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Original article

Course of measured energy expenditure over the first 10 days of critical illness: A nested prospective study in an adult surgical ICU

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SUMMARY

Background & aims: Various factors may cause significant daily variations in energy expenditure in and between critically patients. This nested, prospective study (ClinicalTrials.gov Identifier: NCT04099108) in a predominantly trauma surgical ICU, aimed to determine the course of measured energy expenditure over the first 10 days of critical illness, and to identify factors contributing to energy expenditure.

Methods: Indirect calorimetry was performed on alternate days from ICU Day 3 ± 1 until Day 10 ± 1. The mean daily measured energy expenditure, respiratory quotient and total energy delivery as a percentage of measured energy expenditure were modelled using linear mixed regression with two fractional polynomial terms to accommodate non-linear responses over time.

Results: Fifty ICU patients (mean age 36.9 ± 11.8 years, Acute Physiology and Chronic Health Evaluation (APACHE II) 13.5 ± 6.6, Sequential Organ Failure Assessment (SOFA) 4.5 ± 3.2) were included. Mean body mass index (BMI) was 24.8 ± 4.0 kg/m² and mean ventilation duration 7.7 ± 2.7 days. Mean daily measured energy expenditure showed a significant non-linear response ($p = 0.006$) increasing over the first 4 days peaking on day 5 and then plateauing. Mean daily respiratory quotient increased over the first 7 days, thereafter plateauing with a slight downward trend from day 8 despite a progressive increase in total energy delivery as a percentage of measured energy expenditure. Mean daily measured energy expenditure was significantly lower in the early than in the late acute phases ($p = 0.024$), whereas the late- and post-acute phases were similar. Age, sex and BMI significantly influenced measured energy expenditure.

Conclusion: Measured energy expenditure showed a significant non-linear response over the first 10 days in ICU, increasing over the first 4 days peaking on day 5 then plateauing. The observed variability highlights the complexity of managing critically ill patients and the importance of personalised nutrition therapy. Additionally, the observed trend with a peak in measured energy expenditure around day five could inform timing and strategies for nutritional intervention in this patient cohort.

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Abbreviations: IC, indirect calorimetry; MEE, measured energy expenditure; RQ, respiratory quotient; TED, total energy delivery; TED/MEE%, TED as a percentage of MEE; ICU, intensive care unit; BMI, body mass index.

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1. Introduction

The optimal amount and timing of nutrient delivery for critically ill patients remains controversial [1]. Resting energy expenditure may vary greatly during critical illness and measuring it by indirect calorimetry (IC) [1–6] may help to prevent over- and underfeeding, both of which have been shown to affect patient outcomes adversely in the ICU [2–4]. According to two recent meta-analyses IC-guided nutritional support may positively impacts short-term mortality [5,6].

However, until recently limited availability and technical difficulties associated with the use of IC, have hindered its routine use and predictive equations which correlate poorly with IC values are still often used in clinical practice [4]. In the largest study to date, Zusman et al. [4] compared predictive equations with measured energy expenditure (MEE) in a large cohort of critically ill patients ($n = 1440$), and found that agreement, within 10 % of energy needs, was met only in a third of patients. Furthermore, they found that initial MEE measurements were below those of subsequent measurements, illustrating the dynamic and complex nature of the metabolic stress response that may cause daily variations in resting energy expenditure [4]. The various factors that may cause daily variations in MEE, such as the type of injury, severity of disease, nutritional status, physical immobility, change in the clinical course, and medical treatment (e.g. ventilation, surgery, sedation), illustrate the need for continuous monitoring of energy expenditure in patients during their intensive care unit (ICU) stay [2,3]. In fact, guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) caution against full feeding in the early phase of critical illness when a large proportion of the energy expenditure is provided by endogenous energy production from unmeasured non-inhabitable catabolic processes [7,8]. Mitochondrial dysfunction may also cause exogenous substrate to be bioenergetically underutilized [1], increasing the risk for overfeeding. As such, ESPEN recommends provision of no more than 70 % of MEE in the early acute phase (day 1–3), 80–100 % of MEE in the late acute phase (day 4–7) and, in the absence of IC, restriction of energy intake to 70 % of estimated needs during the first week [7,8]. Furthermore, the ratio of carbon dioxide production (VCO_2) to oxygen consumption (VO_2) that is, the respiratory quotient (RQ) [9], may help to identify potential underfeeding and overfeeding. With a physiological range between 0.67 and 1.3 [10], depending on substrate oxidation (0.7 for fat; 0.8 for proteins; 1 for carbohydrates) [2], overfeeding may cause a rise in the volume of carbon dioxide produced (VCO_2) by the body and RQ by promoting lipogenesis and underfeeding a reduction in the RQ by promoting lipolysis [10]. Furthermore, apart from the situation in which a patient is fasting, a lower RQ early in critical illness could indicate an inability to utilize carbohydrates as an energy source, owing to mitochondrial dysfunction [11].

Due to the dynamic nature of critical illness, this study aimed to gain deeper insight into the daily variations in MEE over the first 10 days in a predominantly trauma surgical ICU, and to identify potential factors that may cause variations in MEE. As a secondary outcome, we also investigated daily variations in RQ and total energy delivery (TED), expressed as a percentage of MEE (TED/MEE%).

2. Materials and methods

2.1. Study design and ethical considerations

This was a prospectively planned sub-analysis of a single-center randomized controlled trial (ProMob-ICU; clinical [trials.gov](https://www.trials.gov), NCT04099108) undertaken in an adult surgical ICU of a tertiary hospital in Cape Town, South Africa. The primary study was

approved by the Stellenbosch University Health Research Ethics Committee (M20/08/023) and was performed in accordance with the ethical standards as laid down in the Declaration of Helsinki. The primary study investigated the impact of a combined strategy of intravenous bolus amino acid supplementation and in-bed cycling, versus standard care only, on skeletal muscle during the acute phase of critical illness, and integrated IC into the standard care nutrition provided to all participants in accordance with the ESPEN guidelines for nutrition support in critical illness [8]. The primary aim of this sub-analysis was to investigate the course of MEE over the first 10 days in the ICU among all study participants, treated as a single cohort. In this analysis, adjustments were made for the intervention, which was treated as a confounding variable and served as a proxy for its components: amino acid supplementation and exercise.

2.2. Inclusion and exclusion criteria

All adult patients (>18 years) admitted to the 14 bed surgical ICU of Tygerberg Hospital, a university-affiliated tertiary-care medical centre, from May 2021 to September 2022, that had been entered into the primary study were included in this secondary analysis of MEE. Patients expected to remain in ICU for ≥ 7 days, require mechanical ventilation for ≥ 48 h and who would receive enteral and/or parenteral nutrition for a minimum of 5 days, were eligible for the primary study. As per the primary study, the following conditions were excluded, spinal cord lesions or intracranial processes associated with muscle weakness, acute or chronic degenerative neuromuscular conditions (e.g. Guillain Barre), fulminant hepatic failure or severe chronic liver disease [Model for End-stage Liver Disease (MELD) score ≥ 20] or new-onset or worsening renal failure [acute kidney injury network (AKIN) stage 3 and not on renal replacement therapy], untreated thrombosis, or thrombosis where therapeutic levels of anticoagulants had not been reached at the time of inclusion, or any evidence of active bleeding, an estimated BMI ≥ 35 kg/m² and/or estimated weight ≥ 150 kg, potential for imminent death or withdrawal of treatment, pregnancy, readmission after previous randomisation, as well as any other condition deemed inappropriate. The eligibility criteria for the primary study are listed in full in [Supplementary file 1](#). Written consent was obtained from the patient or legal representative.

2.3. Management of nutritional support and mobilisation

All participants recruited to the primary study received nutrition according to the 2019 ESPEN clinical practice guideline for intensive care [8], hereafter referred to as “standard care nutrition” (SCN). SCN was initiated early and gradually increased over the first 72 h as tolerated. Total energy targets were set at ≤ 70 % of MEE during the first 72 h, 80–100 % of MEE between day 4–7, and 100 % of MEE after day 7. Study participants who were randomised to the intervention arm of the primary study received an additional intravenous amino acid supplement from ICU day 4 ± 1 for a mean of 6 days and this was incorporated into their daily energy allowance, in order to avoid overfeeding. The number of hours spent in ICU on the day of admission was taken into account when targets were set. In the absence of IC (e.g. contraindication to IC), daily energy targets were kept at 20 kcal/kg (maximum 25 kcal/kg) from day 4 until day 7 and increased to 25 kcal/kg (maximum 30 kcal/kg) from day 7–10. All participants were monitored for refeeding syndrome and received adequate vitamin and trace element supplementation.

All study participants received routine mobilisation as per the unit's protocol and practice and this was carried out by the on-site physiotherapist. Routine mobilisation included respiratory

physiotherapy, as well as physical rehabilitation, such as positioning, range of motion and strengthening exercises and in-bed mobility. Routine mobilisation was not altered because of inclusion in the study. Half of the participants received an additional 45 min of progressive lower limb in-bed cycling using a bedside cycle ergometer, in combination with the intravenous amino acid supplement, from ICU Day 4 $\pm$ 1 for a mean of 6 days.

2.4. Indirect calorimetry

IC measurements were performed using the Q-NRG+® (COSMED®, Italy) system on ICU Day 3 $\pm$ 1 and on alternate days thereafter according to a standardised operating procedure based on the recommendations and technical specifications of the manufacturer. Measurements were performed with the device in ventilator mode, and after extubation, in canopy mode. An in-vitro validation study of the Q-NRG+® device against mass spectrometry confirmed its accuracy within 5 % at oxygen enrichments up to 70 %, i.e. the maximum expected for clinical use [12], and it is currently the only commercially available device that has been evaluated against mass spectrometry to ensure gas accuracy [13]. Furthermore, in a clinical validation study by the ICALIC group, Oshima et al. [13] established that the Q-NRG+® required a much shorter time than most other devices to measure energy expenditure in mechanically ventilated ICU patients.

The pneumotach (Flow-REE) flowmeter was calibrated before each measurement, and the gas analysers, and internal turbine flowmeter once per month as per the manufacturer's recommendations. Measurements were carried out for 30 min (10 min for canopy hood measurements) in the morning during resting steady state conditions, which was determined by a calculated coefficient of variation (CV) % for VO_2 and VCO_2 of <10 % [14]. To achieve this, a resting period of at least 60 min was ensured in the case of any potentially strenuous or stressful event, such as those involving patient hygiene, physiotherapy, or any invasive or diagnostic procedures. In participants allocated to the intervention arm of the primary study, IC was performed in the mornings at least an hour prior to the cycling intervention to eliminate the potential impact that cycling may have on the MEE. Before the measurements, operators excluded any leak in the airway circuit, and confirmed that participants were hemodynamically stable and in a supine position, ventilated with fraction of inspired oxygen (FiO_2) less than 0.6, a positive end expiratory pressure (PEEP) of ≤ 12 cm H_2O , and that no change in ventilator settings had been performed within 1–2 h of the IC measurement. Furthermore, the RQ had to be within the physiological range of 0.67–1.2 in order to rule out any measurement inaccuracies [14,15]. None of the study participants received non-invasive oxygen therapy, peritoneal- or haemodialysis, haemodiafiltration, or continuous renal replacement therapy. The instructions for use of the metabolic monitor are described in [Supplementary File 2](#).

2.5. Data collection and management

Data were collected from ICU admission up to ICU Day 10. If a participant was discharged from the ICU before Day 10, data collection continued until the time of ICU discharge. Data were captured and stored on REDCap, ensuring that only authorized investigators with appropriate permissions could access the data. Patient information was stored using unique study numbers rather than names, maintaining strict confidentiality. Additionally, all data were anonymized for analysis to further protect patient privacy. We adhered to rigorous protocols to ensure that only investigators had access to the data throughout the study.

The following data were collected:

- **Demographic and baseline data:** age, gender, body-mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, modified Nutrition Risk in Critically Ill (mNUTRIC) score, Global Leadership in Malnutrition (GLIM) classification, inflammatory markers (C-reactive protein(CRP)), number of comorbidities, presence of sepsis and septic shock, mean epinephrine infusion dose at ICU day 1 and day 4, and administration of sedatives.
- **ICU stay (up to day 10):** ICU length of stay, length of ventilation, mortality.
- **Indirect calorimetry:** MEE, RQ, VO_2 and VCO_2 , and CV% for VO_2 and VCO_2 .
- **Nutritional data:** Time to initiation of SCN, route of SCN, daily TED from nutritional and non-nutritional exogenous sources (expressed as kcal/day and kcal/kg/day), daily TED expressed as a percentage of MEE (TED/MEE%).

2.6. Sample size and statistical analysis

The sample size was calculated according to the requirements of the primary study, which included a minimum of 46 participants, allowing for a potential drop-out rate of 20 % (including in-hospital mortality).

Descriptive statistics for the study variables included means, standard deviations, frequencies and percentages. The repeated MEE measurements were modelled on time using a linear mixed regression model with two time-related, fractional polynomial terms to accommodate for the non-linear response profile over time and participants were taken as the random effect with random intercepts and slopes for time. The MEE model was further adjusted for age, BMI, gender, number of pre-hospital days, CRP, APACHE II, SOFA and mNUTRIC score at baseline, as well as for the primary study arm allocation to rule out any potential confounding effects that the intervention performed in the primary study (additional amino acid supplementation and in-bed cycling) may have had on MEE. For displaying the unadjusted mean trends over time for RQ and TED as a percentage of MEE (TED/MEE%), a non-parametric Lowess smoother was used. The ICU time was stratified into early, late and post-acute periods. Mean values were estimated for various outcomes using linear mixed effects models to account for the repeated measurements within participants. The statistical analyses were conducted using STATA 18 and a significance level of 0.05 was used.

3. Results

3.1. Demographics and baseline characteristics

A total of 50 participants were recruited to the primary study during the study period, and were included in this secondary analysis, which focused on the MEE. The demographics and disease severity characteristics are presented in [Table 1](#). The mean age was 37 years and 90 % were male. The time to initiation of SCN was 25.67 ± 22.45 (n = 46, median 19, 0–71) hours. In four participants, nutrition support had already been initiated in the general ward prior to ICU admission. The initial route of SCN was enteral for 78 % of participants (39/50), parenteral for 10 % (5/50) and mixed for 12 % (6/50). Fifty-six percent of participants (30/50) received supplemental parenteral nutrition during the first 10 days in ICU in order to meet set nutrient targets. Participants received sedation as a continuous intravenous infusion for an average of 4 days (median 3) during the first 10 days of ICU stay with 236 total sedation days for all participants. The most common analgesic/sedative agent administered as a continuous infusion was fentanyl in 76.3 % of

Table 1
Demographics and disease severity characteristics of study participants.

Variables	Mean $\pm$ SD
Demographics	
Male (n, %)	45 (90)
Age, years	36.9 $\pm$ 11.8 (35.65)
Number of comorbidities	0.5 $\pm$ 1.0 (0)
Type of admission	
Surgical (n, %)	45 (90)
Medical (n, %)	5 (10)
Primary admission diagnosis	
Trauma (n, %)	38 (76)
Gastrointestinal (n, %)	9 (18)
Respiratory (n, %)	3 (6)
Nutritional status/risk	
Body height, m	1.7 $\pm$ 0.1 (1.7)
Body weight, kg	72.6 $\pm$ 13.5 (72.0)
BMI, kg/m ²	24.8 $\pm$ 4.0 (24.6)
Malnourished according to GLIM (n, %)	12 (24 %)
mNUTRIC score	2.2 $\pm$ 1.8 (2.0)
Disease severity	
APACHE II, admission	13.5 $\pm$ 6.6 (12.0)
SOFA, admission	4.5 $\pm$ 3.2 (4.5)
SOFA, D4	1.4 $\pm$ 1.8 (1.0)
CRP, admission, mg/L	244.4 $\pm$ 158.8 (195.5)
CRP D4 $\pm$ 1, mg/L	251.8 $\pm$ 106.4 (252.5)
CRP D7 $\pm$ 1, mg/L	186.9 $\pm$ 98.7 (166.0)
CRP D10 $\pm$ 1, mg/L	163.8 $\pm$ 91.2 (155.0)
Epinephrine dose, μg/kg/min	
Baseline (n = 31)	0.3 $\pm$ 0.3 (0.2)
D4 (n = 4)	0.2 $\pm$ 0.2 (0.1)
Sedation days ^a	4.4 $\pm$ 3.5 (3.0)
ICU length of stay at D10, days	9.3 $\pm$ 1.1 (10.0)
Length of ventilation at D10, days	7.7 $\pm$ 2.7 (9)
Mortality at D10 (n, %)	2 (4 %)

^a Sedation days: number of days a participant received an analgesic/sedative agent via intravenous infusion.

Abbreviations: BMI: body mass index; GLIM: Global Leadership in Malnutrition (GLIM) classification; mNUTRIC: modified Nutrition Risk in Critically Ill; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; CRP: C-reactive protein; D4: ICU Day 4, D7: ICU Day 7, D10: ICU Day 10.

participants, for a total of 180 analgesia/sedation days, followed by propofol in 28.4 % for a total of 67 sedation days. By ICU day 10, 78 % of participants (38/50) still remained in the ICU.

IC measurements were performed in 48 of the 50 participants, for a total of 115 measurements. Of these, 94 (81.7 %) were performed in the ventilator mode and 21 (18.3 %) in the canopy mode. A total of 38 (79.17 %) patients had ≥ 2 IC measurements, and 23 (47.9 %) had ≥ 3 measurements. IC measurements were not performed in 2 of the 50 participants due to dependency on supplemental oxygen after extubation, high PEEP, or a coefficient of variation exceeding 10 %.

3.2. Mean daily measured energy expenditure, respiratory quotient and energy delivery over ICU days

Table 2 provides the mean daily MEE, VCO₂, RQ, TED and TED as a % of MEE delivered from ICU Day 0 (as the day of ICU admission) until Day 10 of ICU admission. It depicts a daily variation in MEE, RQ and TED/MEE% over time. For patients with more than one measurement (n = 38), the mean difference between maximum and minimum MEE was 358.9 ($\pm$ 173.0) kcal).

3.3. Mean daily measured energy expenditure grouped according to the phases of critical illness

IC measurements were also analysed according to the exact number of hours after ICU admission that they were performed, grouping them according to the following arbitrary time intervals,

Table 2
Mean daily measured energy expenditure, respiratory quotient and total energy and protein delivery.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Measured energy expenditure (MEE)											
n-size	0	0	19	15	18	17	8	16	14	8	0
kcal/d	–	–	1858.6 $\pm$ 283.4 (1833)	2104.3 $\pm$ 236.3 (2109.0)	1976.3 $\pm$ 462.0 (1884.0)	2123.60 $\pm$ 285.2 (2152.0)	1810.4 $\pm$ 343.1 (1832.0)	2313.9 $\pm$ 323.1 (2265.0)	1915.1 $\pm$ 396.9 (1936.5)	2178.4 $\pm$ 255.6 (2199.5)	–
kcal/kg/d	–	–	28.5 $\pm$ 3.5 (28.0)	30.3 $\pm$ 4.1 (31.0)	29.7 $\pm$ 4.7 (29.0)	29.5 $\pm$ 3.0 (30.0)	28.8 $\pm$ 4.9 (28.5)	32.5 $\pm$ 5.7 (32.5)	28.7 $\pm$ 5.0 (28.0)	28.6 $\pm$ 3.6 (28.5)	–
VCO ₂	–	–	203.1 $\pm$ 52.6 (210.0)	245.8 $\pm$ 30.2 (244.0)	233.2 $\pm$ 50.2 (217.5)	249.5 $\pm$ 31.5 (252.00)	222.4 $\pm$ 35.0 (232.5)	287.1 $\pm$ 41.7 (278.0)	232.6 $\pm$ 45.6 (234.0)	259.9 $\pm$ 29.7 (255.0)	–
RQ	–	–	0.79 $\pm$ 0.07 (0.78)	0.80 $\pm$ 0.04 (0.80)	0.82 $\pm$ 0.11 (0.80)	0.81 $\pm$ 0.05 (0.82)	0.87 $\pm$ 0.08 (0.84)	0.86 $\pm$ 0.07 (0.83)	0.85 $\pm$ 0.05 (0.86)	0.83 $\pm$ 0.08 (0.84)	–
Total energy and protein delivery^a											
n-size	50	50	50	50	50	50	50	49	46	39	34
kcal/d	197.1 $\pm$ 301.2 (109.0)	573.6 $\pm$ 418.2 (500.25)	944.9 $\pm$ 480.6 (878.0)	1357.9 $\pm$ 445.3 (1451.6)	1687.7 $\pm$ 400.3 (1714.2)	1828.0 $\pm$ 411.1 (1861.8)	1954.2 $\pm$ 460.9 (1984.1)	1983.2 $\pm$ 457.5 (2042.8)	1889.3 $\pm$ 582.1 (1996.9)	1788.9 $\pm$ 613.1 (1943.7)	1768.8 $\pm$ 697.8 (1949.5)
kcal/kg/d	4.7 $\pm$ 7.5 (2.0)	8.7 $\pm$ 6.8 (7.0)	14.0 $\pm$ 7.5 (14.0)	19.8 $\pm$ 6.8 (21.0)	24.3 $\pm$ 6.0 (24.5)	26.6 $\pm$ 6.4 (27.5)	28.3 $\pm$ 7.4 (28.0)	29.0 $\pm$ 6.2 (29.0)	29.7 $\pm$ 5.9 (29.0)	27.4 $\pm$ 7.1 (28.0)	28.3 $\pm$ 7.7 (30.0)
g Prot/d	6.1 $\pm$ 12.8 (0.0)	21.8 $\pm$ 24.6 (11.0)	47.4 $\pm$ 36.3 (44.0)	78.8 $\pm$ 34.1 (87.0)	103.1 $\pm$ 26.2 (110.0)	108.2 $\pm$ 24.5 (106.0)	113.2 $\pm$ 25.5 (103.0)	113.7 $\pm$ 28.6 (117.0)	103.1 $\pm$ 32.8 (109.0)	95.6 $\pm$ 38.9 (104.0)	88.5 $\pm$ 39.5 (94.5)
Total energy delivery (TED) as a percentage of MEE^b											
n-size	0	0	19	15	18	17	8	16	14	8	0
TED/MEE %	–	–	59.5 $\pm$ 21.1 (58.0)	64.9 $\pm$ 16.3 (87.0)	84.4 $\pm$ 20.0 (88.5)	88.8 $\pm$ 23.4 (96.0)	100.2 $\pm$ 9.4 (102.5)	94.2 $\pm$ 11.1 (95.5)	103.0 $\pm$ 27.7 (99.0)	100.8 $\pm$ 8.9 (103.0)	–

Data presented as mean $\pm$ SD (median).

Abbreviations: MEE: measured energy expenditure; RQ: Respiratory quotient; VCO₂: Carbon dioxide production; VO₂: Oxygen consumption; TED: total energy delivery.

^a Day 0: Day of ICU admission.

^b This included nutritional and non-nutritional exogenous energy sources (e.g. propofol, dextrose-containing intravenous fluids).

^c This was only calculated for patients with an indirect calorimetry measurement for the day.

i.e., <72 h (denoted as the early acute phase), 72–168 h (denoted as the late acute phase) and >168 h (as the post-acute phase) after ICU admission. Table 3 provides the daily MEE, RQ and VCO₂ according to these time intervals. Mean daily MEE was significantly lower in the early (<72 h) than in the late acute phases (72–168 h), and mean daily RQ significantly lower in the early versus the late acute (72–168 h) and post-acute (>168 h) phases.

3.4. Mean daily MEE, RQ and TED modelled over time using a linear regression model

In figures 1a and b the mean daily MEE, RQ and TED as a percentage of MEE is modelled over time using a linear regression model with two fractional polynomial terms to accommodate the non-linear response profile over time. MEE increased over the first 4 days, peaking on day 5 and then plateauing, whereas the RQ increased over the first 7 days, thereafter showing a slight downward trend despite a progressive increase in TED and TED/MEE%. Table 4 provides the modelled daily MEE values for Fig. 1a along with its confidence intervals.

3.5. Factors influencing daily measured energy expenditure

In multiple regression modelling of daily MEE as depicted in Fig. 1a the following factors were significantly associated with MEE (Table 5), age, BMI and sex, whereas primary study arm allocation, IC mode (ventilator versus canopy), SOFA, APACHE II, mNUTRIC scores on admission, and CRP were not. Figure 2 shows that MEE and CRP operate independently; CRP decreasing over time whilst MEE rises or remains flat.

4. Discussion

Due to the dynamic nature of critical illness and various internal and external patient factors, energy expenditure can vary daily both within and between patients [1]. This study confirmed these variations in that MEE exhibited a significant non-linear response over time ($p = 0.0058$) especially in the early acute phase. Various factors may indeed have contributed to the daily variations in MEE in this study. Firstly, despite the majority of participants being young, trauma-related, surgical patients, there was still inherent heterogeneity in terms of the nature of their injuries, severity of the inflammatory response, and type of surgical procedures performed [1,9]. These differences could lead to substantial variations in metabolic responses and, consequently, resting energy expenditure. Secondly, day-to-day physiological fluctuations, such as changes in infection status, body temperature, medication administration (e.g., sedatives, vasopressors), feeding state and level of mobilisation, can cause metabolic variations and impact resting energy expenditure [1,9]. Methodological factors may further contribute to variation. Even when following a protocol and excluding measurements with high coefficients of variance, small

methodological differences could still introduce variability. For example, variations in equipment calibration, environmental factors, or slight deviations in how measurements are conducted (e.g., small differences in the timing of measurements relative to feeding or medication administration) could contribute to the observed spread in values [1]. Given that this was a secondary analysis of a primary study, there could be concerns that study arm allocation (intervention vs. control group) might have influenced the MEE, especially since the intervention group received daily cycling and an additional amino acid supplement. However, we did account for these potential confounders by including study arm allocation in the multiple regression model. The analysis showed no significant interaction between study arm allocation and MEE. Therefore, while we observed significant variations in MEE, these were unlikely to be attributable to study arm allocation.

Furthermore, a linear mixed regression model which accommodated the non-linear response profile over time demonstrated that MEE increased over the first 4 days, peaking on day 5 then plateauing. This observed trend may reflect the progression of the patient's physiological response to critical illness as previously described [16]. Initially, during the early acute phase, patients are likely to be still in the “ebb” phase of the stress response, characterized by shock and reduced metabolic activity, which could be the reason for the lower MEE observed on day 2. As patients transition into the “flow” phase of the stress response, marked by a hyper-inflammatory state and increased metabolic demands, there is a more significant increase in MEE, culminating on day five. The plateau observed after day five may indicate the beginning of a resolution phase, where the inflammatory process begins to subside, leading to stabilization in resting energy expenditure [1]. A similar trend was observed in a recent prospective observational study by Moonen et al. [17], where MEE increased significantly from 26 (24–27) kcal/kg on the day of ICU admission to 29 (29–30) kcal/kg/day ($p < 0.001$) on ICU-admission-day 4. Thereafter, MEE was not significantly different between days 4 and 7 or on subsequent ICU measurements. Their study cohort ($n = 56$) was predominantly medical (80 % medical versus 20 % surgical) and had more females (38 % females) compared to our study, showing that the change in MEE observed in our study could be extrapolated to a wider ICU population.

The IC measurements, when grouped according to the phases of critical illness based on hours since ICU admission, revealed that MEE was significantly lower in the early (≤ 72 h) compared to the late acute phase (72–168 h; i.e. day 4–7), whereas the late- and post-acute- phases were similar. This finding underscores the reduced metabolic activity that occurs during the early acute phase of the stress response, typically defined as the first 72 h in the ICU. This reduction in metabolic activity is thought to result from mitochondrial dysfunction, which may serve as an adaptive strategy for metabolic downregulation. This adaptation potentially helps prevent cell death by avoiding overload of energy substrate at a time when mitochondria are unable to meet the heightened

Table 3

Mean daily measured energy expenditure, respiratory quotient and carbon dioxide production according to the phase of critical illness.

	Early acute (<72 h) (n = 20)	Late acute (72–168hr) (n = 45)	Post-acute (>168hr) (n = 23)
MEE, kcal/d (mean, CI)	1979.9 (1875.7; 2084.2) ^a	2091.5 (1992.0; 2191.0) ^a	2024.1 (1886.5; 2161.8)
MEE, kcal/kg/d (mean, CI)	29.0 (27.8; 30.3)	30.1 (CI 28.9; 31.3)	29.0 (CI 27.1; 30.9)
RQ (mean, CI)	0.80 (CI 0.77; 0.82) ^b	0.84 (0.82; 0.85) ^b	0.85 (CI 0.82; 0.85) ^b
VCO ₂ (mean, CI)	223.3 (CI 208.8; 237.7) ^c	249.4 (235.8; 263.0) ^c	242.9 (CI 225.1; 260.8) ^c

MEE: measured energy expenditure; RQ: respiratory quotient; CI: confidence interval; VCO₂: Carbon dioxide production.

^a MEE comparison of early acute with late acute phase: $p = 0.024$.

^b RQ comparison of early acute with late acute phase: $p = 0.005$; RQ comparison of early acute with post-acute phase: $p = 0.004$.

^c VCO₂ comparison of early acute with late acute phase: $p = 0.000$; VCO₂ comparison of early acute with post-acute phase: $p = 0.022$.

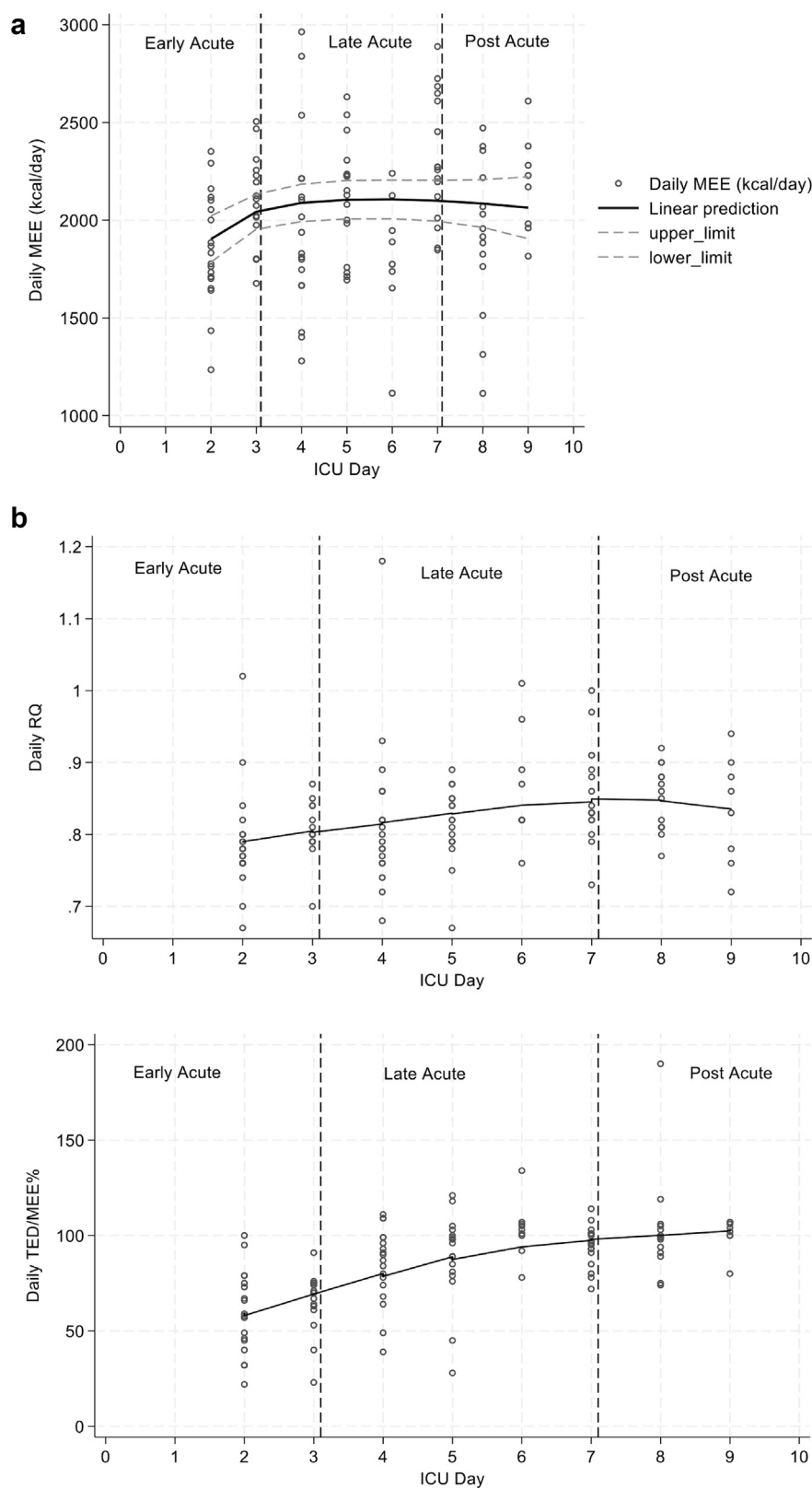


Fig. 1. a Daily MEE (kcal/day) modelled over time using fractional polynomials with the three clinical acute periods indicated. b Respiratory quotient (RQ) and total energy delivery (TED) as a % of MEE (kcal/day) modelled over time using a non-parametric Lowess smoother with the three clinical acute periods indicated.

Table 4
Measured energy expenditure (MEE) modelled over time using a linear regression model.

	ICU Day 2	ICU Day 3	ICU Day 4	ICU Day 5	ICU Day 6	ICU Day 7	ICU Day 8	ICU Day 9
Modelled MEE (kcal/day)	1903.7	2043.3	2063.8	2085.3	2088.7	2099.8	2104.7	2106.8
Confidence interval	1785.8; 2021.7	1905.7; 2132.7	1954.0; 2184.3	1962.9; 2202.9	1993.1; 2204.3	1995.2; 2205.9	2006.5; 2207.7	2007.7; 2221.9

Table 5
Regression of daily measured energy expenditure (kcal/day) on baseline factors.

	Regression coefficient	Confidence interval	P value
Primary study arm	−99.7	−227.8; 28.3	0.127
IC mode (ventilator/canopy)	28.0	−119.2; 175.1	0.710
Age	−13.8	−21.2; −6.4	0.000*
BMI	65.9	45.6; 86.3	0.000*
Sex	−387.1	−611.3; −163.0	0.001*
Hospital days prior to ICU	−2.7	15.9; 10.5	0.689
SOFA	−11.4	−43.5; 20.8	0.488
APACHE II	11.4	−10.3; 33.0	0.302
mNUTRIC	7.9	−78.9; 94.7	0.859
CRP	0.3	−0.2; 0.8	0.318

Abbreviations: MEE: measured energy expenditure; BMI: body mass index; SOFA: sequential organ failure assessment; APACHE II: acute physiology and chronic health evaluation II; mNUTRIC: modified Nutrition Risk in Critically Ill; CRP: C-reactive protein.

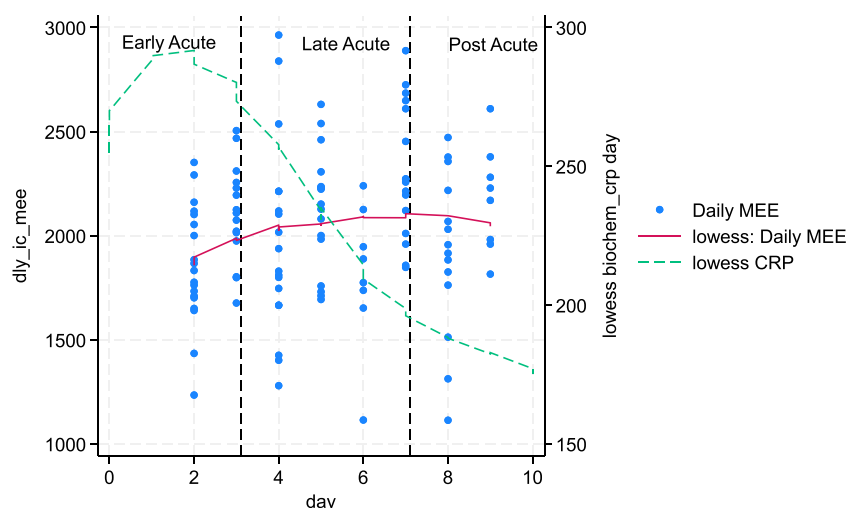


Fig. 2. Change in daily MEE (kcal/day) and CRP over time.

energy demand [1]. In a larger prospective observational study ($n = 180$) undertaken in a predominantly medical ICU (54 % medical, 29 % surgical, 17 % trauma), Tah et al. [18] found that MEE performed before or on day 5 differed significantly from that performed after day 5 (1747 ± 429 kcal/d vs 1865 ± 462 kcal/d, respectively) ($p < 0.001$). Their cohort of patients was older (54.3 vs 36.9 years) and sicker (APACHE II 23.4 vs 13.54, SOFA 13.8 vs 4.54 and mNUTRIC 5.6 vs 2.2) compared to ours, indicating a higher nutritional risk despite a similar BMI (25.1 vs 24.8 kg/m²). In contrast, a study by Lakenman et al. [19] undertaken in critically ill COVID-19 patients ($n = 21$, 67 % males, 57 % obese, mean BMI 31.5), found no significant difference in MEE measured on day 4 (2–5) versus day 11 (9–12).

In this study the increase in TED as a percentage of MEE over time is in line with the current ESPEN recommendation to administer <70 % of MEE during the early acute, and 80–100 % of MEE in the late acute phase of critical illness, and can be attributed to the fact that this study was nested within a larger clinical study where nutrition support was IC-guided as per the 2019 ESPEN

guidelines, in which energy and protein delivery was meticulously monitored and tailored to meet set targets. Various strategies were employed in the larger study to reach the set targets, such as daily feeding prescriptions provided by the dietitian, and two regular in-person follow-up visits during the day and one telephonically at night to monitor actual intake and alter the feeding prescription as needed, with volume based changes in the case of unforeseen feeding interruptions. If EN was contraindicated or if EN alone failed to meet energy and protein targets by day 4 ± 1 , supplemental parenteral nutrition was routinely initiated. If patients were extubated, feeding tubes were kept in situ until sufficient oral intake was established. In patients with inadequate oral intake who refused the feeding tube, oral nutrition supplements were prescribed and patients were encouraged to drink them and were assisted by the nursing staff or dietitian to ensure that they were consumed. Overall, the RQ ranged between 0.77 and 0.86, indicating that these subjects were neither under- nor overfed for the duration of the study [2]. Furthermore, the mean daily MEE of 29 and 30 kcal/kg/day observed in the early and late acute phase of

this study respectively, supports the need to limit exogenous energy intake to <20 kcal/kg/day in the absence of IC, which would provide the recommended <70 % of MEE [7]. This would compensate for factors such as endogenous energy production and mitochondrial dysfunction that may otherwise result in overfeeding in this early acute phase.

Lastly, and similar to previous studies [18,20] this study found a significant correlation between MEE and age, sex, and BMI, but not with markers of disease severity (APACHE II, SOFA score, CRP) and nutritional risk (mNUTRIC). Interestingly, daily CRP as an inflammatory marker seemed to operate independently from MEE which rose or plateaued, despite a progressive decline in CRP.

This study has several strengths. Firstly, we performed two or more IC measurements in 91 % of participants, and 3–4 measurements in over half (54.72 %), which included measurements in canopy mode following extubation. This allowed deeper insight into the dynamic metabolic changes seen during the first 7–10 days in ICU. Another strength is that calories provided by non-nutritional energy sources, such as propofol and glucose solutions were taken into account, which has not always been the case in previous studies [21] and which have been shown to be a risk factor for overfeeding by contributing as much as 10 % to total energy intake.

There were some limitations. Firstly, the exclusion criteria were based on those of the primary trial, which excluded certain patient groups, and our patient cohort consisted predominantly of young males with normal BMI who had undergone trauma-related surgery, placing a question mark on its generalisability with regard to other critically ill patients, especially those with medical illnesses, as well as the morbidly obese. Another reason for the homogeneity of our patient cohort was that the inclusion period was disrupted by the COVID-19 pandemic which resulted in the cessation of most elective surgeries and the transformation of the medical ICU into a COVID ICU. Nonetheless, Moonen et al. [17] as mentioned above, using a different patient cohort observed a similar trend in energy expenditure, indicating that the results from our study are likely to be similar in other ICU settings. Secondly, as the patients included in this study had their nutritional intake closely monitored and targeted as per the primary study's feeding protocol, we cannot tell what would have occurred in patients not included in the study. Furthermore, despite being able to measure the resting energy expenditure with IC, we still lack a tool that can accurately measure endogenous glucose production, which may provide up to 50–75 % of MEE during the acute phase of critical illness, making it difficult to predict exactly what percentage of MEE should be targeted in the early course of critical illness [22]. Lastly, although our study focused on differences in MEE across various phases of critical illness, it is important to acknowledge that we currently lack a validated biomarker to accurately identify the transition between these phases. As highlighted in recent literature, there remains a need for reliable biomarkers to delineate the early acute, late acute, and post-acute phases of critical illness. Nevertheless, our study offers valuable insights beyond the identification of distinct phases. By analysing daily variations in MEE over the first week in the ICU, we have provided important information on the dynamic changes in energy expenditure that occur even when phase transitions are not clearly defined. This approach enhances our understanding of how MEE fluctuates on a daily basis during the early period of critical illness, which can inform more precise nutritional support strategies.

5. Conclusion

This study has furthered our understanding of the dynamic metabolic changes that occur during the first 10 days in a

predominantly trauma surgical ICU. The observed variability highlights the complexity of managing critically ill patients. It suggests that while trends can be identified at a population level, individual patient management requires close monitoring and potentially more personalized adjustments to nutritional and therapeutic interventions. Understanding and acknowledging this variation is crucial for tailoring energy provision in the ICU to meet individual patient needs without overfeeding or underfeeding, both of which can have adverse outcomes. Future studies could benefit from exploring the specific factors contributing to variability in energy expenditure. This might involve stratifying patients based on key characteristics (e.g., type of surgery, severity of illness) or employing more sophisticated models that account for patient-specific factors in predicting energy needs. Additionally, the observed trend with a peak in MEE around day five could inform timing and strategies for nutritional intervention in the ICU.

Author contributions

Lizl Veldsman: Conceptualization, Methodology, Investigation, Project administration, Writing - Original Draft. **Guy Richards:** Methodology, Supervision, Writing- Reviewing and Editing. **Carl Lombard:** Formal analysis, Visualisation. **Renée Blaauw:** Methodology, Supervision, Writing- Reviewing and Editing.

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Declaration of competing interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2024.11.009>.

References

- [1] Moonen HPFX, Beckers KJH, van Zanten ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. *J Intensive Care* 2021;9(1).
- [2] Achamrah N, Delsoglio M, De Waele E, Berger MM, Pichard C. Indirect calorimetry: the 6 main issues. *Clin Nutr* 2021;40(1):4–14.
- [3] Oshima T, Berger MM, De Waele E, Guttormsen AB, Heidegger CP, Hiesmayr M, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. *Clin Nutr (Phila)* 2017;36(3):651–62.
- [4] Zusman O, Kagan I, Bendavid I, Theilla M, Cohen J, Singer P. Predictive equations versus measured energy expenditure by indirect calorimetry: a retrospective validation. *Clin Nutr* 2019;38(3):1206–10.
- [5] Duan JY, Zheng WH, Zhou H, Xu Y, Huang H Bin. Energy delivery guided by indirect calorimetry in critically ill patients: a systematic review and meta-analysis. *Crit Care* 2021;25(1).
- [6] Pertzov B, Bar-Yoseph H, Menndel Y, Bendavid I, Kagan I, Glass YD, et al. The effect of indirect calorimetry guided isocaloric nutrition on mortality in critically ill patients—a systematic review and meta-analysis. *Eur J Clin Nutr* 2022;76(1):5–15.
- [7] Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. ESPEN practical and partially revised guideline: clinical nutrition in the intensive care unit. *Clin Nutr [Internet]* 2023;42(9):1671–89. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/37517372>.

- [8] Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019;38(1):48–79.
- [9] Delsoglio M, Achamrah N, Berger MM, Pichard C. Indirect calorimetry in clinical practice. *J Clin Med* 2019;8(9).
- [10] McClave SA, Lowen CC, Kleber MJ, McConnell JW, Jung LY, Goldsmith LJ. Clinical use of the respiratory quotient obtained from indirect calorimetry. *J Parenter Enteral Nutr* 2003;27(1):21–6.
- [11] Li A, Mukhopadhyay A. Substrate utilization and energy expenditure pattern in sepsis by indirect calorimetry. *Crit Care* 2020;24(1).
- [12] Oshima T, Dupertuis YM, Delsoglio M, Graf S, Heidegger CP, Pichard C. In vitro validation of indirect calorimetry device developed for the ICALIC project against mass spectrometry. *Clin Nutr ESPEN* 2019;32:50–5.
- [13] Oshima T, Delsoglio M, Dupertuis YM, Singer P, De Waele E, Veraar C, et al. The clinical evaluation of the new indirect calorimeter developed by the ICALIC project. *Clin Nutr* 2020;39(10):3105–11.
- [14] Wasyluk W, Zwolak A, Jonckheer J, De Waele E, Dąbrowski W. Methodological aspects of indirect calorimetry in patients with sepsis—possibilities and limitations. *Nutrients* 2022;14(5).
- [15] De Waele E, van Zanten ARH. Routine use of indirect calorimetry in critically ill patients: pros and cons. *Crit Care* 2022;26(1).
- [16] Cuthbertson DP, Glasg D. Post-shock metabolic response. *Lancet* 1942;1: 433–7.
- [17] Moonen HPFX, Hermans AJH, Bos AE, Snaterse I, Stikkelman E, van Zanten FJL, et al. Resting energy expenditure measured by indirect calorimetry in mechanically ventilated patients during ICU stay and post-ICU hospitalization: a prospective observational study. *J Crit Care* 2023;78.
- [18] Tah PC, Poh BK, Kee CC, Lee ZY, Hakumat-Rai VR, Mat Nor MB, et al. Do we need different predictive equations for the acute and late phases of critical illness? A prospective observational study with repeated indirect calorimetry measurements. *Eur J Clin Nutr* 2022;76(4):527–34.
- [19] Lakenman PLM, van der Hoven B, Schuijs JM, Eveleens RD, van Bommel J, Olieman JF, et al. Energy expenditure and feeding practices and tolerance during the acute and late phase of critically ill COVID-19 patients. *Clin Nutr ESPEN* 2021;43:383–9.
- [20] Mtaweh H, Soto Aguero MJ, Campbell M, Allard JP, Pencharz P, Pullenayegum E, et al. Systematic review of factors associated with energy expenditure in the critically ill. *Clin Nutr ESPEN* 2019;33:111–24.
- [21] Veldsman L, Richards GA, Blaauw R. The dilemma of protein delivery in the intensive care unit. *Nutrition* 2016;32(9):985–8.
- [22] Occhiali E, Urli M, Pressat-Laffouilhère T, Achamrah N, Veber B, Clavier T. Dynamic metabolic changes measured by indirect calorimetry during the early phase of septic shock: a prospective observational pilot study. *Eur J Clin Nutr* 2022;76(5):693–7.