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Original article

# Accuracy of predictive equations for the measurement of resting energy expenditure in older subjects

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*Background and aims:* The measurement of resting energy expenditure (REE) is important to assess individual total energy requirements in older subjects. The validity of REE prediction equations in this population has not been thoroughly evaluated and therefore the main aim of this analysis was to assess the accuracy of REE prediction equations in older subjects.
*Methods:* Weight, height and body mass index (BMI) were measured. REE was measured by indirect calorimetry (IC) in 68 older subjects (age: 60–94 years, M/F: 13/55, BMI: 26.3 ± 5.0 kg/m$^2$). Measured REE was compared to 14 equations for the calculation of REE estimates. In addition, two novel approaches (Aggregate model and meta-regression equations) for the prediction of REE were evaluated. Paired *t* test and Bland–Altman method were used to assess the agreement of the equations.
*Results:* The average measured REE was 1298 ± 264 kcal/day. The equation with the smallest bias was proposed by Muller (Bias ± 2SD = +3 ± 294 kcal/day) whereas the Mifflin equation was associated with the largest error (Bias ± 2SD = −172 ± 282 kcal/day). The Aggregate, Muller, Harris–Benedict and Fredrix equations were characterised by a prediction within ±10% of measured REE in more than 60% of subjects. Of the four algorithms, only the Aggregate equation did not show a significant association of the measurement bias with age, BMI and gender.
*Conclusions:* The Aggregate algorithm was characterised by a higher, overall accuracy for the prediction of REE in older subjects and its use should be advocated in older subjects. However, due to the large variability of the estimates, the measurement of REE by IC is still recommended for an accurate assessment of individual REE.


## 1. Introduction

The measurement of individual total energy expenditure (TEE) is a critical component of diagnostic protocols for the assessment of nutritional status. Resting energy expenditure (REE) contributes to approximately 70% of the TEE and therefore is routinely used as the primary step to define total energy requirements after accounting for physical activity energy expenditure (PAEE) and thermic effect of food (TEF).[1] REE can be precisely measured using indirect calorimetric systems but the instruments are expensive and, as a result, the measurements are still confined to specialised settings. Predictive equations based on demographic (age, sex, ethnicity), anthropometric (weight, height) and body composition variables (fat free mass, fat mass) have been developed over the last century to allow simple and rapid calculations of REE.

However, new prediction equations are continuously developed using a variety of socio-demographic factors (age, ethnicity, BMI, gender) as predictors and applied in different physiological states (growth, menopause, physical activity level) and disease processes (acute and chronic diseases). Therefore, the growing number of equations makes difficult the selection of a specific equation that will work well in different contexts.

Ageing-related changes in body composition and cellular energy metabolism influence total energy expenditure and its subcomponents. The decrease in REE is mainly related to the progressive, reciprocal changes in higher (fat-free mass (FFM),

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decrease) and less metabolically active (fat mass (FM), increase) tissues, which appears to be due to a reduction in organ mass and specific metabolic rates of individual tissues.[2] Hence, REE predictions equations validated in young populations may not be applicable to older subjects, particularly to the very old (>80 y). The applications of these equations may lead to an increased measurement error, inaccurate estimation of energy requirements and, particularly in frail older individuals, development of inadequate nutritional interventions to maintain an optimal nutritional status. Three prediction equations have been specifically developed in geriatric populations but the association of the measurement bias with age has not been evaluated. In addition, two novel approaches have been recently proposed. Wells et al.[3] developed an "Aggregate" approach based on the hypothesis that pooling together independent REE estimates derived from different algorithms would improve accuracy and reduce error variability. The Aggregate approach showed greater accuracy compared to other prediction equations in a population of young women but the accuracy of this approach has not been evaluated in older subjects. Secondly, a new array of 20 algorithms taking into account weight, age (young, old), gender (male, female) and ethnicity (White Caucasian, African American, Asian, Hispanics) has been derived from a meta-regression of 47 algorithms published in the literature.[4] Neemalat et al. have recently evaluated the accuracy of REE predictive equations in hospitalised malnourished older patients and reported a proportional bias of predictive equations, with overestimation of low REE values and underestimation of high REE values.[5] The accuracy of the REE algorithms has not been tested in an independent sample of non-hospitalised older subjects.

The main aim of this study was to evaluate the accuracy of established (Harris–Benedict,[6] Owen,[7] Mifflin,[8] Bernstein, Muller,[9] Fredrix,[10] WHO,[1] EU,[11] Luhrmann,[12] De Lorenzo,[13] Korth,[14] Schofield[15]) and novel equations (Aggregate[3] and meta-regression[4]) for the measurement of REE in older subjects. We have also evaluated whether the bias of each individual equation is influenced by age, gender and BMI.

## 2. Methods

### 2.1. Subjects

Subjects were recruited consecutively among patients who attended the International Center for the Assessment of Nutritional Status (ICANS, University of Milan) for body composition evaluation between 2009 and 2010. Eligible for the study were white Caucasian subjects of both genders fulfilling the following criteria: 1) age ≥60 years; 2) body mass index (BMI) ≤50 kg/m$^2$; 3) absence of significant cardiovascular or pulmonary diseases, uncontrolled metabolic disease (diabetes, anaemia or thyroid disease), cancer or inflammatory conditions, any use of drugs (corticosteroids, hormones, etc.) that might interfere with REE 4) absence of weight loss or gain (>5 kg) in the last year and 5) no treatment with special diets. All measurements were performed, in the same morning, in 84 subjects, including seven smokers, after an overnight fast. Sixteen subjects were excluded from the final analysis due to: 1) a respiratory quotient outside the expected physiological range (0.71–1.00) (11 subjects), BMI less than 18.0 kg/m$^2$ (3 subjects) and measured REE greater than ±3SD (2 subjects). Sixty-eight subjects (Male/Female: 13/55) were included in the final analysis. The higher prevalence of female subjects is representative of the higher number of female subjects attending our outpatient nutritional clinic. The study procedures were approved by the local Ethical Committee and all subjects gave informed consent. The STROBE statement for cross-sectional studies[16] has been adopted to provide detailed information on the study design and sample characteristics.

### 2.2. Measurements

#### 2.2.1. Anthropometry

Measurements were collected by the same operator, according to standardised procedures.[17] Body weight (WT, Kg) and Height (HT, cm) were measured to the nearest 0.1 kg and 0.5 cm, respectively. BMI was calculated using the formula: BMI (Kg/m$^2$) = WT (Kg)/HT$^2$ (m).

#### 2.2.2. Measured REE

An open-circuit ventilated-hood system indirect calorimetry was used (Sensor Medics 29, Anaheim, CA, USA). Resting $VO_2$ and $VCO_2$ measurements were taken in the early morning, after an overnight fast, under standardised conditions, with the person lying awake and emotionally undisturbed, completely at rest and comfortably supine on a bed, their head under a transparent ventilated canopy, in a thermally neutral environment (24–26 °C), and after at least 8 h of sleep. Respiratory gas samples were taken by a ventilated hood system, every minute for 30–40 min and the data collected during the first 5–10 min were discarded, as recommended by Isbell et al.[18] This allowed the subjects to acclimatize to the canopy and instrument noise. The calorimeter was calibrated daily before starting the tests, using a two-point calibration method based on two separate mixtures of known gas content. The flow rate was calibrated with a 3-liter syringe, according to the calorimeter manufacturer's instructions. The average of the last 20 min of measurements was used to determine 24 h REE according to standard abbreviated Weir equation.[19]

#### 2.2.3. Predicted REE

The measured REE was then compared to the following published REE prediction equations: 1) Harris–Benedict,[6] 2) Owen,[7] 3) Mifflin,[8] 4) Bernstein,[20] 5) World Health Organization (WHO),[21] 6) Fredrix,[10] 7) Livingston,[22] 8) Muller,[9] 9) Luhrmann,[12] 10) Schofield,[15] 11) European Community,[11] 12) Henry,[23] 13) Korth,[14] 14) De Lorenzo.[13] In addition two recent computational approaches based on meta-regression of data from 47 published studies and on the calculation of the Aggregate estimates of REE were also evaluated. The first approach[4] provides meta-regression equations with different independent factors, including those that only rely on a subset of easily measured covariates (weight, age, height, gender and race). This procedure incorporates the coefficients or slopes of previously developed equations into a single slope. The latter approach[3] is based on the assumption that the REE predictions are independent of one another; that the individual predictions are based on different underlying assumptions and that these independent predictions are then aggregated. Under these conditions, the error will not be correlated across the predictions, but will rather be randomly distributed across them and hence tend to cancel out, increasing the accuracy of the REE Aggregate prediction. The algorithm of each equation for the prediction of REE is reported in Table 1. The difference between measured and predicted REE (ΔREE) was expressed in absolute values (kcal/day, mean bias) and percentage (%, relative bias). Relative Bias (%) was calculated as: $(\Delta REE_{Mean\ Bias})/REE_{Measured}$ *100. A measurement was considered inaccurate when the relative bias was greater than ±10% of measured REE; the number of subjects with an inaccurate prediction was calculated together with the maximal overestimation (MOE) and maximal underestimation (MUE) for REE. The association between age, BMI and gender with REE estimates was evaluated to indicate whether these factors had a significant influence on the measurement bias.

#### 2.2.4. Statistical analysis

The data are reported as mean ± SD. The Bland–Altman method was used to evaluate the agreement between measured and

**Table 1**
Characteristics of equations for the prediction of resting energy expenditure (REE).

| | Characteristics | Prediction equation |
|---|---|---|
| $REE_{Harris-Benedict}$ | $N$ = 239 (136 M, 103 F)<br>Age = 29 ± 14 y | REE = 655 + 9.5*WT+1.9*HT − 4.7*AGE |
| $REE_{Owen}$ | $N$ = 104 (60 M, 44 F)<br>Age range = 18–82 y | M: REE = WT*10.2 + 879<br>F: REE = WT*7.18 + 795 |
| $REE_{Mifflin}$ | $N$ = 498 (251 M, 248 F)<br>$N$ = 264 normal weight (129 M, 135 F),<br>$N$ = 234 obese (122 M, 112 F)<br>Age range = 19–78 y, BMI = 17–42 kg/m$^2$ | REE = 9.99*WT+6.25* HT − 4.92*AGE + 166*SEX − 161 |
| $REE_{Bernstein}$ | $N$ = 202 (48 M, 154 F)<br>mean age = 40 y<br>mean BMI = 37 kg/m$^2$ | M: REE = 11.02*WT + 10.23*HT − 5.8*AGE − 1032<br>F: REE = 7.48*WT − 0.42*HT − 3*AGE + 844 |
| $REE_{Fredrix}$ | $N$ = 40 (18 M, 22 F)<br>mean age = 65±8 y<br>mean BMI = 25.9 ± 2.5 kg/m$^2$ | REE = 1641 + 10.7*WT − 9*AGE − 203*SEX |
| $REE_{Livingston}$ | $N$ = 655 (299 M, 356 F)<br>age range = 18–95 y<br>body weight range = 33–278 kg | M: REE = 293*WT$^{0.4330}$ − 5.92*AGE<br>F: REE = 248*WT$^{0.4356}$ − 5.09*AGE |
| $REE_{WHO}$ | Based on Schofield equation.<br>Large database including ~11,000 subjects. | M: $REE_{>60y}$ = 13.5*WT + 487<br>F: $REE_{>60y}$ = 10.5*WT + 596 |
| $REE_{Muller}$ | *Development*: $N$ = 2528 (1027 M, 1501 F)<br>*Cross validation*: 1046 (388 M, 658 F)<br>age 5–80 y<br>mean BMI = 27 kg/m$^2$ | REE = 0.047*WT − 0.01452*AGE + 1.009*SEX + 3.21 |
| $REE_{Luhrman}$ | 179 F (age = 67.8 ± 5.7 y, BMI = 26.4 ± 3.7 kg/m$^2$)<br>107 M (age = 66.9 ± 5.1 y, BMI = 26.3 ± 3.1 kg/m$^2$) | REE = 3169 + 50.0*BW − 15.3*AGE + 746*SEX |
| $REE_{Schofield}$ | Data from several populations including European,<br>North American and tropical countries<br>$N$ = 7173<br>Mean BMI range of studies: 21–24 kg/m$^2$ | M: $REE_{>60y}$ = 11.711*WT + 587.7<br>F: $REE_{>60y}$ = 9.082*WT + 658.5 |
| $REE^3_{EU}$ | These equations are based on the WHO and Schofield<br>equations except for the data on the two older groups<br>where selected data taken from Schofield have been<br>amplified by data collected on Scottish and<br>Italian elderly subjects | M: $REE_{60-74y}$ = 11.9*WT + 700<br>F: $REE_{60-74y}$ = 9.2*WT + 688<br>M: $REE_{\geq 75y}$ = 8.4*WT + 819<br>F: $REE_{\geq 75y}$ = 9.8*WT + 624 |
| $REE_{Henry}$ | $N$ = 10,552 (5794 M, 4702 F).<br>The data was obtained from 166<br>separate investigations. | M: $REE_{60-70y}$ = 13*WT + 567<br>F: $REE_{60-70y}$ 10.2*WT + 572<br>M: $REE_{>70y}$ = 13.7*WT + 481<br>F: $REE_{>70y}$ = 10*WT + 577 |
| $REE_{Korth}$ | $N$ = 104 (50 M, 54 F)<br>age range = 21–68 y<br>BMI range = 18–41 kg/m$^2$ | REE = 41.5*WT + 35.0*HT + 1107.4*SEX − 19.1*AGE − 1731.2 |
| $REE_{De\ Lorenzo}$ | $N$ = 320 (127 M, 193 F)<br>age range = 18–59 y<br>BMI range = 17–40 kg/m$^2$ | M: REE = 53.284*WT + 20.957*HT − 23.859*AGE + 487<br>F: REE = 46.322*WT + 15.744*HT − 16.66*AGE − 944 |
| $REE_{Meta\ Regression}$ | The analysis included 47 studies which contained detailed<br>information for development of meta-regression equations.<br>Utilising these studies, meta-equations were developed<br>targeted to 20 specific population groups. | BMR was estimated based on the most appropriate equation<br>after user-entry of individual age, race, gender and weight.<br>An online BMR prediction tool is available at: www.sdl.ise.vt.edu/tutorials.html |
| $REE_{Aggregate}$ | Based on model proposed by Wells et al. (ref). | Average of individual predicted REE of all algorithms included in the database |

N = number of subjects; M = male; F = female; BMI = body mass index; WT = weight (kg); HT = height (cm); SEX = Male = 1, Female = 1.
All algorithms calculate REE in kcal/day.

predicted REE.[24] The method entails the calculation of the mean bias and limits of agreements (±2SD) between measured REE and predicted REE. The paired $t$ test was used to determine the statistically significant differences between the measured and predicted REE estimates. Pearson's correlation was used to assess the association of predicted and measured REE and to evaluate whether age and BMI were significantly associated with mean bias. The analysis was stratified by age in order to evaluate between-gender differences in the accuracy of the different equations. SPSS 17.0 for Windows was used (IBM) to conduct the statistical analysis. Statistical significance was set at $p < 0.05$.

## 3. Results

Sixty-eight older aged men ($N = 13$) and women ($N = 55$) were included in the analysis for the assessment of accuracy of REE predictions. The mean age was 74.4 ± 9.3 years and the mean BMI was 26.3 ± 5.0 kg/m$^2$. The mean measured REE was 1298 ± 264 kcal/day (Table 2). REE was significantly higher in men than women (1654 ± 218 kcal/day vs 1214 ± 195 kcal/day, $p < 0.001$) but the differences were removed after adjustment for body weight (20 ± 3 kcal/day vs 20 ± 2 kcal/day, $p > 0.05$, respectively) (data not shown).

The absolute difference between predicted and measured REE (Table 3) showed that several equations[3,4,6–10,12,13,15,23] were characterised by a non-significant bias compared to measured REE. The Muller's[9] equation was associated with the smallest bias (Bias ± 2SD = +3 ± 294 kcal/day) whereas the Mifflin[8] equation was characterised by the largest bias (Bias ± 2SD = −172 ± 282 kcal/day, $p < 0.001$). However, all equations showed wide limits of agreements (±2SD) which ranged from 279 kcal/day (Fredrix[10]) to 345 kcal/day (Bernstein). The analysis of the relative bias (%) showed a similar agreement pattern and relative bias ranged from 0.01% (De Lorenzo) to −12.0% (Mifflin) (Fig. 1A). Four

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**Table 2**
Anthropometric characteristics and measured and predicted resting energy expenditure (REE) in 68 older subjects (F/M = 55/13).

| | Mean | SD | Min | Max |
|---|---|---|---|---|
| Age (years) | 74.4 | 9.3 | 60.0 | 94.0 |
| Height (m) | 158.4 | 10.3 | 138.0 | 184.0 |
| Weight (kg) | 66.4 | 15.7 | 44.3 | 115.0 |
| BMI (kg/m$^2$) | 26.3 | 5.0 | 18.1 | 48.1 |
| $REE_{IC}$ | 1297.9 | 264.2 | 756.0 | 1806.9 |
| $REE_{Harris-Benedict}$ | 1271.1 | 242.8 | 941.2 | 2116.0 |
| $REE_{Owen}$ | 1271.0 | 112.9 | 1113.1 | 1620.7 |
| $REE_{Mifflin}$ | 1126.8 | 223.7 | 756.2 | 1806.9 |
| $REE_{Bernstein}$ | 1184.1 | 131.1 | 979.5 | 1578.1 |
| $REE_{Fredrix}$ | 1314.4 | 266.4 | 899.4 | 2071.5 |
| $REE_{Livingston}$ | 1154.2 | 172.4 | 856.9 | 1620.1 |
| $REE_{WHO}$ | 1403.9 | 135.8 | 1212.6 | 1821.6 |
| $REE_{Muller}$ | 1301.9 | 257.9 | 969.9 | 2062.0 |
| $REE_{Luhrman}$ | 1281.4 | 199.4 | 975.9 | 1880.6 |
| $REE_{Schofield}$ | 1290.1 | 189.8 | 1060.8 | 1934.4 |
| $REE_{EU}$ | 1329.0 | 223.3 | 1058.1 | 2068.5 |
| $REE_{Henry}$ | 1289.9 | 231.0 | 1020.0 | 2062.2 |
| $REE_{Korth}$ | 1280.8 | 321.0 | 839.0 | 2222.9 |
| $REE_{De\ Lorenzo}$ | 1286.8 | 257.3 | 923.1 | 2117.6 |
| $REE_{Meta\text{-}Regression}$ | 1293.3 | 277.2 | 945.0 | 2092.0 |
| $REE_{Aggregate}$ | 1271.8 | 242.8 | 981.9 | 1934.3 |

BMI = Body Mass Index. F=Female. M = Male. IC = Indirect Calorimetry. WHO = World Health Organization. REE estimates are in kcal/day.

equations were characterised by a prediction within ±10% of measured REE in more than 60% of subjects, which include the Aggregate (63%), Muller (63%), Harris–Benedict (64%) and Fredrix (66%) algorithms (Fig. 1B). We explored the correlation between REE bias with age and BMI (Fig. 2A). Six equations showed a lack of differential bias. The Fredrix and Aggregate equations were the only two equations of the 4 equations with a higher accuracy that showed a non-significant association with age (Fredrix: $r = -0.05$; Aggregate: $r = 0.15$) and BMI (Fredrix: $r = 0.18$; Aggregate: $r = 0.06$). However, the REE prediction estimates of the Fredrix's equation were significantly influenced by gender since the mean bias was significant in men and not in women. The Aggregate equation was instead not significant in both men and women (Fig. 2B). The exclusion of the 6 active smokers from the analyses did not modify the results as the Fredrix and Aggregate equations were associated with the most accurate REE estimates (data not shown).

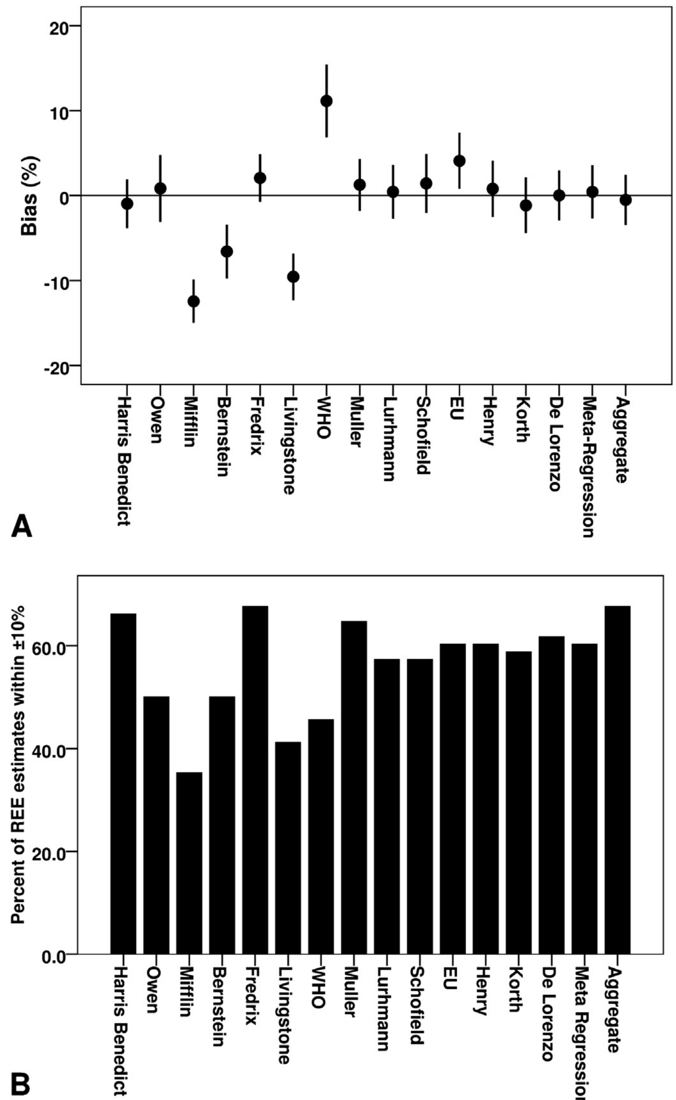


**Fig. 1.** Accuracy of prediction equations for the measurement of REE. A: Percent bias of Resting Energy Expenditure (REE) prediction equations compared to measured REE. Mean Relative Bias (%) was calculated as: $(\Delta REE_{Predicted})/REE_{Measured})$*100. Error bars are ±95% CI. B: Percent of REE estimates with a Mean Relative Bias (%) within ±10% of measured REE for each prediction equation.

**Table 3**
Calculation of mean absolute (kcal/day) and relative (%) differences (Δ) to test the accuracy of the prediction equations against measured Resting Energy Expenditure ($REE_{IC}$).

| | ΔREE kcal/day | ±2SD | MUE | MOE | r |
|---|---|---|---|---|---|
| $REE_{Harris-Benedict}$ | −26.7 | 282.4 | −387.1 | 311.6 | 0.85 |
| $REE_{Owen}$ | −26.0 | 383.9 | −439.3 | 453.0 | 0.76 |
| $REE_{Mifflin}$ | −171.5*** | 282.1 | −566.6 | 176.5 | 0.85 |
| $REE_{Bernstein}$ | −113.9*** | 345.0 | −494.4 | 306.2 | 0.82 |
| $REE_{Fredrix}$ | 16.5 | 279.3 | −380.0 | 317.3 | 0.86 |
| $REE_{Livingston}$ | −143.8*** | 309.6 | −489.3 | 233.0 | 0.82 |
| $REE_{WHO}$ | 105.2*** | 366.8 | −284.2 | 577.0 | 0.76 |
| $REE_{Muller}$ | 3.0 | 294.2 | −362.2 | 364.9 | 0.84 |
| $REE_{Luhrman}$ | −16.4 | 311.1 | −361.1 | 376.0 | 0.81 |
| $REE_{Schofield}$ | −7.2 | 314.5 | −292.8 | 432.5 | 0.81 |
| $REE_{EU}$ | 31.8 | 291.1 | −289.0 | 441.8 | 0.83 |
| $REE_{Henry}$ | −8.7 | 305.0 | −326.0 | 407.0 | 0.81 |
| $REE_{Korth}$ | −16.9 | 350.1 | −486.7 | 522.9 | 0.84 |
| $REE_{De\ Lorenzo}$ | −11.9 | 288.8 | −408.7 | 334.7 | 0.85 |
| $REE_{Meta\text{-}Regression}$ | −4.5 | 314.9 | −401.0 | 351.4 | 0.83 |
| $REE_{Aggregate}$ | −26.0 | 283.3 | −364.9 | 413.0 | 0.85 |

WHO = World Health Organization. ΔREE = $REE_{Predicted}$-$REE_{IC}$; MUE = Maximal ΔREE underestimation; MOE = Maximal ΔREE overestimation; $r$: coefficient of correlation.
Paired $t$-test was performed to detect significant differences between measured REE and predicted. $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.
All coefficients of correlation are statistically significant at $p < 0.001$.

## 4. Discussion

We have conducted a comprehensive analysis of anthro pometry-based prediction equations for the measurement of REE in older men and women. Several equations showed a non-significant absolute (kcal/day) and relative (%) measurement bias compared to measured REE. However, more detailed analyses of their predictive accuracy identified four equations as being associated with a higher accuracy, calculated as the number of REE estimates within a ±10% level of accuracy. The prediction of REE using the Fredrix and the Aggregate equations was independent of age and BMI but Fredrix's REE estimates were influenced by gender.

This analysis has included anthropometric algorithms frequently applied in clinical practice and cross-validated in

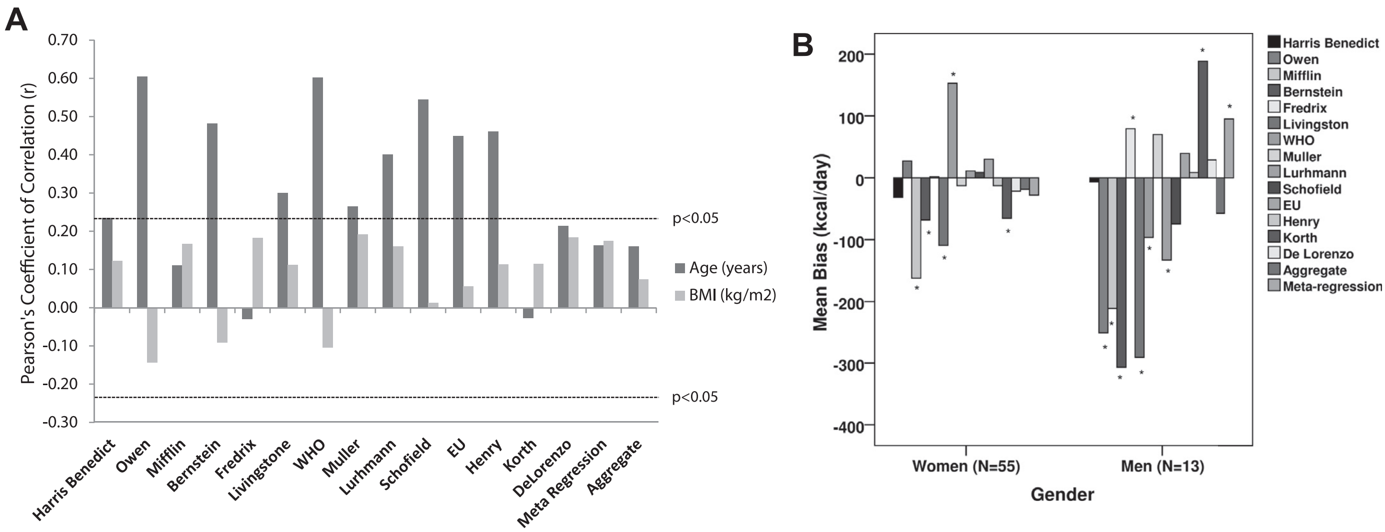


**Fig. 2.** Association of REE measurement bias with age, gender and BMI. A: Correlation between Mean Relative Bias (%) with age and Body Mass Index (BMI) is showed for each prediction equation. Dotted lines indicate threshold for statistical significance of the associations ($r = 0.23$, $n = 68$). The results did not change when absolute mean bias was included in the analyses (results not shown). B: Description of the differences between predicted and measured REE (mean bias) in men and women. The asterisks (*) indicate a significant difference ($p < 0.05$) of predicted REE compared to measured REE (paired *t* test).

previous research studies. In addition, we have included in our analyses prediction equations that were: 1) derived in older subjects; 2) included older subjects in the original sample and 3) frequently applied equations in clinical practice and validation studies. An important limitation of several predictive equations which question their applicability in older aged subjects is related to the small number of older subjects (60 y+) in the validation samples (for example the Harris–Benedict[6] sample included only 9 subjects over 60 years of age).

The first two equations specifically validated for the prediction of REE in older subjects were proposed by Arciero[25,26] and Fredrix.[10] However, the former was not included in this analysis since the formula included parameters (chest skinfold and a measure of leisure physical activity) that were not measured in this study. The latter has been consistently identified in previous validation studies as one of the most accurate equations for the REE prediction in older subjects. A limitation of Fredrix's[10] equation is the very small sample size ($n = 40$) and the age range (age: 51–82 y) which may introduce some reservations in regards to the statistical robustness of the equation and the applicability in the oldest old, respectively. More recently, Luhrmann et al.[12] has validated a new equation in older aged subjects. The study included a large sample size ($n = 286$) and was characterised by an age range between 60 and 85 years old. To our knowledge, this is the first study to externally validate the performance of the Luhrmann's equation in older aged subjects.

The Aggregate[3] approach pools the prediction estimates of several equations under the assumption that each independent REE prediction contributes to minimise the prediction error. Wells et al.[3] validated this approach in a population of young women by reporting a greater accuracy and less variability of the Aggregate approach compared to other REE equations. The results have been essentially confirmed in this analysis since the Aggregate approach was consistently associated with less variability, higher proportion of accurate measurements (within ±10% of measured REE) and age, BMI and gender-independent measurement bias. The Fredrix's[10] equation was the only other equation that had a similar performance in our sample.

This study has followed a rigorous, phased analytical plan to identify the various components contributing to the ascertainment of the accuracy of a prediction equation. The application of a simple paired *t* test showed that several equations were associated with a non-significant measurement bias. However, the results of the *t* test can be misleading as they are based on the average of the estimates and a small measurement bias could be simply the result of large opposite errors counterbalancing each other. This scenario essentially justifies the application of other methods such as the Bland–Altman method[24] (differential bias association with mean REE and calculation of limits of agreements of the measurement bias (±2SD)) and the calculation of the proportion of predictive estimates within ±10% of measured REE. Using this approach we were able to identify four accurate equations and we had not anticipated the presence in this group of the Harris–Benedict[6] equation together with the Muller,[9] Fredrix[10] and Aggregate[3] algorithms. The accuracy of the Harris–Benedict equation in older aged subjects has been previously reported in two other studies. Taaffe[27] showed that the mean measurement bias of the Harris–Benedict equation was about 116 kcal/day in older women. In healthy subjects over 70 years of age the Harris–Benedict showed the lowest mean measurement (−40.9 kcal/day) and the highest predictive accuracy having 72.4% of the cases within ±10% of measured REE. The final step of the analysis plan was to evaluate the absence of a differential measurement bias associated with age, BMI and gender. These analyses identified the Aggregate equations as the most accurate in our population since there was no evidence of a significant interaction with the aforementioned, potential confounding factors.

This analysis is the most comprehensive assessment of the accuracy of recognised REE prediction equations in older aged subjects. Additional strengths are the examination of the validity of two recently proposed algorithms for the REE prediction (Aggregate[3] and Meta-Regression[4]) and the inclusion of 22 subjects over 80 years of age. The validity of prediction equations in the very old (aged 70–98 y) was tested in 116 healthy Caucasian subjects. Unexpectedly the Harris–Benedict[6] was more accurate than the Luhrmann's[12] equation whereas a poor accuracy was reported for the Owen'[7] and Mifflin's[8] equations, which has been replicated in our analysis.

The results overall have shown that the performance of the equations, including the Aggregate algorithm, is relatively modest as they were collectively able to provide predictions within ±10% of measured REE in about 65% of subjects. The limits of agreement of the estimates were also wide (range: 279–350 kcal/day), which has clear implications for the measurement of individual REE. This prompts again the canonical recommendation provided in the conclusions of the majority of previous studies, which essentially advocated for the direct measurement of energy expenditure by indirect calorimetry.

By definition, each published equation performed well in the population in which it was derived, but it may not necessarily perform well in other population. In the present study, the Fredrix equation performed well, but we cannot be sure whether this finding would generalise across other elderly populations. In contrast, the ability of the Aggregate approach to reduce error by randomising it across multiple equations indicates that this approach is expected to generalise across populations more successfully. Therefore, we recommend the Aggregate approach as the best option.

Resting energy expenditure accounts for most of TEE but a large variability in the contribution to TEE measurement in older aged subjects can be also attributed to PAEE. This could not be explored in this analysis but it provides the opportunity to discuss the approaches currently used for the prediction of total energy requirements.[28] Resting energy expenditure is an integral component of the factorial method to estimate TEE but it is associated with limitations in the assessment of both components (REE and PAEE). Goran[28] has proposed that a regression approach for TEE could improve accuracy as well as it could be more evidence based, easier to apply and more statistically and physiologically more appropriate. Prediction equations based on body composition measures were essentially excluded for two main reasons: 1) anthropometric equations are more easily applied in clinical practice and 2) a previous study reported the poor performance of a FFM-derived prediction equation[29] in older aged subjects. However, it is possible that inclusion of equations based on predicted FFM or indices of the fat/FFM ratio might improve the overall Aggregate approach.

## 5. Conclusions

The Aggregate[3] and Fredrix's[10] equations appear to be the most accurate equations in older subjects. However, the REE estimates are still characterised by a large variability and their use should be limited to measurement of REE at group level and when direct measurement in not possible at individual level. Advanced statistical modelling techniques may help to refine the Aggregate approach and offers scope to improve the prediction of REE at individual level.

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## Statement of authorship

MS analysed the data and wrote the manuscript. SB and AB contributed to the collection of the data and to the critical revision of the manuscript. JCW and JL contributed to the interpretation of the results and to the critical revision of the manuscript. CF and AT contributed to the design of the study and to the critical revision of the manuscript.

## Conflicts of interest

None.

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