	1392	197.5	-122.4	-6.7	-465.2	220.4	94.9	0.68 (0.36 – 0.82)	54.0	40.0	6.0
cREE Wang	1284	245.7	-229.3	-14.3	-607.7	149.1	95.8	0.56 (-0.03 - 0.80)	32.1	65.5	2.4
cREE Rosenbaum	1378	196.9	-135.2	-7.4	-504.1	233.8	94.8	0.64 (0.30 - 0.79)	46.7	46.0	7.3

CI: confidence interval; C-M: calculated REE minus measured REE; HB: Harris & Benedict; ICC: intraclass correlation coefficients; IQR: interquartile range; Mifflin: Mifflin St. Jeor; PA: phase angle; REE: resting energy expenditure; cREE: calculated resting energy expenditure; SD: standard deviation; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield.

Table 4: Prediction of calculated resting energy expenditure with the 11 formulas and the constructed formula compared to measured resting energy expenditure in the validation sample (n = 143).

	REE		Bias		95% limits of agreement			ICC (95% CI)	Prediction		
	Mean (kcal/24 h)	SD	C-M (kcal/24h)	%	From	to	% between limits		Accurate (± 10%) (%)	Under 10% (%)	Over 10% (%)
Measured REE	1514	373.2	-	-	-	-	-	-	-	-	-
cREE HB1919	1356	222.2	-158.1	-9.6	-497.8	181.5	95.1	0.70 (0.20 – 0.86)	45.5*	51.0*	3.5*
cREE HB1984	1375	212.8	-139.3	-8.2	-473.4	194.8	95.1	0.72 (0.32 – 0.87)	49.7*	46.2*	4.2*
cREE WSchofield	1381	207.1	-133.7	-7.7	-493.1	225.7	97.2	0.69 (0.38 – 0.83)	49.0*	45.5*	5.6*
cREE De Lorenzo	1376	224.9	-138.4	-8.3	-465.0	188.2	95.1	0.74 (0.30 – 0.88)	51.7*	44.8*	4.9*
cREE Johnstone	1326	215.5	-187.9	-11.6	-516.5	140.7	95.1	0.70 (0.05 – 0.88)	34.3*	62.9*	2.8*
cREE Mifflin	1285	241.6	-229.4	-14.7	-561.2	102.4	95.1	0.62 (-0.07 – 0.86)	26.6*	71.3*	2.1*
cREE WHO/FAO	1421	213.2	-93.7	-5.1	-443.1	255.6	97.2	0.68 (0.48 – 0.80)	55.2	34.3*	10.5
cREE Owen	1418	206.9	-96.2	-5.1	-464.6	272.3	95.8	0.65 (0.45 – 0.77)	56.6	33.6*	9.8
cREE Fleisch	1398	189.0	-120.9	-6.8	-448.8	207.0	95.1	0.66 (0.31 – 0.81)	55.9	39.9*	4.2*

cREE Wang	1281	224.0	-233.5	-14.5	-618.9	151.8	95.8	0.48 (-0.06 – 0.75)	30.1*	66.6*	3.5*
cREE Rosenbaum	1369	178.0	-145.0	-8.2	-500.1	210.2	95.1	0.58 (0.17 – 0.77)	43.4*	50.3*	6.3*
cREE Constructed Formula	1492	236.3	-21.6	-0.5	-347.7	304.4	95.1	0.85 (0.79 – 0.89)	65.0	17.5	17.5

\*: comparison cREE CF vs other cREE formulas  $p < 0.05$

CI: confidence interval; C-M: calculated REE minus measured REE; HB: Harris & Benedict; ICC: intraclass correlation coefficients; IQR: interquartile range; Mifflin: Mifflin St. Jeor; PA: phase angle; REE: resting energy expenditure; cREE: calculated resting energy expenditure; SD: standard deviation; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield.

Table 5: Studies on patients with amyotrophic lateral sclerosis with measured and calculated resting energy expenditure and bias.

First autor /	Number of patients	Age (years)	Weight (kg)	FFM (kg)	Height (cm)	mREE (kcal / 24h)	cREE (kcal / 24h)	Bias (%)
years		Mean $\pm$ SD or median (IQR)	Mean $\pm$ SD or median (IQR)	Mean $\pm$ SD	Mean $\pm$ SD or median (IQR)	Mean $\pm$ SD or median (IQR)	Mean $\pm$ SD or median (IQR)	Mean $\pm$ SD or median (IQR)
Sherman et al. / 2004 (16)6	Ventilated: 18 Non ventilated: 16	67.2 $\pm$ 3.2 56.2 $\pm$ 14.5	70.6 $\pm$ 15.6 76.2 $\pm$ 26.6	- -	172.0 $\pm$ 10.0 169.6 $\pm$ 10.8	1654.9 $\pm$ 362.9 1340.8 $\pm$ 471.6	HB 1919: 1461.0 $\pm$ - HB 1919: 1505.0 $\pm$ -	-10.1 $\pm$ 17.6 18.6 $\pm$ 24.9
Desport et al. / 2005 (9)9	168	-	64.5 $\pm$ 13.9	43.8 $\pm$ 10.7*	162.5 $\pm$ -	1521.9 $\pm$ 307.5	HB 1919: 1334.0 $\pm$ 234.7	-12.3 $\pm$ - <sup>#</sup>
Bouteloup et al. / 2009 (10)0	61	64.3 $\pm$ 9.9	-	43.8 $\pm$ 11.6*	-	1449.0 $\pm$ 300.7	HB 1919: 1315.5 $\pm$ 242.2	-9.2 $\pm$ - <sup>#</sup>
Siirala et al. / 2010(21)4	Ventilated: 5	55 (50 – 76)	83 (58 – 98)	-	177 (155 – 192)	1060 (960 – 1480)	HB 1919: 1580 (1190 – 2020)	49.1 (-) <sup>#</sup> 56.2 (-) <sup>#</sup>

							WHO/FAO: 1656 (1374 – 2039)	46.9 (-) <sup>#</sup>
							Mifflin: 1557 (1399 – 1909)	62.8 (-) <sup>#</sup>
							Owen: 1726 (1183 – 1879)	53.8 (-) <sup>#</sup>
							Fleisch: 1630 (1210 – 1938)	
Kasarskis et al. / 2014	80	58.7 ± 11.9	80.1 ± 16.8	50.7 ± 11.1*	171.9 ± -	1539.0 ± 366.0	HB 1919: 1596.0 ± 283.0	3.7 ± - <sup>#</sup>
							Mifflin: 1523.0 ± 283.0	-1.0 ± - <sup>#</sup>
							Rosenbaum: 1508.0 ± 203.0	- 2.0 ± - <sup>#</sup>
							Wang: 1315.0 ± 264.0	- 14.6 ± - <sup>#</sup>
							Owen: 1589.0 ± 250.0	3.2 ± - <sup>#</sup>

<sup>#</sup> Bias not calculated in the study, a posteriori calculation with mean or median cREE and mREE.

FFM: fat-free mass (\*: in bioimpedance analysis); HB: Harris and Benedict; IQR: interquartile range; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; mREE: measured resting energy expenditure; cREE: calculated resting energy expenditure; SD: standard deviation; WHO/FAO: world health organization / food and agriculture organization of the United Nation.