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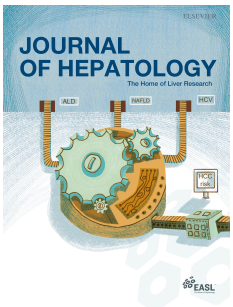

Predicted estimates of resting energy expenditure have limited clinical utility in patients with cirrhosis

Ana Teresa Limon-Miro, Clive Douglas Jackson, Tannaz Eslamparast, Hisami Yamanaka-Okumura, Lindsay Dudley Plank, Christiani Jeyakumar Henry, Angela Mary Madden, Livia Garcia Ferreira, Evangelos Kalaitzakis, César Prieto de Frías, Anne Wilkens Knudsen, Leah Gramlich, Maitreyi Raman, Cathy Alberda, Dawn Belland, Vanessa Den Heyer, Puneeta Tandon, Marsha Yvonne Morgan

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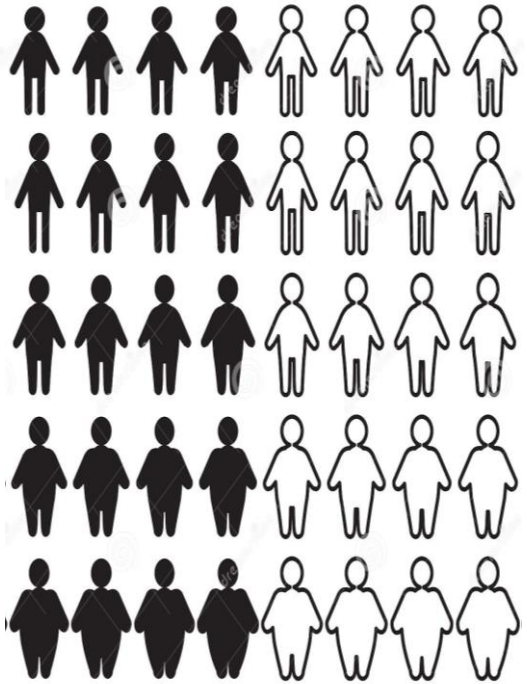
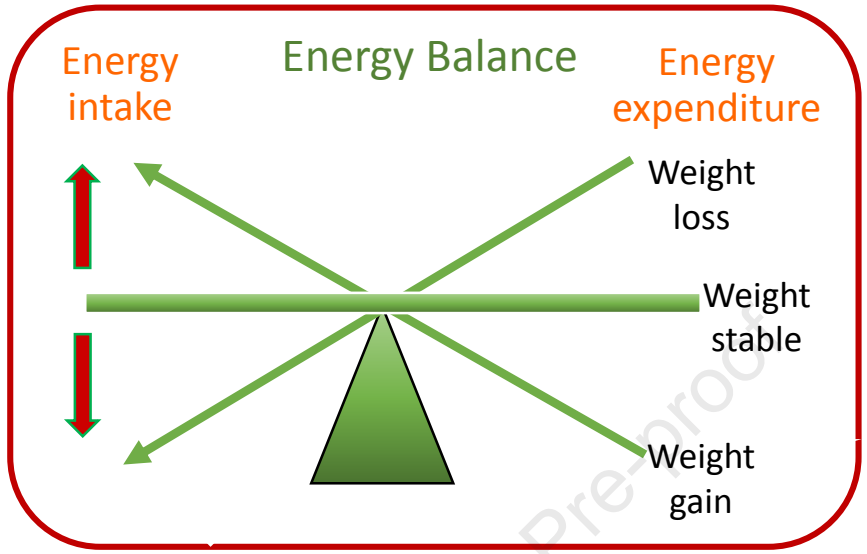
Predicted estimates of energy expenditure have limited clinical utility in patients with cirrhosis

People with cirrhosis are often malnourished

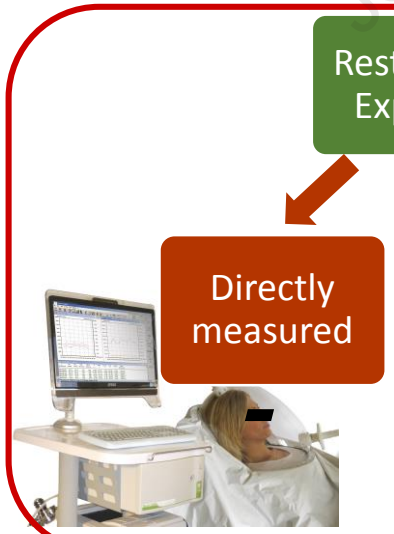


Poor outcome



Accurate assessments of energy requirements are needed to optimize dietary intake

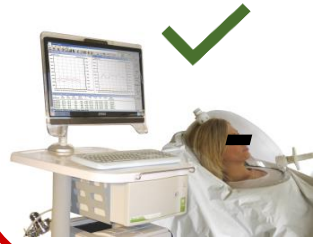
Individual **measured** and **predicted** energy expenditure data compared in 900 patients with cirrhosis and 282 healthy controls



Predicted values *vs.* Measured values

Discordance

-501 to +548 kcal/kg/24 hr



Prediction Equations

(i) Harris-Benedict (ii) Mifflin
(iii) Schofield (iv) Henry

JHEPAT-D-21-01918R3

Predicted estimates of resting energy expenditure have limited clinical utility in patients with cirrhosis

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Keywords: energy requirements; ethnicity; indirect calorimetry; liver disease; prediction equations; resting energy expenditure; sex

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Authors' contributions

Authors' initials	Study concept/ design	Acquisition of data	Analysis & interpretation of data	Drafting of manuscript	Critical revision of manuscript	Statistical analysis	Support	Study supervision
ATL-M			✓	✓	✓			
CDJ	✓		✓	✓	✓	✓	✓	✓
TE		✓	✓	✓	✓			
HY-O		✓			✓			
LDP		✓			✓			
CJH		✓			✓			
AMM		✓			✓			✓
GF		✓			✓			
EK		✓			✓			
CPfF		✓			✓			
AWK		✓			✓			
LG					✓			
MR					✓			
CA	✓				✓			
DB					✓			
VDH					✓			
MYM	✓	✓	✓	✓	✓	✓	✓	✓
PT	✓	✓	✓	✓	✓		✓	✓

Abstract

Background & Aim: Malnutrition is associated with adverse clinical outcomes in patients with cirrhosis. Accurate assessment of energy requirements is needed to optimize dietary intake. Resting energy expenditure (REE), the major component of total energy expenditure, can be measured using indirect calorimetry (mREE) or estimated using prediction equations (pREE). This study assessed the usefulness of predicted estimates of REE in this patient population.

Methods: Individual mREE data were available for 900 patients with cirrhosis (mean [±1SD] age 55.7±11.6 yr; 70% men; 52% south-east Asian) and 282 healthy controls (mean age 36.0±12.8 yr; 52% men; 18% south-east Asian). Metabolic status was classified using thresholds based on the mean±1SD of the mREE in the healthy controls. Comparisons were made between mREE and pREE estimates obtained using the Harris-Benedict, Mifflin, Schofield and Henry equations. Stepwise regression was used to build three new prediction models which included sex, ethnicity, body composition measures, and MELD scores.

Results: The mean mREE was significantly higher in patients than controls when referenced to dry body weight (22.4±3.8 *cf.* 20.8±2.6 kcal/kg/24hr; p<0.001); there were no significant sex differences. The mean mREE was significantly higher in Caucasian than Asian patients (23.1±4.4 *cf.* 21.7±2.9 kcal/kg/24hr; p<0.001). Overall, 37.1% of Caucasians and 25.3% of Asians were classified as hypermetabolic. The differences between mREE and pREE were both statistically and clinically relevant; in the total patient population, pREE estimates ranged from 501 kcal/24hr less to 548 kcal/24hr more than the mREE. Newly-derived prediction equations provided better estimates of mREE but still had limited clinical utility.

Conclusions: Prediction equations do not provide useful estimates of REE in patients with cirrhosis. REE should be directly measured.

Word count: 271

Lay summary

- People with cirrhosis are often malnourished and this has a detrimental effect on outcome.
- Provision of an adequate diet is very important and is best achieved by measuring daily energy requirements and adjusting dietary intake accordingly.
- Prediction equations, which use information on age, sex, weight, and height can be used to estimate energy requirements; however, the results they provide are not accurate enough for clinical use, particularly as they vary according to sex and ethnicity.

Introduction

Malnutrition is common in patients with cirrhosis (1-5) and is a substantial risk factor for bacterial infections, hepatic encephalopathy, hospitalization, and mortality (6-12); improving nutritional status has a beneficial effect on several of these outcome variables (13-19). Several guidelines for the nutritional management of patients with cirrhosis exist and provide recommendations for daily energy intakes based on body weight (20-25). However, the recommended daily energy intakes are inconsistent varying, for example, in patients with compensated disease from 25 kcal/kg (20) to at least 35 kcal/kg (24,25). In addition, several factors mitigate against the use of generic dietary prescriptions *viz:* (i) energy requirement may increase in patients with cirrhosis who develop acute complications (22); (ii) approximately one-quarter to one-third of patients with cirrhosis are hypermetabolic but are not identifiable based on demographic or clinical features (26-30); and, (iii) during the natural course of the disease patients with cirrhosis tend to spontaneously reduce their dietary intake (29) and to reduce their levels of physical activity (31)and this will have compensatory, but not necessarily identifiable effects, on intake requirements.

The inter-patient variability in energy requirement, in patients with cirrhosis, is high and the risk of under- and overfeeding, resulting from a formulaic approach to dietary provision, is likely to be significant. It has, therefore, been recommended that energy requirements should be determined, in this patient population, whenever possible, by indirect calorimetric measurements of resting energy expenditure (mREE) (20-22,24,25). However, this guidance is rarely adopted in clinical practice. Instead estimates of REE from prediction equations (pREE) are used as a substitute even though there are considerable concerns about their accuracy in this patient population (30,32). Further the prediction equations are generic despite substantial evidence of ethnic diversity in energy homeostasis (33-35). Thus, in a recent systematic review of 17 studies involving 1883 patients with cirrhosis, pREE estimates

significantly underestimated mREE in the majority of Caucasian patients while tending to overestimate mREE in patients of south-east Asian origin (32).

The present study utilized individual data from a large cohort of patient with cirrhosis to: a) determine the effects of ethnicity on mREE; b) delineate the prevalence and predictors of hypermetabolism; c) compare REE estimates predicted using the Harris Benedict (36), Mifflin (37), Schofield (38) and Henry (39) equations with mREE; and d) devise new models for predicting both the hypermetabolic state and REE and to determine their clinical utility.

Subjects and methods

Data sources

The authors of the 17 studies included in a recent systematic review of REE in patients with cirrhosis (32) were approached to determine if they had access to and permission to share individual data on the patients included in their studies and, if available, corresponding data in healthy controls. Additional potential sources of healthy control data were identified from the literature and network contacts.

Individual data extraction

The patient data accessed included: hospitalization status (inpatient vs. outpatient), sex, age, self-reported ethnicity, liver disease aetiology, the presence/absence of fluid retention, height, body weight, estimated dry weight, Pugh's score and Child-Pugh grade (40), Model for End-stage Liver Disease (MELD) score (41), mREE, and, where available, measures of body composition, such as fat free mass (FFM). Patients with ascites, in whom the dry weight had not been estimated, and patients with hepatocellular carcinoma were excluded from the analyses. The healthy controls data accessed included: sex, age, self-reported ethnicity, height, body weight, mREE, and, where available, measures of body composition.

The studies from which data were obtained had been undertaken according to the ethical guidelines of the 1975 Declaration of Helsinki (42) and approved by the appropriate institutional review committees. All participants had provided written informed consent.

Resting energy expenditure

REE was *measured* (mREE) using indirect calorimetry as recommended (32). REE was *predicted* (pREE) using the formulae proposed by Harris-Benedict (36), Mifflin (37), Schofield (38) and Henry (39) (Appendix). mREE and pREE data were expressed both in absolute (kcal/24 hr), and relative (kcal/kg dry body weight/24 hr) terms.

Data curation and statistical analysis

Statistical analyses were performed using R software (43); p-values of <0.05 were considered significant.

Differences in demographic, clinical, anthropometric and metabolic variables between patients with cirrhosis and healthy controls and between patient subgroups were compared using the Wilcoxon rank and χ^2 tests.

Patients' metabolic status was classified using the mean (±1SD) of the mREE in the relevant healthy controls as: hypometabolic (<mean-1SD), normometabolic (mean±1SD), or hypermetabolic (>mean+1SD) (30). The relationships between patients' demographic/clinical features and metabolic status were examined using the Jonckheere-Terpstra test for ordered differences among classes. Logistic regression modelling was used to derive equations suitable for predicting metabolic status, in particular, the hypermetabolic state. Models were built for the total combined control and patient populations and separately, by sex and ethnicity based on both absolute and relative mREE (Supplementary Methods 1).

The interchangeability of mREE and pREE values, identified by the limits of agreement between the two measures and their directionality, were assessed using a modified Bland and Altman approach (44) in which the differences between mREE and pREE were plotted against pREE in order to assess the residuals and hence reduces bias.

The associations between mREE and sex, age, ethnicity, dry weight, height, body mass index (BMI) and MELD score were examined using simple regression. A stepwise regression with forward selection was applied utilizing the available data in the patient and healthy control populations to derive two new prediction models (*Basic and London*) and a third new prediction model (MELD) based on information available in the patient population alone (Supplementary Methods 2). The validity of the newly devised

models was then examined by application to the patient population. The estimates of pREE provided using the new models and the estimates provided by the four standard prediction equations were compared using *standard* Bland and Altman plots (44).

Results

Study subjects

A total of 900 patients with cirrhosis and 282 healthy control subjects were identified and included in the analyses (30,45-51) (Supplementary Table 1).

Patients with cirrhosis

The patients were predominantly middle-aged and male (Table 1). Overall, 61% had viral-related cirrhosis; 69% were either Child-Pugh Grade B or C; 48% were Caucasian while 52% were south-east Asian. The expected male: female differences in anthropometric measurements were observed in both the Caucasian and Asian subpopulations but there was no significant sex-related difference in mean BMI, based on estimated dry body weight (Table 2: Supplementary Table 1). There were, however, a number of significant differences in the demographic and derived variables in the ethnic subpopulations (Table 2). The Asian patients were older (mean [±1SD] 59.8±10.9 *cf*. 51.3±10.8 yr; p<0.001), had a lower mean dry BMI (22.2±3.2 *cf.* 25.5±4.9 kg/m^2; p<0.001), were more likely to have HBV/HCV-related cirrhosis (89.7 *cf.* 32.2%; p<0.001), and to have less decompensated disease (MELD score 9.2±4.2 *cf.* 13.7±5.2; p<0.001) (Table 2).

Healthy controls

The control population comprised of 282 healthy people (51.8% men; mean age 36.0±12.8 yr; mean BMI 26.2±5.1 kg/m^2) (Table 2). Of these, 50 (17.7%) were Caucasian while the remainder were south-east Asian. The Asian healthy controls were significantly younger than their Caucasian counterparts (mean age 32.8±10.5 *cf.* 50.6±12.4 yr; p<0.001), and significantly shorter (166.3±8.5 *cf.* 169.6±8.4 cm; p<0.05) but were otherwise comparable (Table 2).

Matching of patient and control populations

There were no significant differences in demographic and derived variables between the Caucasian patients and healthy Caucasian controls except for an imbalance in the proportion of men

(Supplementary Table 2). In contrast, there were several potentially confounding differences between the Asian patients and the healthy Asian controls, notably in sex distribution, BMI and age (Supplementary Table 2). However, the difference in sex distribution was accounted for by correcting the analyses for sex and the differences in weight were largely off-set by correcting REE for body weight. Likewise, the difference in age was non-consequential as there was no significant relationship between age and weight-corrected REE in the healthy Asian controls (correlation coefficient – 0.169; Supplementary Figure 1); in particular there was no significant difference in mREE/kg body weight in healthy Asian controls aged <40 and ≥40 yr (20.8±2.6 *cf.* 20.3±2.2 kcal/kg; p = 0.12).

Measured REE

The mean mREE was significantly higher in men than in women in both the total patient and healthy control populations when expressed in absolute terms; the difference was retained in the control population when referenced to body weight (21.3±2.6 *cf.* 20.2±2.5 kcal/kg/24 hr; p<0.001) but was negated in the patient population (22.4±3.7 *cf.* 22.2±3.9 kcal/kg dry body weight/24 hr) (Table 3).

The mean mREE was significantly *lower* in the total patient population compared to the healthy controls when expressed in absolute terms (1447±354 *cf.* 1499±293 kcal/24 hr; p<0.02) but was significantly *higher* than in healthy controls when expressed relative to dry body weight (22.4±3.8 *cf.* 20.8±2.6 kcal/kg/24 hr (p<0.001) (Table 3).

In the Caucasian population, the mean mREE, expressed in absolute terms, was significantly *higher* in the total patient population than in the healthy controls, and was also significantly higher in the group as a whole, and by sex, relative to dry body weight (Table 3). In the Asian population the mean mREE, expressed in absolute terms, was significantly *lower* in the patients than in the healthy controls both in the group as a whole, and by sex. However, the mean mREE, expressed relative to body weight, was significantly higher in the patients than the healthy controls in the whole group and in women but was comparable in men (Table 3).

Overall, the mean mREE did not differ significantly between the Caucasian and Asian healthy controls whether expressed in absolute or relative terms. However, the mean mREE in the Caucasian patients was significantly higher than in the Asian patients as a whole and by sex whether expressed in absolute or relative terms (Table 3).

Metabolic status in patients with cirrhosis

The thresholds for determining metabolic status were based on the mean (±1SD) of the mREE in the corresponding healthy control populations (30) (Supplementary Table 3). Significant differences in the classification of metabolic status were observed in the Caucasian and Asian patients, when expressed in absolute terms with approximately 30% of Caucasians classified as *hyper*metabolic but almost 45% of Asians patients classified as *hypo*metabolic (Table 4; Supplementary Tables 4A-F). However, when mREE was expressed relative to dry body weight approximately a quarter to one- third of Caucasian and Asian patients were classified as *hyper*metabolic (Table 4; Supplementary Tables 4G-L). There was no sex- difference in the prevalence of hypermetabolism in the Caucasians (men 33.2%: women 37.1%) but a notable, unexplained, sex-difference in prevalence in the Asians (men 20.5%; women 35.2%; p=0.001). Patients classified as *hyper*metabolic, based on relative REE, were younger, weighed less and had more decompensated liver disease than their *normo*- or *hypo*metabolic counterparts (Supplementary Tables 4G-L).

Predicting metabolic status

Logistic regression modelling was used to determine if it were possible to predict the hypermetabolic state in patients with cirrhosis. The performance of the prediction models based on absolute mREE was fair to moderate (total population: sensitivity 59%, specificity 95%, positive predictive value (PPV) 71%, negative predictive value (NPV) 92%; accuracy 89%) with no notable differences by sex or ethnicity (Supplementary Table 5). The performance of the prediction models based on mREE relative to dry

body weight was also fair to moderate (total population: sensitivity 40%, specificity 91%, PPV 64%, NPV 79%; accuracy 77%) again with no notable differences, by sex or ethnicity.

pREE using standard equations

Differences were observed between mREE and pREE estimates, in the healthy controls, relative to the prediction equation, sex and ethnicity (Supplementary Table 6). Overall pREE estimates were within the mean±2SD of mREE in 65.2-72.7% of healthy controls; were under-predicted in 3.9-12.4% and over-predicted in 14.9-29.1%, depending on the equation used. pREE estimates were within the mean±2SD of mREE in 69.9-85.6% of healthy male controls; 79.4-89.0% of healthy female controls; 74.0-78.0% of healthy Caucasian controls and 63.4-69.0% of healthy Asian controls.

Differences were observed between mREE and pREE estimates, in the patients with cirrhosis, again relative to the prediction equation, sex and ethnicity (Table 5)**.** Overall, pREE estimates were within the mean±2SD of mREE in 82.0-86.3% of the patients but were under-predicted in 4.3-13.4% and over-predicted in 3.8-10.9%, depending on the equation used (Table 5). pREE estimates were within the mean±2SD of mREE in 80.1-91.9% of men with cirrhosis and 70.9%-94.0% of women with cirrhosis. In the Caucasian patients as a whole, and by sex, the mean REE estimates provided by all four prediction equations were significantly *lower* than the mean mREE (Table 5). In contrast, in the Asian patients the mean Schofield and Henry pREEs significantly *over-estimated* the mean mREE in the total population and in men (Table 5) while the mean Mifflin and Harris–Benedict pREEs significantly over-estimated the mean mREE in men and under-estimated mREE in women (data not shown).

Limits of Agreement between the mREE and pREE

Information on data interchangeability was determined by the limits of agreement between measures of mREE and pREE and their directionality.

In the 282 healthy controls, the pREE estimates, provided by the four prediction equations, were from -432 kcal/24 hr less to 301 kcal/24 hr more than the mREE (Supplementary Table 7). In the 900 patients

with cirrhosis, the pREE estimates, provided by the four equations, were from 501 kcal/24 hr less to 548 kcal/24 hr more than the mREE (Table 6). Similar differences in the limits of agreement between mREE and pREE estimates were observed in the patient populations by sex and by ethnicity (Table 6; Figure 1).

The pREE estimates were within the limits of agreement for all four equations in 50% of the patients with cirrhosis. However, these individuals could not be distinguished clinically.

New models to predict REE

Three separate models were built (Supplementary Material 2):

(i) *Basic* model: in the total patient population the limits of agreement, ranged from -427 to 413 kcal/24 hr (Supplementary Table 8); these are marginally narrower than those provided by the four standard prediction equations (Table 6).

(ii) *MELD* model: the limits of agreement, in the total population, ranged from -441 to 441 kcal/24 hr (Supplementary Table 8); these are also marginally narrower than those obtained with the standard prediction equations (Table 6).

(iii) *London* model: the limits of agreement, in the total population, ranged from -398 to 398 kcal/24 hr (Supplementary Table 8); these are the narrowest of the limits of agreement provided by any of the standard and newly devised prediction equations (Table 6).

Discussion

The key findings in the present study were: (i) mREE must be referenced to a measure of body composition, for example, dry body weight; (ii) ethnicity is an important determinant of mREE; (iii) the commonly used prediction equations do not provide REE estimates that can be used interchangeably with mREE and hence have limited clinical utility; and (iv) the major determinants of REE in patients with cirrhosis have yet to be fully delineated limiting the accuracy of any model derived to predict metabolic status and REE.

Expressing mREE in absolute rather than relative terms provides misleading results and inaccurate comparisons. Thus, the mean mREE was significantly *lower* in patients with cirrhosis than in healthy controls, when expressed in absolute terms, but was significantly higher when expressed relative to dry body weight. Likewise, approximately 30% of Caucasian patients were classified as *hyper*metabolic based on absolute mREE values while over 45% of south-east Asian patients were classified as *hypo*metabolic; referencing the mREE to dry body weight identified an excess of *hyper*metabolic patients in both populations.

The unique composition of this cohort of patients allowed the effects of ethnicity on metabolic status in cirrhosis to be explored. The mean mREE was significantly higher in the Caucasian patients than in their south-east Asian counterparts even when allowance was made for differences in BMI. In addition, whilst the frequency of hypermetabolism was comparable in Caucasian men and women (33.6 % *cf.* 37.8%) there was a distinct and unexplained sex-related difference in frequency in the south-east Asians (20.2% *cf.* 36.8%). Similarly, the performance of the prediction equations differed substantially, by ethnicity. Thus, in the Caucasian patients the mean pREE estimates provided by the four prediction equations were significantly lower than the mean mREE. In contrast, in the south-east Asian patients the mean pREEs were either significantly higher than the mean mREE or else did not differ from it significantly. The limits of agreement between the pREE estimates and mREE were considerably wider in the Caucasian patients as were the ranges between the minimum and maximum differences between these variables.

These findings clearly identify ethnicity as a major determinant of mREE and this undoubtedly relates to the well-documented variation in body composition between races, more especially to differences in the size and composition of the FFM (52). Variation in the size of the FFM explains 65 to 90% of the inter-subject variation in mREE in healthy adults (53-55). However, the composition of the FFM is equally as important as REE may be significantly influenced by variation in the ratios of high to low energy-requiring FFM contributors (56-59). In healthy Caucasian adults, skeletal and liver mass are the major FFM contributors to REE (57). Healthy African Americans have significantly lower mREE than their white counterparts largely accounted for by a smaller summed mass of specific high-metabolic-rate organs (60). Asian Indians living in Singapore have a significantly lower mREE than their Chinese counterparts; this difference remains significant after adjustment for total FFM and skeletal muscle mass but is attenuated when adjusted for visceral FFM (61).

Approximately a quarter to one third of patients, in the present study, were classified as hypermetabolic, in line with previous findings (26-30). However, there is little or no consensus on the most accurate method for defining metabolic status in this patient population. Classification has been based on threshold relating to the ratio of mREE to pREE (29), the range of values in healthy controls (28) or, as in this study, the mean + 1SD of healthy control values (30). A universally acceptable, evidence-based classification of metabolic status is clearly required. Patients who are hypermetabolic may be particularly vulnerable to nutritional insult (62,63) and the ability to identify them is a significant unmet need. Several models were built to facilitate prediction of the hypermetabolic state, based on the available individual patient and healthy control data, but their diagnostic performance was only fair to moderate. Future prediction modelling requires accurate information on the factors that underpin the hypermetabolic state (29) which is being actively pursued (50).

The pREE estimates, in the patients with cirrhosis, ranged from 501 kcal/24 hr less to 548 kcal/24 hr more than the mREE rendering them of little value in the clinical setting. This finding is not specific to this patient

population as the accuracy of the pREE estimates is notably poor in several conditions, for example, obesity, malignancy, and critical illness (64-67). This prediction inaccuracy in disease states has been attributed to the fact that the original equations were developed in cohorts of healthy, non-hospitalized Caucasian individuals of normal weight in first two decades of the 20th century. However, the pREE estimates in the healthy controls, in the present study, were equally as poor ranging from 432 kcal/24 hr less to 301 kcal/kg more than the mREE.

The novel prediction models developed in the present study provided better mREE estimates than those provided by the established prediction equations. Of these the *London* model, which included a measure of FFM derived from skinfold anthropometry (68), provided the best estimates with the narrowest limits of agreement. However, none of the models provided pREE estimates that would be useful clinically.

Currently between 50 to 65% of the variance in mREE in patients with cirrhosis can be explained by demographic and body composition variables (30). Clearly more information is needed on the factors responsible for the remaining variance in REE if clinical useful prediction tools are to be developed (69).

It is likely that referencing mREE not just to FFM but to more specific metabolic components of the FFM would provide more meaningful results and comparisons (69,70). Data on the composition of the FFM in patients with cirrhosis and the contribution of the various FFM components to the variance in REE are lacking and are not easily obtained (57). However, this knowledge might allow development of novel energy expenditure body composition models in the future (69,70).

The present study has a number of strengths: (i) the patient population was large and thus subgroup analyses for differences in potentially important confounders such as sex, body composition, and ethnicity were possible; (ii) the patients were drawn from study centres in Europe, south-east Asia, New Zealand and South America; the findings are, therefore, more generally applicable than if the population were more refined; (iii) a healthy control population was included which allowed for a more precise classification of

metabolic status than the techniques used in previous publications (48,50,71); and, (iv) the pREE estimate were calculated *de novo* for the four most widely-used equations, for all included patients and healthy controls, hence ensuring consistency.

This study also has a number of limitations: (i) the patients were of either of south-east Asian or Caucasian descent; information was not available on south Asian or African/Afro-Caribbean populations; (ii) the majority of patients had HBV/HCV-related cirrhosis although patients with alcohol-related cirrhosis were well-represented; only 6% had non-alcoholic fatty liver-related cirrhosis, which is not reflective of current clinical practice; (iii) data on the level of functional hepatic reserve, assessed using the Child-Pugh or MELD scores, were available for 51% and 79% of the patient population respectively; however the number of patient available for analysis was still substantial; (iv) data on nutritional status were not generally available and so could not be included - this has particular relevance when determining the appropriateness of recommended energy intakes, by nutritional status (46,72); (v) dry BMI was used as a surrogate for nutritional status but the methods of ascertainment differed between populations; (vi) measures of FFM and skeletal muscle mass were not available for the majority of patients; these would have provided a more robust and less variable tissue reference for REE expression; (vii) the number of Caucasian healthy controls was relatively small but still adequate for analysis, and (vii) it is likely that there were differences in preparation of both the patients and the healthy controls for REE measurements e.g. fasting state; concomitant medication with β-blockers (46) and in measurement techniques e.g. type of indirect calorimeter used, the calibration; the equilibration and measurement periods and the calculation of REE, in particular whether it included an adjustment for 24 hr urinary nitrogen excretion (32).

Conclusions

Prediction equations do not provide estimates of REE that are sufficiently accurate to determine dietary requirements in patients with cirrhosis. These findings further strengthen the recommendation made in recent nutritional guidelines that REE should be directly measured in these patients and not predicted.

Further studies are needed to identify the variables which contribute to the variance in REE in this patient population. It may then be possible to devise accurate prediction models obviating the need for direct REE measurement. If, in addition, evidence-based information on the relationship between mREE and TEE, can be obtained then future recommended weight–based dietary prescriptions could be more securely formulated.

Abbreviations: BMI: Body mass index; FM: fat mass; FFM: fat-free mass; HBV/HCV: hepatitis B/C; ht: height; IPD: individual patient data; MELD: Model for End-stage Liver Disease; mREE: measured resting energy expenditure; NAFLD: non-alcoholic fatty liver disease; NPV: negative predictive value; PPV: positive predictive value; pREE: predicted resting energy expenditure; REE: resting energy expenditure; TEE: total energy expenditure; wt: weight.

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Appendix

Published equations used to predict REE

Harris-Benedict (36)

Men: 66.47 + (13.75 x wt) + (500.33 x ht) - (6.76 x age)

Women: 655.10 + (9.56 x wt) + (184.96 x ht) - (4.68 x age)

Mifflin (37)

Men: (9.99 x wt) + (625 x ht) - (4.92 x age) + 5

Women: (9.99 x wt) + (625 x ht) - (4.92 x age) – 161

Schofield (38)

Men: (18-30 yr) = (15.06 x wt) - (10.04 x ht) + 706.12

(>30-60 yr) = (11.48 x wt) - (2.63 x ht) + 877.57

(60+ yr) = (9.09 x wt) + (972.74 x ht) - 834.77

Women: (18-30 yr) = (13.63 x wt) + (283.12 x ht) + 98.28

(>30-60 yr) = (8.13 x wt) + (1.43 x ht) + 844.09

(60+ yr) 5 (7.89 x wt) + (458.39 x ht) + 17.69

Henry (39)

Men: (18-30 yr) = (14.4 x wt) + (313 x ht) + 113

(>30-60 yr) = (11.4 x wt) + (541 x ht) - 137

(60+ yr) = (11.4 x wt) + (541 x ht) - 256

Women: (18-30 yr) = (10.4 x wt) + (615 x ht) - 282

(>30-60 yr) = (8.18 x wt) + (502 x ht) – 11.6

(60+ yr) = (8.52 x wt) + (421 x ht) + 10.7

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Legends to Figure

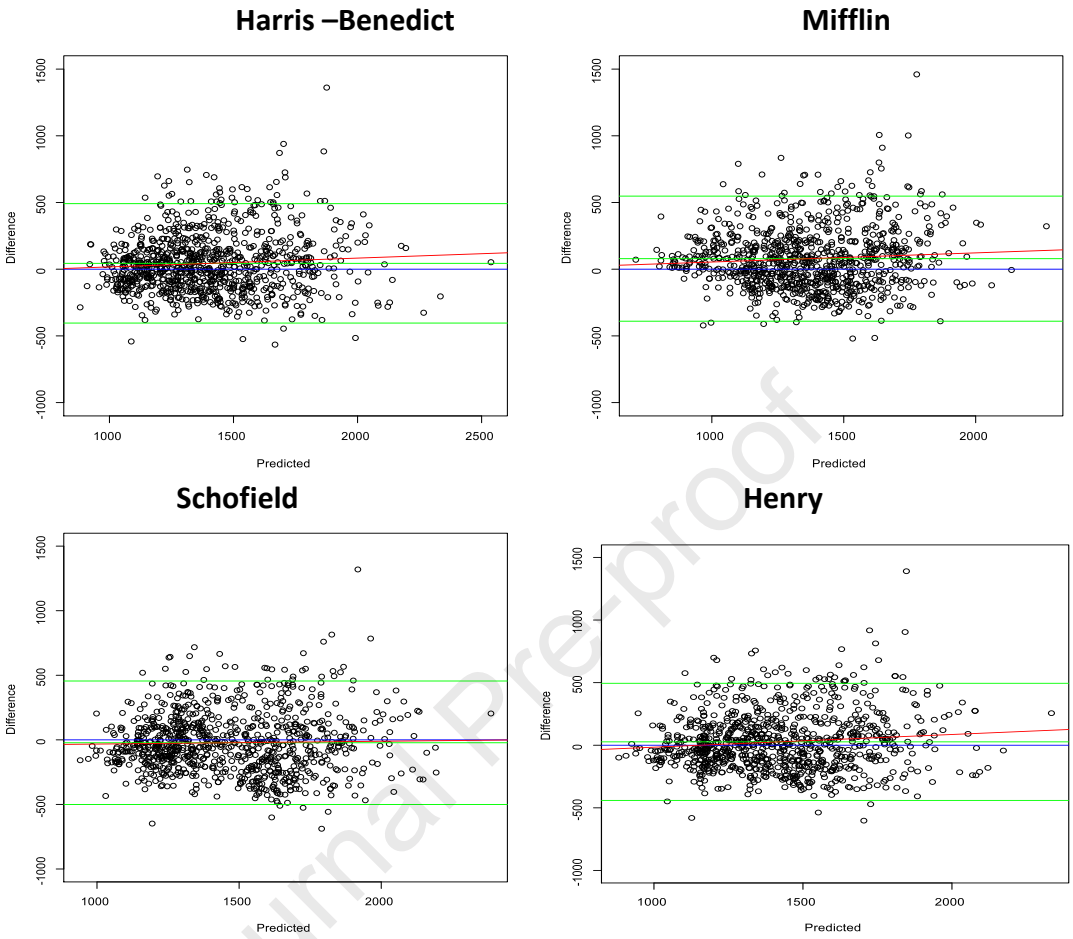

Figure 1: The degree of agreement between measured REE in 900 patients with cirrhosis and the estimates provided by the Harris–Benedict (36), Mifflin (37), Schofield (38) and Henry (39) equations. The blue horizontal line is the line of identity; the horizontal green lines represent the mean and limits of agreement of the data; the difference between the line of identity and the mean represents the bias; the red line represents the best fit through the data set

Table 1: Measured and derived demographic variables and hospital status in the total patient population

Variable	Number	Population		
		Total	Men	Women
Sex (n: %)	900		**632 (70.2)**	**268 (29.8)**
Age (yr)	900	55.7 ± 11.6 (20.0 - 84.0)	56.4 ± 11.3 (20.0 - 84.0)	54.3 ± 12.3 (20.0 - 78.0)
Height (cm)	900	165.5 ± 9.3 (134.0 - 190.0)	168.8 ± 7.7 (146.0 - 190.0)	157.5 ± 8.0*** (134.0 - 178.0)
Scale weight (kg)	900	67.0 ± 15.6 (33.5 – 131.8)	69.7 ± 15.7 (40.2 - 131.8)	60.8 ± 13.7*** (33.5 - 105.5)
Ascites (n: %)	900	193 (21.4)	127 (20.1)	66 (24.6)***
Dry weight (kg)	900	65.3 ± 14.9 (33.5 – 131.8)	68.0 ± 14.8 (40.2 - 131.8)	58.9 ± 13.1*** (33.5 - 105.5)
Dry BMI (kg/m^2)	900	23.7 ± 4.5 (13.1 - 41.1)	23.8 ± 4.5 (14.8 - 41.1)	23.7 ± 4.5 (13.1 - 40.7)
Cirrhosis aetiology (n: %)	858		**610 (71.1)**	**248 (28.9)**
Alcohol		198 (23.1)	142 (23.3)	56 (22.6)
NAFLD		48 (5.6)	34 (5.6)	14 (5.6)
HBV		167 (19.5)	136 (22.3)	31 (12.5)
HCV		356 (41.5)	258 (42.3)	98 (39.5)
Other		89 (10.4)	40 (6.6)	49 (19.8)
MELD score	707		**497 (70.3%)**	**210 (29.7%)**
		12.0 ± 5.3 (6.0 - 36.0)	11.6 ± 5.0 (6.0 - 33.0)	12.8 ± 5.8* (6.0 - 36.0)
Pugh's score	379		**251 (66.2%)**	**128 (33.8%)**
		8 ± 2 (5 - 14)	8.0 ± 2.4 (5.0 - 14.0)	8.2 ± 2.3 (5.0 - 13.0)
Child-Pugh Grade (n: %)	460		**310 (67.4)**	**150 (32.6)**
A		143 (31.1)	104 (33.5)	39 (26.0)
B		186 (40.4)	118 (38.1)	68 (45.3)
C		131 (28.5)	88 (28.4)	43 (28.7)
Hospital inpatient (n: %)	900		**397 (62.8)**	**145 (54.1)**

BMI: body mass index; NAFLD: non-alcoholic fatty liver disease; HBV/HCV: hepatitis B/C; MELD: model of end stage liver disease

Data are presented as mean ± 1SD (range) or as number (%)

Significance of the difference between men and women: * $p < 0.05$; ** $p < 0.01$; *** $p<0.001$

JHEPAT-D-21-01918R3

Table 2: Comparison of measured and derived variables in the patients with cirrhosis and healthy controls, by sex and ethnicity

Variable	Patients with Cirrhosis (n = 900)					
	Caucasian			Asian		
	All (n = 429)	Men (n = 286)	Women (n = 143)	All (n = 471)	Men (n = 346	Women (n = 125)
Sex (% men**)**		66.7%			73.5%*	
Age (yr)	51.3 ± 10.8	51.3 ± 10.0	51.3 ± 12.2	59.8 ± 10.9***	60.5 ± 10.6***	57.7 ± 11.5***
Height (cm)	169.0 ± 9.1	173.0 ± 7.0	161.0 ± 7.3	162.3 ± 8.3***	165.4 ± 6.4***	153.6 ± 6.8***
Scale weight (kg)	76.2 ± 15.1	80.6 ± 14.3	67.4 ± 12.6	58.7 ± 10.7***	60.7 ± 10.0^^^	53.2 ± 10.6***
Ascites (%)	183 (42.7%)	120 (42.0%)	63 (44.1%)	10 (2.1%)***	7 (2.0%)***	3 (2.4%)***
Dry weight (kg)	72.8 ± 15.4	77.2 ± 14.7	64.0 ± 13.0	58.5 ± 10.5***	60.5 ± 9.8***	53.0 ± 10.4***
Dry BMI (kg/m^2)	25.5 ± 4.9	25.9 ± 4.9	24.7 ± 4.9	22.2 ± 3.2***	22.1 ± 3.1***	22.4 ± 3.6***
Aetiology (% viral)	32.2%	36.4%	23.8%	89.7%***	89.5%***	90.5%***
MELD score	13.7 ± 5.2	13.6 ± 5.0	14.1 ± 5.5	9.2 ± 4.2***	9.0 ± 3.7***	10.1 ± 5.5***
Variable	**Healthy Controls** (n = 282)					
	Caucasian			Asian		
	All (n = 50)	Men (n = 25)	Women (n = 25)	All (n = 232)	Men (n = 121)	Women (n = 111)
Sex (% men)		50.0%			52.2%	
Age (yr)	50.6 ± 12.4	51.4 ± 12.8	49.9 ± 12.2	32.8 ± 10.5***	32.3 ± 9.9***	33.4 ± 11.2***
Height (cm)	169.6 ± 8.4	175.4 ± 6.9	163.8 ± 5.1	166.3 ± 8.5*	172.0 ± 6.0*	160.1 ± 6.2**
Scale weight (kg)	74.0 ± 12.9	79.6 ± 11.0	68.4 ± 12.3	72.9 ± 16.8	79.2 ± 14.9	66.1 ± 16.1
BMI (kg/m^2)	25.7 ± 3.9	25.9 ± 3.2	25.5 ± 4.5	26.3 ± 5.4	26.8 ± 4.9	25.7 ± 5.8

BMI; body mass index
Data are presented as mean ± 1SD (range) or as number (%)
Significance of the difference between Caucasian and Asian populations: *p <0.05; **p<0.01; *** p<0.001

JHEPAT-D-21-01918R3

Table 3: Measured REE in patients and healthy controls expressed in absolute and relative terms, by sex and ethnicity

Variable	Patients			Healthy controls		
	Total	**Caucasian**	**Asian**	**Total**	**Caucasian**	**Asian**
			Total			
	(n = 900)	(n = 429)	(n = 471)	(n = 282)	(n = 50)	(n = 232)
REE: kcal/24hr	1447 ± 354^^	1652 ± 349^	1261 ± 236^^^,+++	1499 ± 293	1542 ± 283	1489 ± 295
REE: kcal/kg/24hr	22.4 ± 3.8^^^	23.1 ± 4.4^^	21.7 ± 2.9^^^,+++	20.8 ± 2.6	21.0 ± 3.0	20.7 ± 2.5
			Men			
	(n = 632)	(n = 286)	(n = 346)	(n = 146)	(n = 25)	(n = 121)
REE: kcal/24hr	1515 ± 362^^	1765 ± 333	1309 ± 230^^^,+++	1668 ± 248	1691 ± 254	1663 ± 248
REE: kcal/kg/24hr	22.4 ± 3.7^^^	23.2 ± 4.4^	21.8 ± 2.9+++	21.3 ± 2.6	21.4 ± 3.0	21.3 ± 2.5
			Women			
	(n = 268)	(n = 143)	(n = 125)	(n = 136)	(n = 25)	(n = 111)
REE: kcal/24hr	1287 ± 276***	1426 ± 260***	1128 ± 198^^^***,+++	1317 ± 221***	1393 ± 229***	1300 ± 217***
REE: kcal/kg/24hr	22.2 ± 3.9^^^	22.7 ± 4.5^	21.5 ± 3.1^^^,++	20.2 ± 2.5***	20.6 ± 2.9	20.1 ± 2.4***

REE: resting energy expenditure
Data are presented as mean ± 1SD in kcal/24 hr or kcal/kg dry body weight/24 hr
Significance of difference between patients and healthy controls: ^ $p < 0.05$, ^^ $p < 0.02$, ^^^ $p < 0.001$
Significance of the difference between men and women: ***$p < 0.001$
Significances of the difference between Caucasians and Asians populations ++ $p < 0.02$; +++$p < 0.001$

Table 4: Metabolic status in the Caucasian and Asian patients with cirrhosis, by sex expressed in absolute and relative terms

Population	Number	Metabolic status*		
		Hypometabolic	Normometabolic	Hypermetabolic
REE kcal/24 hr				
Total (n:%)				
Total	900	251 (27.9)	491 (54.6)	158 (17.6)
Men	632	290 (45.9)	250 (39.6)	92 (14.6)
Women	268	74 (27.6)	145 (54.1)	49 (18.3)
Caucasian (n:%)				
Total	429	49 (11.4)	254 (59.2)	126 (29.4)
Men	286	50 (17.5)	157 (54.9)	79 (27.6)
Women	143	16 (11.2)	94 (65.7)	33 (23.1)
Asian (n:%)				
Total	471	210 (44.6)	246 (52.2)	15.(3.2)
Men	346	245 (70.8)	98 (28.3)	3 (0.9)
Women	125	59 (47.2)	59 (47.2)	7 (5.6)
REE kcal/kg dry body weight/24 hr				
Total (n:%)				
Total	900	95 (10.6)	519 (57.7)	**286 (31.8)**
Men	632	86 (13.6)	369 (58.4)	**177 (28.0)**
Women	268	30 (11.2)	135 (50.4)	**103 (38.4)**
Caucasian (n:%)				
Total	429	45 (10.5)	225 (52.4)	**159 (37.1)**
Men	286	32 (11.2)	159 (55.6)	**95 (33.2)**
Women	143	17 (11.9)	73 (51.0)	**53 (37.1)**
Asian (n:%)				
Total	471	50 (10.6)	302 (64.1)	**119 (25.3)**
Men	346	51 (14.7)	224 (64.7)	**71 (20.5)**
Women	125	13 (10.4)	68 (54.4)	**44 (35.2)**

*Thresholds for determination of metabolic status were derived from the mean ± 1SD of the relevant healthy control population

Table 5: Distribution of predicted REE relative to measured REE in 900 patients with cirrhosis, by sex and ethnicity

Method	REE (kcal/24 hr)	Measured vs. Predicted		
		Under	Within	Over
Total (n = 900)				
Measured	1447 ± 354			
Harris-Benedict	1403 ± 258^{++}	95 (10.6%)	738 (82.0%)	67 (7.4%)
Mifflin	1368 ± 249^{+++}	121 (13.4%)	745 (82.8%)	34 (3.8%)
Schofield	1469 ± 256	39 (4.3%)	763 (84.8%)	98 (10.9%)
Henry	1420 ± 243	61 (6.8%)	777 (86.3%)	62 (6.9%)
Men (n = 632)				
Measured	1515 ± 362			
Harris-Benedict	1466 ± 267^{++}	84 (13.3%)	506 (80.1%)	42 (6.6%)
Mifflin	1463 ± 208^{++}	36 (5.7%)	581 (91.9%)	15 (2.4%)
Schofield	1550 ± 251^{+}	28 (4.4%)	550 (87.0%)	54 (8.5%)
Henry	1503 ±225	18 (2.8%)	580 (91.8%)	34 (5.4%)
Women (n = 268)				
Measured	1287 ± 276			
Harris-Benedict	1256 ± 157	6 (2.2%)	249 (92.9%)	13 (4.9%)
Mifflin	1145 ± 188^{+++}	73 (27.2%)	190 (70.9%)	5 (1.9%)
Schofield	1279 ± 143	6 (2.2%)	252 (94.0%)	10 (3.7%)
Henry	1225 ± 154^{++}	15 (5.6%)	247 (92.2%)	6 (2.2%)
Caucasian (n = 429)				
Measured	1652 ± 349			
Harris-Benedict	1540 ± 252^{+++}	80 (18.6%)	333 (77.6%)	16 (3.7%)
Mifflin	1481 ± 244^{+++}	107 (24.9%)	317 (73.9%)	5 (1.2%)
Schofield	1591 ± 250^{++}	62 (14.5%)	344 (80.2%)	23 (5.4%)
Henry	1535 ± 244^{+++}	84 (19.6%)	332 (77.4%)	13 (3.0%)
Asian (n = 471)				
Measured	1261 ± 236			
Harris-Benedict	1279 ± 193	24 (5.1%)	379 (80.5%)	68 (14.4%)
Mifflin	1265 ± 205	66 (14.0%)	345 (73.2%)	60 (12.7%)
Schofield	1359 ± 207^{+++}	7 (1.5%)	323 (68.6%)	141 (29.9%)
Henry	1316 ± 188^{+++}	20 (4.2%)	365(77.5%)	86 (18.3%)

Data are presented as mean ± 1SD or as number (%)

Significance of the difference between mREE and pREE estimates: $^{++}$ $p < 0.01$; $^{+++}$ $p < 0.001$

Table 6: Degree of agreement between measured REE and the estimates provided by the four prediction equations in patients with cirrhosis, by sex and ethnicity

Method	REE (kcal/24 hr)	Mean/SD of Differences	Limits of Agreement	Range^
		Total (n = 900)		
Measured	1447 ± 354			
Harris-Benedict	1403 ± 258^{++}	44 + 224	-404 to 492	-565 to 1361
Mifflin	1368 ± 249^{+++}	79 + 234	-390 to 548	-520 to 1460
Schofield	1469 ± 256	-22 + 239	-501 to 456	-688 to 1319
Henry	1420 ±243	27 + 234	-441 to 495	-602 to 1390
		Men (n = 632)		
Measured	1515 ± 362			
Harris-Benedict	1466 ± 267^{++}	49 + 234	-419 to 518	-565 to 1361
Mifflin	1463 ± 208^{++}	52 + 246	-440 to 545	-520 to 1460
Schofield	1550 ± 251^{+}	-35 + 250	-535 to 465	-688 to 1319
Henry	1503 ±225	12+ 245	-477 to 501	-602 to 1390
		Women (n = 268)		
Measured	1287 ± 276			
Harris-Benedict	1256 ± 157	31 + 197	-362 to 425	-542 to 706
Mifflin	1145 ± 188^{+++}	142 + 190	-238 to 522	-421 to 835
Schofield	1279 ± 143	7 + 208	-409 to 424	-648 to 665
Henry	1225 ± 154^{++}	62 + 203	-343 to 467	-581 to 757
		Caucasian (n = 429)		
Measured	1652 ± 349			
Harris-Benedict	1540 ± 252^{+++}	112 + 263	-414 to 638	-565 to 1361
Mifflin	1481 ± 244^{+++}	171 + 263	-356 to 698	-515 to 1460
Schofield	1591 ± 250^{++}	61 + 268	-475 to 597	-688 to 1319
Henry	1535 ± 244^{+++}	117 + 266	-414 to 648	-602 to 1390
		Asian (n = 471)		
Measured	1261 ± 236			
Harris-Benedict	1279 ± 193	-18 + 157	-333 to 297	-524 to 510
Mifflin	1265 ± 205	-5 + 165	-335 to 325	-520 to 499
Schofield	1359 ± 207^{+++}	-69 + 178	-455 to 258	-601 to 528
Henry	1315 ± 188^{+++}	-55 + 162	-379 to 269	-538 to 487

Data are presented as mean ± 1SD

^Range: minimum/maximum difference between measured and predicted REE

Significance of the difference between measured REE and predicted estimates; $^{++}$ $p < 0.01$;$^{+++}$ $p < 0.001$

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Highlights

- Malnutrition has a significant negative effect on outcome in patients with cirrhosis
- Accurate information on daily energy requirements is essential for effective nutritional management
- Prediction equations provide estimates of daily energy expenditure but these vary significantly by ethnicity and can range from 501 kcal less to 548 kcal more than measured values
- Where available, resting energy expenditure should be measured using indirect calorimetry