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Original article

Resting energy expenditure in children with cerebral palsy: Accuracy of available prediction formulae and development of a population-specific formula

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SUMMARY

Background and aims: Energy requirements are difficult to estimate in children with cerebral palsy (CP). Resting energy expenditure (REE), necessary for personalized nutritional intervention, is most commonly estimated using prediction formulae because the reference method, i.e. indirect calorimetry (IC), is not available in all Nutrition Units. The main aim of the present study was to evaluate the accuracy of the most commonly used REE prediction formulae in children with CP. The secondary aim was to develop a new population-specific formula for the estimation of REE in children with CP.

Methods: REE was measured by IC in 54 children and adolescents with spastic quadriplegic cerebral palsy (SQCP) and estimated from the five most commonly used prediction formulae, i.e. the World Health Organization (WHO), Harris–Benedict, Schofield weight, Schofield weight & height, and Oxford formulae.

Results: The mean (standard deviation, SD) difference between the estimated and measured REE was 64 (238) kcal/day for the WHO formula, 79 (226) kcal/day for the Schofield weight formula, 79 (223) kcal/day for the Schofield weight and height formula, 55 (226) kcal/day for the Oxford formula, 37 (224) kcal/day for the Harris–Benedict formula and 0 (213) kcal/day for the purposely developed population-specific formula. Owing to the large SD of the bias, none of these formulae can be reliably applied at the individual level to estimate REE.

Conclusions: The most commonly used REE prediction formulas are inaccurate at both the population and individual level in children with SQCP. A purposely developed population-specific formula, despite being accurate at the population level, does not perform better than the most commonly used REE formulae at the individual level.

1. Introduction

Malnutrition is highly prevalent among children with cerebral palsy (CP), ranging from to 46%–90% [1]. In children with CP, both under- and over-nutrition have a negative impact on linear growth, peripheral circulation, wound healing, spasticity, irritability, and respiratory and gastro-intestinal functions, with increased morbidity and reduced quality of life.

Abbreviations: BC, body composition; CCF, classification fraction; CP, cerebral palsy; EE, energy expenditure; FFM, fat-free mass; IC, indirect calorimetry; REE, resting energy expenditure; RQ, respiratory quotient; SD, standard deviation; SQCP, spastic quadriplegic cerebral palsy; TEE, total energy expenditure; TSF, triceps skinfold; WHO, World Health Organization.

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Energy requirements are difficult to evaluate in children with CP. The estimation of resting energy expenditure (REE), necessary for the calculation of total energy expenditure (TEE), is the first step towards a personalized nutritional intervention [2,3]. Indirect calorimetry (IC) is the reference method for the measurement of REE but its cost and the need of specialized personnel impede its widespread use. REE is thus commonly estimated using prediction formulae [4] developed in the general population and not specific for ill children such as those with CP. Children with CP are indeed expected to have different energy requirements compared to healthy children not only because of lower activity and reduced food intake but also because of different muscle tone and body composition.

Few studies are available on energy expenditure (EE) in children with CP. Stallings et al. compared the EE of 61 CP children and adolescents with that of 37 healthy peers [5]. In that study, CP children with low fat stores had a lower REE adjusted for fat-free mass (FFM) compared to CP children and healthy children with adequate fat stores. TEE, evaluated in a subsample of children, was lower in the CP group than in the control group. The TEE to REE ratio, representing energy for non-basal needs, was significantly lower in CP than in control children and the adequately nourished CP children had lower TEE to REE ratios than the malnourished ones. Azcue et al. [6] evaluated the relationship between REE and body composition in 13 children with spastic quadriplegic cerebral palsy (SQCP) compared to 21 healthy controls. In that study, REE was measured with IC, fat mass estimated from skinfolds, total body water measured by isotope dilution, and extracellular water estimated by bioelectrical impedance analysis. REE was significantly lower in SQCP than in control children and was overestimated by the WHO equations. There was also a poor association between REE and weight and height in both SQCP and control children and between REE and the estimated body cell mass among SQCP children. In an interventional study, Gracìa-Contreras et al. showed that TEE and REE were higher in 57 healthy children compared to 13 CP children when expressed in kcal/day and in kcal/cm height/day and lower when expressed in kcal/kg weight/day [7]. Moreover, intensive nutritional support for four weeks produced a significant increase in energy expenditure in children with CP. Gale et al. measured REE using IC in 16 hospitalized ventilated CP children and adolescents [8]. The REE of the CP patients was 46% lower than the estimated REE and the patients received on average 32% more energy than that suggested by REE measurement. Koehler et al. assessed the validity of the SenseWear Armband vs. IC in 10 CP adolescents at rest and during a treadmill session [9]. The SenseWear Armband was found to give similar results similar to those of IC.

None of the above-mentioned studies aimed at evaluating the accuracy of the most commonly used predictive formulae to estimate REE in CP children and none has attempted to develop a population specific formula. The aims of the present study were therefore: 1) to evaluate the accuracy of the five most commonly used REE prediction formulae, i.e. the WHO [4], Harris-Benedict [4], Schofield weight [10], Schofield weight & height [10] and Oxford [11] formulae; 2) to develop a REE population-specific formula for CP children.

2. Materials and methods

2.1. Study patients

From 01 September 2016 to 30 September 2017, 54 SQCP patients aged 6–18 years were consecutively studied at the Outpatient Nutrition Clinic of the “V. Buzzi” Children's Hospital (Milan, Italy). Written informed consent for participation into the study was obtained from the parents or legal guardians of the patients of from the patients themselves when aged 18 years.

2.2. Nutritional assessment

Weight, length (children < 2 years of age) and triceps skinfold (TSF) were measured following international guidelines [12]. Weight was measured using a wheelchair scale (Soehnle 7808 digital multifunction scale). Height (children $\geq$ 2 years) was estimated from knee height [13]. TSF was measured using a skinfold caliper (GIMA, Italy) on the non-dominant or less asymmetrical side of the body. Body mass index (BMI) was calculated as weight (kg)/length or height $(m)^2$. Standard deviation scores (SDS) of weight, length, height, weight-for-length, weight-for-height, BMI and TSF were calculated using the WHO reference data [14,15]. REE was estimated using the following formulae: WHO [4], Harris-Benedict [4], Schofield weight [10], Schofield weight and height [10], and Oxford [11].

2.3. Indirect calorimetry

REE was measured in a silent and thermo-neutral room using an open-circuit indirect calorimeter (Vmax 29, Sensor Medics, Yorba Linda, CA) in subjects fasting from at least 12 h. All subjects were spontaneously breathing. A canopy was positioned around the patient's head and the expired air was drawn from the hood at a fixed rate [16]. Steady state was defined as at least 5 min with <5% variation in respiratory quotient (RQ), <10% variation in oxygen consumption, and <10% variation in minute ventilation [17]. After the steady state was reached, the REE measurement was performed for at least 20 min. REE was obtained from oxygen uptake and carbon dioxide output using Weir's equation [18].

2.4. Statistical analysis

Most continuous variables were not Gaussian-distributed and all are reported as median and interquartile range (IQR). Discrete variables are reported as the number and proportion of subjects with the characteristic of interest. Bland-Altman plots of the bias (estimated REE − measured REE) versus the average [(estimated REE − measured REE)/2] and of the percent bias [(estimated REE − measured REE)/measured REE] versus the average were used to evaluate the presence of proportional bias [19,20]. The association between the bias and the average was evaluated using the Pearson product-moment correlation coefficient [19,20]. Because proportional bias was detected in all cases, the Bland–Altman limits of agreement were not calculated [21]. The absolute bias was Gaussian-distributed, as determined by using kernel density plots and the Shapiro–Wilk test. The comparison of the measured and estimated values of REE was performed using Student's t-test for paired data. The percent bias was not Gaussian-distributed. We evaluated the contribution of weight and height to REE using two pre-specified linear regression models. The response variable of both models was REE. The first model had weight or height as predictor and the second model added age (continuous) and gender (discrete; male = 1; female = 0) as predictors. Not surprisingly for growing children, weight and height were collinear so that they were not evaluated in the same model. Standard diagnostic plots were used to evaluate model fit [22]. The adjusted coefficient of determination (R^2_{adj}) and the root mean squared error of the estimate (RMSE) were used as measures of model fit. The 95% confidence intervals of the regression coefficients, R^2_{adj} and RMSE were calculated using bootstrap on 1000 random samples of 54 subjects [23]. The bootstrap offers an efficient way of correcting for over-optimism and is presently considered the best method for

performing internal cross-validation. The correct classification fraction (CCF) of an equation was defined as the fraction of subjects whose estimated REE was within 10% of measured REE [24]. Statistical analysis was performed using Stata 15.1 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Anthropometric and metabolic status of the children

54 consecutive SQCP children (17 girls, 31%) were consecutively studied. Their anthropometric and metabolic measurements are given in Table 1.

WHO SDS could be calculated for the following intervals of age and anthropometric dimensions: 1) weight-for-age from age 0–10 years; 2) height-for-age from age 2–18 years; 3) BMI for-age from age 2–18 years; 4) arm circumference-for-age from age 0.25–5 years; 5) triceps skinfold-for-age from age 0.25–5 years. The median weight for age was −2.09 SDS (1.8th percentile), the median length for age was −2.21 (1.4th percentile) and the median BMI for age was −1.96 (2.5th percentile). The number of children with weight-for-age, length- or height-for-age, and BMI-for age under the 5th percentile (<−1.644 SDS) was 26%, 48% and 54% respectively. The median (IQR) REE was 876 (699; 1229) kcal/day, corresponding to 40 (32; 50) kcal per kg of weight. The REE of our children is thus comparable to that of a recently studied population of hospitalized Italian children [25].

3.2. Accuracy of the prediction formulae

Table 2 gives the absolute and percent bias of the evaluated prediction formulae and of the population-specific formula (see below for the development of the population-specific formula).

The absolute bias was calculated as (estimated resting energy expenditure − measured resting energy expenditure). The absolute bias was Gaussian-distributed and Student *t*-test for paired data was used to compare estimated and measured values. The percent bias was calculated as [(estimated resting energy expenditure − measured resting energy expenditure)/measured energy expenditure)] and was not Gaussian-distributed.

Table 1
Anthropometric and metabolic measurements of the children.

	N	Median (IQR) or n (%)
Age	54	11 (7; 14)
Baclofen	54	23 (43%)
Nutrition	54	
Enteral or mixed		22 (39%)
Enteral PEG		15
Enteral PEGJ		2
Mixed PEG		3
Mixed PEGJ		1
Oral		33 (61%)
Weight (kg)	54	22.3 (16.8; 27.5)
Weight-for-age (SDS WHO)	24	−2.09 (−3.08; −1.14)
Height (m)	54	1.25 (1.15; 1.42)
Height-for-age (SDS WHO)	51	−2.21 (−3.36; −1.62)
BMI kg/m^2	54	14.2 (12.3; 16.3)
BMI-for-age (SDS WHO)	51	−1.96 (−3.82; −0.78)
Triceps skinfold thickness (mm)	51	8 (6; 10)
Triceps skinfold-for-age (SDS WHO)	3	−0.12 (−2.00; 0.60)
Arm circumference (cm)	52	19.0 (16.0; 20.8)
Arm circumference-for-age (SDS WHO)	4	0.40 (−0.56; 1.25)
Resting energy expenditure (kcal/day)	54	876 (699; 1229)
Resting energy expenditure (kcal/kg, weight/day)	54	40 (32; 50)

Abbreviations: IQR = interquartile range; SDS = standard deviation score; WHO = World Health Organization, PEG = percutaneous endoscopic gastrostomy, PEGJ = percutaneous endoscopic gastro-jejunostomy.

Table 2
Absolute and percent bias associated with the estimation of resting energy expenditure.

	N	Mean	SD	P_{50}	P_{25}	P_{75}
Bias WHO (kcal)	54	64	238	62	−134	283
Bias WHO (%)	54	–	–	108	88	139
Bias Schofield Wt (kcal)	54	79*	226	127	−97	272
Bias Schofield Wt (%)	54	–	–	112	91	139
Bias Schofield Wt & Ht (kcal)	54	79*	223	112	−88	264
Bias Schofield Wt & Ht (%)	54	–	–	112	92	138
Bias Oxford (kcal)	54	55	226	78	−121	219
Bias Oxford (%)	54	–	–	108	88	131
Bias Harris–Benedict (kcal)	54	37	224	12	−139	239
Bias Harris–Benedict (%)	54	–	–	101	87	132
Bias population-specific (kcal)	54	0	213	9	−138	187
Bias population-specific (%)	54	–	–	101	86	122

*$p < 0.05$ (Student's *t*-test for paired data).
Abbreviations: SD = standard deviation; P_x = Xth percentile; WHO = World Health Organization; Wt = weight; Ht = height.

Because proportional bias was detected also for percent bias (data not shown), the Bland–Altman limits of agreement were not calculated [19]. However, because IC is a reference method, the values reported in Table 2 do accurately quantify the bias and its inter-individual variability [25].

3.3. Development of a population-specific formula

Table 3 gives the regression models evaluated in order to develop a population-specific equation (see Statistical analysis for details).

The best prediction was obtained from weight alone with an R^2_{adj} of 0.60 (bootstrapped 95%CI 0.44 to 0.75) and a RMSE of 212 (bootstrapped 95%CI 183 to 241) kcal (Model M1). The population-specific formula is:

$$\text{REE (kcal/day)} = 24^{*}\text{weight (kg)} + 380$$

Although the mean bias of the population-specific formula is (not surprisingly) 0, its SD is as large as that of the other formulae. Moreover, the population-specific formula shows a clear negative proportional bias as the other formulae (Fig. 1).

3.4. Correct classification fraction of the formulae

Table 4 reports the CCF of the REE formulae.

The estimated REE was <90% and >110% of measured REE in 28% and 48% using the WHO formula; 24% and 56% using the Schofield weight formula; 22% and 54% using the Schofield weight and height formula; 30% and 37% using the Harris- Benedict formula, 26% and 46% using the Oxford formula and 35% and 43% using the population-specific formula. These results show that all the commonly used prediction formulae tend to over- and under-estimate REE in most CP patients.

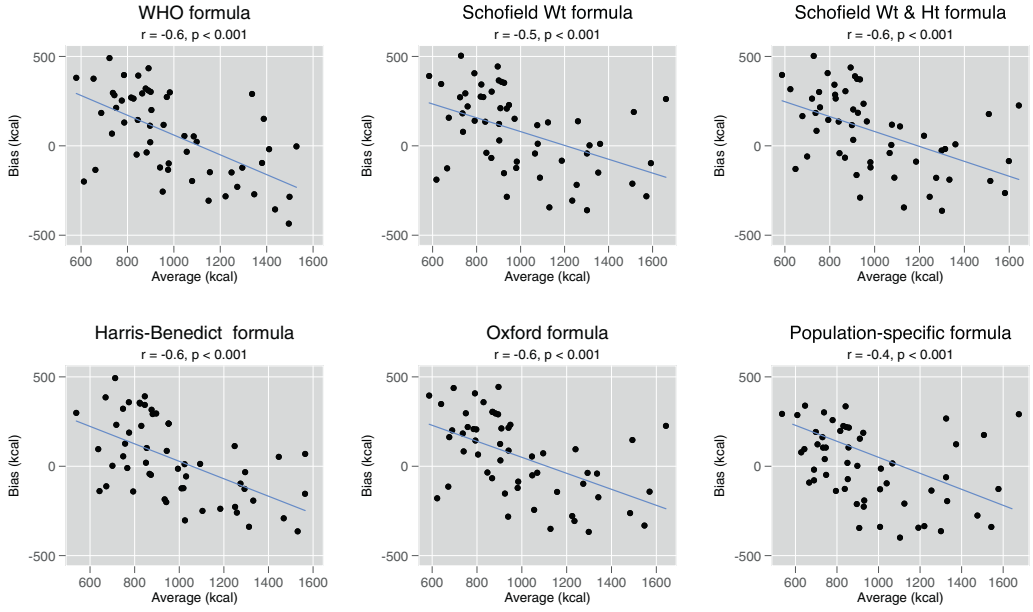
4. Discussion

All the most commonly employed prediction formulae gave inaccurate estimates of REE in our SQCP children at both the population and individual level. The largest mean bias was associated with the Schofield weight and weight and height formulae (79 kcal for both), followed by the WHO formula (64 kcal), the Oxford formula (55 kcal), and the Harris–Benedict formula (37 kcal). The large SD of the bias associated with all the formulae shows however

Table 3
Pre-specified regression models for the prediction of resting energy expenditure.

	M1	M2	M3	M4
Weight (kg)	24*** [18 to 29]	22*** [14 to 30]	–	–
Age (years)	–	6 [−12 to 24]	–	−3 [−27 to 20]
Male (1 = yes; 0 = no)	–	−21 [−162 to 121]	–	−42 [−183 to 99]
Height (cm)	–	–	12*** [9 to 15]	13*** [7 to 19]
Intercept	380*** [247 to 512]	371*** [193 to 550]	−575** [−987 to −163]	−589* [−1160 to −18]
RMSE	212 [183 to 241]	215 [186 to 244]	233 [199 to 267]	237 [203 to 271]
R^2_{adj}	0.60 [0.44 to 0.75]	0.51 [0.43 to 0.74]	0.51 [0.32 to 0.70]	0.50 [0.31 to 0.69]
N	54	54	54	54

Values are regression coefficients and measures of model fit with 95% bootstrapped confidence intervals.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Abbreviations: RMSE = root mean square error of the estimate; R^2_{adj} = adjusted coefficient of determination.



Bias = (estimated resting energy expenditure - measured resting energy expenditure).
Average = [estimated resting energy expenditure + measured resting energy expenditure)/2]
Wt = weight; Ht = height

Fig. 1. Shows the presence of negative proportional bias for all formulae including the population-specific formula (see below for the development of the population-specific formula).

that none of them can be reliably applied at the individual level. As shown in Fig. 2, overestimation was more common than underestimation putting most SQCP patients at risk of overfeeding.

Our findings are in agreement with those of Gale et al. who showed that, in 16 ventilated CP children and adolescents, REE was commonly overestimated with ensuing overfeeding of most patients [8]. Using the CCF as criterion of performance, the prediction equation which performed better was still the Harris-Benedict equation, even if its CCF (33%) was still low on absolute grounds. This finding is different from that obtained by Agostoni et al., who evaluated the accuracy of the same prediction formulae in a heterogeneous population of hospitalized Italian children [25]. In that study, the Harris-Benedict equation showed a poor performance, with a mean (SD) bias of 82 (286) kcal/day vs. the present bias of 37 (224) kcal/day. At the individual patient level, however, our conclusions are similar to those of Agostoni et al., because the large inter-individual variability of the bias makes also the Harris–Benedict formula unsuitable for use in single children.

A likely explanation for the inaccuracy of the commonly employed prediction equations is that most of them were obtained on healthy and non-hospitalized individuals (although some were developed and validated in mechanically ventilated patients, which is however not an issue here). The studies that have attempted to assess the REE prediction equations vs IC in ill and critically ill children had very different case-mixes of disease and are therefore difficult to compare [26-28]. It is widely accepted that one of the main barriers to develop accurate prediction equations in ill children is the large heterogeneity of disease and its severity. Ideally, predictive equations should provide estimates within 10% of measured energy expenditure [29].

As the SQCP-specific REE formula is concerned, it was the most accurate formula at the population level. This was expected because an internally-developed formula nearly always performs better that an externally-derived one, at least at the population level. However, while the bias of the SQCP-specific formula was 0 kcal, its SD was 213 kcal, clearly pointing to a large inter-individual variability, especially in view of the median REE of 876 kcal/day of the study children. Using the CCF as criterion of

Table 4
Correct classification fraction of the prediction formulae.

	N = 54
WHO	
90–110% (CCF)	13 (24%)
< 90%	15 (28%)
> 110%	26 (48%)
Schofield Wt	
90–110% (CCF)	11 (20%)
< 90%	13 (24%)
> 110%	30 (56%)
Schofield Wt & Ht	
90–110% (CCF)	13 (24%)
< 90%	12 (22%)
> 110%	29 (54%)
Harris–Benedict	
90–110% (CCF)	18 (33%)
< 90%	16 (30%)
> 110%	20 (37%)
Oxford	
90–110% (CCF)	15 (28%)
< 90%	14 (26%)
> 110%	25 (46%)
Population-specific	
90–110% (CCF)	12 (22%)
< 90%	19 (35%)
> 110%	23 (43%)

Abbreviations: CCF = correct classification fraction; WHO = World Health Organization; Wt = weight; Ht = height.

performance, only 22% of the children had a correctly classified REE as compared to 33% for the Harris–Benedict formula and similar to the 20% of the Schofield weight formula. This was unexpected and suggests that factor associated with SQCP such as disease severity may have to be taken into account to obtain reasonably accurate population-specific equations. Even with the SQCP-specific formula, most patients (43%) would have their REE overestimated with risk of overfeeding and a substantial number (35%) would have their REE underestimated with risk of underfeeding.

The limitations of the present study should be kept in mind. Our sample size was small and we did not take into account measures of spasticity which may influence REE in SQCP children. The need to test such measures as potential REE predictors, e.g. the modified Ashworth scale score, is strongly suggested by the present evidence that a population-specific anthropometry-based formula did not perform better than an anthropometry-based formula developed on a healthy population. Another limitation is that we did not measure the body composition (BC) of our patients. Especially in view of the fact that weight was not an accurate predictor of REE in our SQCP children, an assessment of the relationship between REE and fat-free mass (FFM) in SQCP vs. control children would be very useful to understand the determinants of REE in SQCP. Unfortunately, most of the BC data available for CP children were obtained from indirect methods. For instance, in the study of Arrowsmith [30] et al., fat mass was estimated from skinfold thicknesses using the Brook equation [31] for pre-pubertal children and the Durnin & Rahman equation [32] for pubertal children. Although their finding that FFM was the strongest predictor of REE, explaining however only 27% of its variance, is clearly important, further studies with direct measures of BC are needed to disentangle the REE-FFM relationship in CP children [31].

We believe that our findings have important implications for the nutritional rehabilitation of children with CP. The WHO, Harris–Benedict, Schofield and Oxford formulae cannot replace IC for the assessment of EE to guide nutritional support in children with SQCP. Unfortunately, even a purposely developed REE population-specific equation did not perform better than commonly used REE equations. There is a serious risk of over- and under-feeding

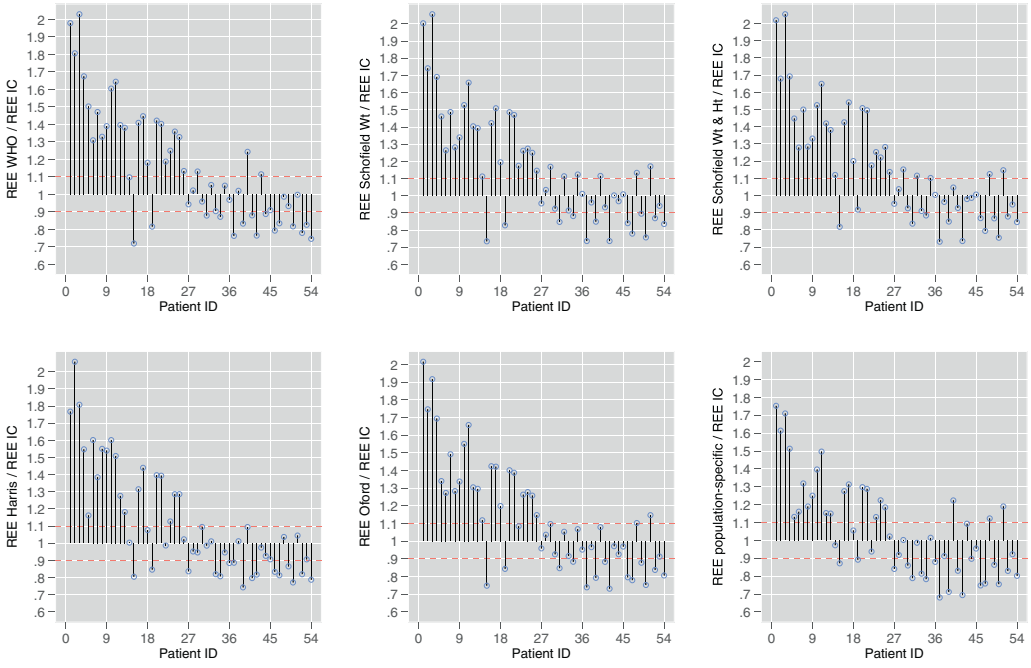


Fig. 2. Plots the relative bias of the REE formulae. The relative bias here is calculated as (estimated REE/measured REE). A ratio >1.0 indicates overestimation and one <1.0 underestimation. This figure offers an insight into the inter-individual variability of the bias outside the CCF region, which is the region between 0.9 and 1.1.

SQCP children using estimated REE. Further studies are needed to try to improve the estimation of REE in SQCP children paying attention to measures of disease severity which can potentially impact on REE.

Author contributions

FP: study design, data collection, data interpretation, drafting of manuscript.

BB: literature search, indirect calorimetry and nutritional assessment, data collection.

AB: literature search, data collection, data interpretation, drafting of manuscript.

CM: data interpretation, critical review.

DD: data interpretation, critical review.

GR: critical review, revision of manuscript and drafting of changes.

FM: study design, data collection, data interpretation, drafting of manuscript.

GB: study design, statistical analysis, data interpretation, critical review, revision of manuscript.

GVZ: study coordination, study design, critical review.

Conflict of interest

None of the Authors have conflicts of interest to declare.

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