Author/s:
Fetterplace, K;Beach, LJ;MacIsaac, C;Presneill, J;Edbrooke, L;Parry, SM;Rechnitzer, T;Curtis, R;Berney, S;Deane, AM;Denehy, L

Title:
Associations between nutritional energy delivery, bioimpedance spectroscopy and functional outcomes in survivors of critical illness

Date:
2019-12-01

Citation:
Fetterplace, K., Beach, L. J., MacIsaac, C., Presneill, J., Edbrooke, L., Parry, S. M., Rechnitzer, T., Curtis, R., Berney, S., Deane, A. M. & Denehy, L. (2019). Associations between nutritional energy delivery, bioimpedance spectroscopy and functional outcomes in survivors of critical illness. Journal of Human Nutrition and Dietetics, 32 (6), pp.702-712. https://doi.org/10.1111/jhn.12659.

Associations between nutritional energy delivery, bioimpedance spectroscopy and functional outcomes in survivors of critical illness

Kate Fetterplace[1,2], Lisa J. Beach[3], Christopher MacIsaac[2,4], Jeffrey Presneill[2,4], Lara Edbrooke[5], Selina M Parry[5], Thomas Rechnitzer[4], Rachel Curtis[3], Sue Berney[6], Adam M. Deane[2,4] and Linda Denehy[5].

1. Department of Allied Health (Clinical Nutrition), level 4 North, Royal Melbourne Hospital, Melbourne, Victoria, Australia
2. Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
3. Department of Allied Health (Physiotherapy), level 4 North, Royal Melbourne Hospital, Melbourne, Victoria, Australia
4. Intensive Care Unit, Royal Melbourne Hospital, Parkville Victoria, Australia
5. Department of Physiotherapy, The University of Melbourne, Melbourne, Victoria, Australia
6. Physiotherapy Department, Austin Health, Melbourne, Victoria, Australia

Statement of Authorship

K. Fetterplace, L. J Beach, L. Denehy, C. MacIsaac and S M. Parry and S. Berney contributed to the conception and design of the research; K. Fetterplace, L. Beach, T. Rechnitzer, R. Curtis, J. Presneill and L. Edbrooke contributed to the acquisition and analysis of the data; K. Fetterplace, J. Presneill, L. Edbrooke and A. M. Deane contributed to the interpretation of the data; and K. Fetterplace, L. J Beach, A. M. Deane and L. Denehy drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JHN.12659

Keywords: Nutrition support, indirect calorimetry, enteral nutrition, muscle strength, bioimpedance spectroscopy and critical care.

Correspondence: Kate Fetterplace,
kate.fetterplace@mh.org.au, Phone +61 9342 7440, Fax +61 93428440
Nutrition Department, level 3 Allied Health**,** Royal Melbourne Hospital, Grattan Street, Parkville, Victoria, Australia 3050

Acknowledgments

The authors would like to thank Audrey Tierney, Adrienne Forsyth their contribution to the manuscript as well as the staff of the Royal Melbourne Hospital Intensive Care Unit, Physiotherapy and Nutrition Departments; the participants for their contribution to the study.

Conflicts of interests

K. Fetterplace has received conference, travel grants and/or honoraria from Baxter, Fresenius Kabi and Nestle Health Science (not related to this study). A. M. Deane or his institution have received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (Not related to this study). The other authors have no potential conflicts to declare.

Funding source

The Melbourne Health Foundation Grant in Aid: Allied Health (2011)

MS KATE EMILY FETTERPLACE (Orcid ID : 0000-0002-1094-1619)

Article type : Original Research

Associations between nutritional energy delivery, bioimpedance spectroscopy and functional outcomes in survivors of critical illness

Abstract

Background: Patients who survive critical illness frequently develop muscle weakness that can impact quality of life; nutrition is potentially a modifiable risk factor. The purpose of this study was to explore associations between cumulative energy deficits (using indirect calorimetry and estimated requirements), nutritional and functional outcomes.

Methods: Prospective single centre observational study of 60 Intensive Care Unit (ICU) patients, who were mechanically ventilated for at least 48 hours. Cumulative energy deficit was determined from artificial nutrition delivery compared to targets. Measurements included: (i) at recruitment and ICU discharge, weight, fat free mass (bioimpedance spectroscopy) and malnutrition (Subjective Global Assessment score B/C); (ii) at awakening and ICU discharge, physical function (Physical Function in Intensive Care Test-scored) and muscle strength (Medical Research Council sum-score (MRC-SS). ICU-acquired weakness was defined as an MRC-SS < 48/60.

Results: The median [IQR] cumulative energy deficit compared with estimated targets to ICU day 12 was 3648 [2514 – 5650] kcal. Adjusting for body mass index, age and severity of illness; cumulative energy deficit (per 1000kcal) was independently associated with greater odds of ICU-acquired weakness (OR 2.1, 95%CI 1.4-3.3, p=0.001) and malnutrition (OR 1.9, 95%CI 1.1-3.2, p=0.02). In similar multivariable linear models, cumulative energy deficit was associated with reductions in fat free mass (-1.3kg, 95%CI -2.4 to -0.2,

p=0.02) and physical function scores (0.6 points, 95%CI -0.9 to -0.3, p=0.001).

Conclusion: Cumulative energy deficit from artificial nutrition support was associated with reduced functional outcomes and greater loss of fat free mass in ventilated ICU patients.

Introduction

Patients who survive critical illness frequently develop muscle weakness, which has been termed Intensive Care Unit (ICU)-acquired weakness (ICU-AW). Not only is ICU-AW associated with diminished physical function and lower health-related quality of life but it is also associated with increased ICU and hospital length of stay (LOS), health-care costs and mortality[1-3]. Optimal nutrition may attenuate ICU-AW however; there is a paucity of evidence in this area[1, 4, 5].

The optimal nutrition provision for critically ill patients to improve outcomes is uncertain[6, 7] and the composition of nutrition formulae is currently the subject of research[1, 8-10]. Observational studies have reported energy deficits during critical illness are associated with adverse outcomes; such as increased mortality, ICU LOS and period of mechanical ventilation[11-14]. However recent randomised clinical trials comparing permissive under-, trophic-, standard- or full-feeding have not identified any link between energy deficit and mortality[15-17].

In all of these large randomised clinical trials nutrition prescriptions were based on predictive equations, which reflects standard clinical practice[13, 18]. However, predictive equations are inaccurate estimates of daily energy expenditure during critical illness when compared to 'gold-standard' measurements of energy expenditure using indirect calorimetry[19]. Accordingly, the use of predictive equations to assess energy deficits may contribute to inconsistencies between studies regarding energy deficit and associated outcomes[19, 20].

The primary objective of this study was to determine the cumulative energy deficit from artificial nutrition support using both calculated predictive equations and repeated measured energy expenditure (MEE). The secondary objectives were to explore associations between cumulative energy deficit and nutritional outcomes (change in body weight and fat free mass and the development of malnutrition) and functional outcomes (muscle strength and physical function) at ICU discharge.

Methods and materials:

Study Design and Setting

This prospective single center observational cohort study was conducted in the mixed medical-surgical-trauma ICU of a tertiary-referral Australian hospital. Between 2012 and 2014 consecutive weekday admission patients were screened for eligibility. Initial written informed consent was obtained from the person responsible, with continuation of consent obtained subsequently from competent participants. Ethical approval was obtained from the Melbourne Health Human Research Ethics Committee (project number: 2012.060)[21]. Reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[22].

Patient selection

Inclusion criteria were: age ≥ 18 years; mechanical ventilation commenced within 48 hours of ICU admission and likely to be required > 48 hours, and an estimated minimum stay in the ICU of at least five days. Exclusion criteria were: major trauma necessitating a specific period of immobilisation; new neurological insult, such as spinal cord injury or stroke; poor pre-morbid mobility, defined as inability to walk independently with or without a gait aid; inability to communicate in English; did not have medical insurance cover; ICU re-admission; or if the attending physician did not support inclusion.

Protocol

Standard care for all participants included nutritional assessment by a dietitian within 48 hours of admission, with estimation of their nutritional requirements[23]. Commercially available enteral and parenteral formulas were utilised, which were prescribed based on clinical need as assessed by the dietitian or ICU physician. Enteral feeding followed the standard unit nutrition protocol, which encouraged early initiation of nutritional support within 24 hours of admission and specified prokinetic drug administration if gastric residual volumes were greater than 300ml[24]. All study participants also received respiratory and rehabilitation interventions provided by physiotherapists.

Baseline demographic data including age, gender, admission diagnosis, severity of illness (Acute Physiology And Chronic Health Evaluation (APACHE) II score) and the Nutrition Risk in Critically ill score (NUTRIC) were recorded[25]. Daily nutritional energy delivery from enteral and parenteral nutrition (not including other energy sources) and nutritional outcome data were collected on participants until ICU discharge or day 30 of the ICU admission, which ever came first.

Nutritional outcomes

Nutritional outcomes were collected at baseline and ICU discharge. Weight was determined via bed scales (Hill-Rom®, Indiana USA) for most patients; if the weight was not available an estimated weight was used for the nutrition prescription. Height was estimated using ulna length[20] and body mass index (BMI) in kg/m^2 was calculated. A dietitian measured the mid upper arm circumference (cm)[26] and assessed nutritional status using the Subjective Global Assessment (SGA)[27, 28], with a score of B or C considered as malnourished. Serum albumin (g/L) and transthryretin (preablumin) concentrations (milligram/L) were measured, with the normal ranges being 35-50 g/L and 180-360 milligram/L respectively[28].

Estimated Energy Requirements

Estimated energy requirements were calculated by the dietitian at baseline using both the standard weight-based equations of 25-30kcal/kg per day[29]

and the Schofield equation with appropriate stress factors, in line with standard practice in Australia[30, 31]. For overweight participants ideal body weight (IBW) was used and for obese participants with a BMI greater than 32 kg/m^2, an obesity adjusted weight was used (IBW + 25% (actual body weight - IBW))[32]. The nutrition prescription (prescribed energy target) was determined based on the dietitian assessment of the estimated energy requirements, using their clinical judgment of which estimation was most reflective of the participant's requirements.

Measured Energy Expenditure

Measured energy expenditure (MEE) was determined via indirect calorimetry, in patients with no contraindication, using the Deltatrac® II Metabolic Cart (Datex-Ohmeda, Helsinki, Finland)[33]. MEE was undertaken by a trained physician and completed whilst the participant was mechanically ventilated, on the day of recruitment and on days three and five after enrolment. Standard methods were used; all expired gas was collected from the expiratory port of the ventilator, the measures were continued for 30 minutes and summary data were recorded[34]. Participants were excluded from MEE if they: had an intercostal catheter with an air leak; were receiving a fraction of inspired oxygen > 0.6; were receiving extracorporeal membrane oxygenation; or were in infective isolation. Nutrition support was not stopped during MEE and there was no restriction on the participant's movement prior to MEE. Metabolic Cart outputs recorded, included oxygen consumption (VO_2) mL/min, carbon dioxide production (VCO_2) mL/min, calculated respiratory quotient (RQ) and MEE in kcal/day, using the Weir equation. The average MEE was determined from the mean of available repeated measurements.

Cumulative Energy Deficit

Each participant's cumulative energy deficit from artificial nutrition support was calculated daily for a maximum of 12 ICU days based on *a priori* determination that substantial changes to nutritional tolerance were unlikely after this time[35, 36]. Daily energy provision was measured for all participants receiving any enteral or parenteral nutrition, not including energy from other

sources. Daily energy deficit was determined by deducting the energy delivered from prescribed energy target determined by the dietitian and secondly from the average MEE. The daily energy deficit was summed for the total cumulative energy deficit. The nutritional adequacy was assessed by dividing the daily energy delivery, including the day of admission and the day of discharge if it was greater than eight hours, by the prescribed requirements or the average MEE and expressing as a percentage.

Fat free mass change

Fat free mass was measured using the tetra-polar-configured multifrequency SFB7 bioimpedance device (AU/NZ; ImpediMed™ Limited, Pinkenba, Australia)[37]. This device uses bioimpedance spectroscopy to determine total body water, extracellular fluid and intracellular fluid and subsequently calculates fat free mass and fat mass[37]. Use of this device has been validated in the critically ill[38,39]. Measurements were taken when the participants were supine in bed, after single use gel electrodes were placed on one ipsilateral foot and hand[37,39]. Fat free mass was determined immediately after enrolment and at ICU discharge.

Muscle strength and physical function

Muscle strength was assessed using the Medical Research Council sum-score (MRC-SS) with a score of less than 48/60 considered indicative of ICU-AW[40,41]. Physical function was measured using the Physical Function in Intensive Care Test-scored (PFIT-s)[42]. Muscle strength and physical function testing were all conducted by physiotherapy staff and assessments were performed at ICU awakening[43] and ICU discharge (see Appendix 1).

Participant outcomes

Twenty-eight day mortality, ICU LOS, hospital LOS, length of mechanical ventilation, days of sedation (defined as greater than eight hours on any sedative drug), duration of sepsis determined using the American College of

Chest Physicians Criteria[44] and discharge destination were collected, censored at day 60.

Statistical Analyses

Participant demographics, cumulative energy deficit, nutritional and functional outcomes are reported as mean (standard deviation) (SD) or median [inter-quartile range] [IQR] as appropriate. Comparisons between outcome measures from baseline to ICU discharge used paired t-tests or Wilcoxon signed-rank tests as appropriate. Multivariable generalised linear regression analyses explored associations between cumulative energy deficit (prescribedenergy targets) and continuous outcomes, including weight, fat free mass and physical function scores at discharge. The confounding variables which were adjusted for in these models included age, APACHE II score, BMI and baseline measures where applicable. Logistic regression was performed for the binary outcomes of ICU-AW and malnutrition, adjusted for the same confounding variables, with effect estimates reported as odds ratios with 95% confidence intervals. Sensitivity analyses was performed for the outcome of ICU-AW missing values, were imputed as first having ICU-AW and then not having ICU-AW. Energy deficits calculated from prescribed energy targets were used in the full analyses in preference to energy deficits calculated from MEE, to minimise the risk of bias as this was the most complete data set. The generalised linear regression models that were finally applied were checked using standard diagnostics, including tests of influence and specification of included variables. Protein provision was collected and reported however not analysed in relation to outcomes as this was not planned at the time of designing the study and therefore analysing these data post-hoc would risk incorrect inferences. ..

A two-sided *p* value of <0.05 was set for statistical significance for all tests, with no adjustment for multiplicity. SPSS (IBM® SPSS® Statistics Premium Grad Pack Version 22.0) and Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, 2017) were used to perform the data analyses.

At the time of designing this study no data were known which assessed muscle strength in relation to energy deficit in a critically-ill population. This observational study selected a pragmatic sample size of 60 participants.

Results

Participants

Five hundred and forty-three participants were eligible (Figure 1) after exclusions, 140 (26%) met inclusion criteria and 60 of these (43%) agreed to participate and were enrolled. Of the enrolled participants 57 (95%) remained in ICU until day five, 43 (72%) had at least one MEE measurement and 48 (80%) had a muscle strength assessment at ICU discharge.

Figure 1. Consort diagram

Participant Characteristics

Demographic and clinical characteristics are provided in Table 1. The participants had a mean (SD) age of 58 (16) years, median [IQR] BMI of 28 [24-31] kg/m^2, mean APACHE II score of 23 (7.5) and mean NUTRIC score of 4.6 (2.1).

Nutrition provision

Nutrition provision is summarised in Table 2. The majority of participants were enterally fed (n = 58, 97%), for a median of 5 [3.0 – 8.8] days and had a mean energy delivery of 1182 (443) kcal per day from artificial nutrition support.

Energy requirements

The median [IQR] estimated energy requirements were 1800 kcal/day [1675 – 2025] (weight based equation) and 1952 kcal/day [1733 – 2240] (Schofield equation, with a median stress factor of 1.3 [1.2-1.3]). The median prescribed energy targets, based on the estimated requirements, were 1950 kcal/day [1763 – 2160].

Measured energy expenditure (MEE) was performed in 43 (72%) participants. At baseline (n=36) the median [IQR] MEE was 1695 [1377 – 1882] kcal and the average of up to 3 time points (n=43) was 1690 [1400 – 1895] kcal. There was moderate overall agreement between the MEE and the prescribed daily energy targets, with the former showing a mean bias of -219 kcal (95% CI -307 to -132) compared to the prescribed daily energy targets (r =0.536, p <0.005)[45]. (Supplementary Figure 1. Bland Altman plot of agreement between prescribed energy targets and measured energy expenditure).

Cumulative energy deficit

When energy delivery from nutrition support was compared to estimated prescribed energy targets (n=60), the median [IQR] daily nutritional energy deficit was 281 [193 – 435] kcal/day (Figure 2) and the cumulative energy deficit was 3648 [2514 – 5650] kcal. The mean nutritional energy adequacy using the prescribed energy targets over the 12 days was 64% (22).

Figure 2. Daily energy deficit from nutrition support versus estimated prescribed energy targets and MEE

Comparing energy delivery from artificial nutrition support with MEE the median [IQR] daily nutritional energy deficit was 172 [42 – 362] kcal and the cumulative energy deficit to ICU day 12 was 2234 [541 – 4710] kcal. The mean nutritional energy adequacy using MEE over the 12 days was 74% (26).

Nutritional outcomes

From baseline to ICU discharge there were significant reductions in weight, fat free mass and mid upper arm circumference (Table 3). Serum transthyretin concentrations increased significantly over the ICU stay, however albumin concentrations were similar between time points (Table 3). Where malnutrition was assessed at baseline and discharge (n = 50) there was an observed increase in the proportion of participants who were malnourished at discharge compared to admission (baseline 12 (24%), discharge 18 (36%), (McNemar's exact p = 0.03).

Table 3. Nutritional outcomes

Muscle strength and physical function

Muscle strength at discharge was measured in 48 (80%) participants. Of the 12 participants who did not have this measured nine died prior to discharge and the others were unable to complete the test due to inability to follow commands. The prevalence of weakness at awakening was 23 (38%) and at ICU discharge amongst survivors was 10 (21%). Physical function at ICU discharge was measured in 49 (82%) survivors, with a mean (SD) PFIT-s interval score of 6.5 (2.1) out of 10.

Associations between cumulative energy deficit and outcomes

Participants with energy deficits from artificial nutrition support below prescribed targets, were observed to have a greater risk of ICU-AW and malnutrition. Per 1000kcal cumulative energy deficit, there was approximately a two-fold increased risk of both ICU-AW [OR 2.1 (95%CI 1.4-3.3), p=0.001] and malnutrition [OR 1.9 adjusted for baseline malnutrition (95%CI 1.1-3.2), p=0.02] at ICU discharge. Likewise, adjusted for baseline, subjects were observed to lose on average 1.3kg (95%CI 0.2-3.4, p=0.02) fat free mass per 1000kcal cumulative deficit. A moderate association was observed between reduced physical function at ICU discharge and cumulative energy deficit, with mean physical function score decreasing by 0.6 points (95%CI 0.3 – 0.9, p =0.001) per 1000kcal deficit. There was no strong evidence of an association between weight loss and nutritional energy deficit. When MEE was used to calculate energy deficit a similar result was found for the development of ICU-AW (n=31) [OR 1.9 (95%CI 1.1-3.4), p=0.021] (Supplemental Table 1).

Table 4. Nutritional energy deficit and associated outcomes

There was no strong association observed between cumulative energy deficit from artificial nutrition support and length of stay, length of mechanical ventilation or mortality (Table 1. includes medical outcome data).

Discussion

In a critically ill population this study evaluated energy deficit from artificial nutrition support compared to measured energy expenditure and estimated energy requirements and concurrently assessed fat free mass, muscle strength and physical function. In this mechanically ventilated cohort, the mean cumulative energy deficit was approximately 200 kcal smaller per day when measured energy expenditure was used compared to estimated prescribed energy targets. Cumulative energy deficit from artificial nutrition support was found to be associated with an increased prevalence of ICU-AW and malnutrition, reduced physical function scores at ICU discharge and greater loss of fat free mass over the ICU stay.

The observed energy deficit in this cohort appeared to be slightly lower than some previously reported multi-center studies, where critically ill patients meet a mean of 60 percent of their prescribed energy targets[6, 46, 47]. In this study the mean amount of energy provided from nutrition support compared to estimated energy targets was 64% however when MEE was used it improved to 74%. Cumulative energy deficit has been previously reported to be associated with poorer outcomes, such as lower rates of discharge to home, increased infection rates, reduced ventilator free days and higher mortality rates[11, 48, 49]. These were not observed in the present study however direct comparisons cannot be made due differences in accounting for non-nutritional energy provision.

Indirect calorimetry is infrequently used as part of routine clinical practice to determine energy targets, due to the high cost, time and expertise required[13, 50]. Predictive equations are reported to be inaccurate, with weight based equations being the least accurate[19]. Our finding again showed there was only moderate agreement between prescribed estimated energy requirements and measured energy expenditure. This difference in energy deficit may support the use of indirect calorimetry to more accurately assess nutritional adequacy and its impact on outcomes.

Data evaluating the relationships between energy deficits and muscle mass are sparse and somewhat conflicting[51]. In this study, it was observed that there was substantial change in fat free mass over the ICU stay, and when adjusted for baseline fat free mass, greater energy deficit from artificial nutrition support was associated with greater fat free mass loss. Few previous studies have used BIS to assess change in fat free mass and associations with energy deficits[51], and therefore comparisons with other studies are difficult. Using subjective measures, the administration of early parenteral nutrition, which improved energy delivery appeared to reduce muscle wasting[52]. However in contrast, in a small sub-analysis of a large randomised clinical trial (EPaNIC) greater energy delivery via early parenteral nutrition did not lead to any difference in muscle loss, when assessed using qualitative computed tomography (CT) analysis[53]. There was however, deterioration in muscle quality observed, with increased intramuscular water and lipid content in the group who received early parenteral nutrition, over a seven-day period in the ICU[54]. Observational studies have also reported conflicting results; similar to the present study one found that nutritional adequacy based on estimated energy targets was the only predictor of muscle loss, assessed using CT analysis[55] and in contrast the other found that energy balance made no difference to the rate of muscle loss, assessed using ultrasound[56].

The impact of acute energy deficit on muscle strength and physical function in the critically ill is uncertain[5]. In the present study 21% of survivors had ICU-AW and the mean PFITs was 6.5 (2.1) out of 10 at ICU discharge; Greater energy deficit was associated with an increasing risk of developing ICU-AW and lower physical function scores at ICU discharge. Additionally multivariable analysis suggested that participants with higher BMIs and APACHE II scores had a higher risk of developing ICU-AW. . This is in contrast to another sub-analysis of EPaNIC which reported that lower calorie deficit was associated with greater ICU-AW at awakening (107 (34%) late PN group versus 127 (43%) early PN group, p = 0.03) and slower rates of recovery, however there was no difference in the rates of ICU-AW at ICU discharge (78 (26%) late PN group versus 91 (31%) in the early PN group, p = 0.15)[57]. However, in a

nested cohort study within the EDEN trial, trophic feeding for the first five days of ICU admission when compared to standard care increased early calorie deficit but did not affect physical function scores using the SF-36 at 12-months but did result in a greater proportion of patients admitted to a physical rehabilitation facility (57 (23%) trophic feeding group versus 30 (14%) standard care, p = 0.01)[58].

The differences in the findings between observational studies and recent interventional trials for both muscle mass changes and functional outcomes may be explained by the timing of nutrition support, the route of delivery and the composition of the nutrition provided[8, 9], as well as the methodology and timing of the outcome measures. Further research is required to explore the effect of different methods of nutrition delivery and substrates to minimise muscle wastage as well as standardising the methods to assess muscle mass and functional outcomes.

The strengths of this study include that both measured energy expenditure and estimated prescribed energy targets were used to calculate energy deficit and that simultaneously several other nutrition-associated and patient-centered outcomes were assessed, including fat free mass, muscle strength and physical function. Additionally muscle strength was measured in 80 percent of the cohort. Study limitations included that this was a single centre observational study with a relatively small sample size of 60 participants; therefore, there is the potential for bias and many of the outcome variables are subjective, including the functional outcome measures and the diagnosis of malnutrition. Also importantly the calculation of energy deficits did not include non-nutritional calories or energy provided from oral intake. In addition, measured energy expenditure was only completed in a subset of participants, and as such only 43 participants were included in the MEE cumulative energy deficit analysis and given the missing MEE data, associations between calorie deficit calculated from MEE and outcomes were not performed. The use of clinical measures to assess muscle strength, the diagnoses of ICU-AW and physical function limits findings to a cohort of patients who survived critical illness and who were able to obey commands.

However we attempted to control for this by undertaking sensitivity analysis for the outcome of ICU-AW, and when all missing results were imputed as participants being 'weak' the overall conclusion remained unchanged. This study was not powered to determine important effects on patient-centered outcomes, such as mortality, and it did not explore associations between protein deficits and outcomes. Finally, due to the observational design of this study only associations and not causality, could be reported.

Conclusion

Cumulative energy deficit from artificial nutrition support was lower when measured energy expenditure was used compared to prescribed energy targets. Cumulative energy deficit from artificial nutrition support was observed to be associated with the development of ICU acquired weakness, malnutrition, reduced physical function at ICU discharge and greater loss of fat free mass. Large well-designed randomised controlled trials, exploring the role of protein and absolute energy delivery, that include muscle mass and functional outcomes are warranted and required to confirm these results.

Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned, which was approved by the Melbourne Health Human Research Ethics Committee (project number: 2012.060) have been explained.

References

1. Heyland DK, Stapleton RD, Mourtzakis M, et al. Combining nutrition and exercise to optimize survival and recovery from critical illness: Conceptual and methodological issues. Clin Nutr. 2016;35:1196-206.
2. Kress JP, Hall JB. ICU-Acquired Weakness and Recovery from Critical Illness. N Engl J Med. 2014;370:1626-35.
3. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. Crit Care Med. 2011;39:371-9.

4. Fan E, Dowdy DW, Colantuoni E, et al. Physical Complications in Acute Lung Injury Survivors: A Two-Year Longitudinal Prospective Study. Crit Care Med. 2014;42:849-59.
5. Bear DE, Wandrag L, Merriweather JL, et al. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care. 2017;21:226.
6. Elke G, Wang M, Weiler N, et al. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. Crit Care. 2014;18:1-8.
7. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr 2011;93:569-77 9p.
8. Bear DE, Parry SM, Puthucheary ZA. Can the critically ill patient generate sufficient energy to facilitate exercise in the ICU? Curr Opin Clin Nutr Metab Care. 2018;21:110-5.
9. Puthucheary ZA, Astin R, Mcphail MJW, et al. Metabolic phenotype of skeletal muscle in early critical illness. Thorax. 2018;73:926-35.
10. TARGET Investigators on behalf of the Australian and Zealand Intensive Care Society Clinical Trials Group. Study protocol for the Augmented versus Routine Approach to Giving Energy Trial (TARGET). Crit Care Resusc. 2018;20:6-14.
11. Elke G, Wang M, Weiler N, et al. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. Crit Care. 2014;18(1):R29.
12. Gungabissoon U, Hacquoil K, Bains C, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr. 2015;39:441-8.
13. Zusman O, Theilla M, Cohen J, et al. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016;20:367.
14. Compher C, Chittams J, Sammarco T, et al. Greater Protein and Energy Intake May Be Associated With Improved Mortality in Higher Risk Critically Ill Patients: A Multicenter, Multinational Observational Study. Criti Care Med. 2017;45:156-63.
15. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307:795-803.
16. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. N Engl J Med. 2015;372:2398-408.
17. Chapman M, Peake SL, Bellomo R, et al. Energy-Dense versus Routine Enteral Nutrition in the Critically Ill. New England Journal of Medicine. 2018;379:1823-34.
18. Oshima T, Berger MM, De Waele E, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clin Nutr. 2017;36:651-62.
19. Tatucu-Babet OA, Ridley EJ, Tierney AC. Prevalence of Underprescription or Overprescription of Energy Needs in Critically Ill Mechanically Ventilated Adults as Determined by Indirect Calorimetry: A Systematic Literature Review. JPEN J Parenter Enteral Nutr. 2016;40:212-25.

20. Ridley EJ, Davies AR, Hodgson CL, et al. Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of randomised controlled trials. Clin Nutr. 2018;37:1913-25.
21. Beach LJ, Fetterplace K, Edbrooke L, et al. Measurement of physical activity levels in the Intensive Care Unit and functional outcomes: An observational study. J Crit Care. 2017;40:189-96.
22. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Explanation and Elaboration. Epidemiology 2007;18:805-35.
23. Ridley EJ, Peake SL, Jarvis M, et al. Nutrition Therapy in Australia and New Zealand Intensive Care Units: An International Comparison Study. JPEN J Parenter Enteral Nutr. 2018;42:1349-57.
24. Reintam Blaser A, Starkopf J, Alhazzani W, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017;43:380-98.
25. Rahman A, Hasan RM, Agarwala R, et al. Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool. Clin Nutr. 2016;35:158-62.
26. Ravasco P, Camilo ME, Gouveia-Oliveira A, et al. A critical approach to nutritional assessment in critically ill patients. Clin Nutr. 2002;21:73-7.
27. Detsky AS, Baker JP, O'Rourke K, et al. Predicting nutrition-associated complications for patients undergoing gastrointestinal surgery. JPEN J Parenter Enteral Nutr. 1987;11:440-6.
28. Marshall M. Nutritional assessment; its role in the provision of nutritional support. J Clin Pathol. 2008;61:1083-8.
29. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40:159-211.
30. Schofield W. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39S:5-41.
31. Ferrie S, Ward M. Back to Basics: Estimating energy requirements for adult hospital patients. Nutrition & Dietetics 2007;64:192-9.
32. Frankenfield DC, Rowe WA, Smith JS, et al. Validation of several established equations for resting metabolic rate in obese and nonobese people. J Am Diet Assoc. 2003;103:1152-9.
33. Swinamer DL, Grace MG, Hamilton SM, et al. Predictive equations for assessing energy expenditure in mechanically ventilated critically ill patients. Crit Care Med. 1990;18:657-61.
34. Petros S, Engelmann L. Validity of an abbreviated indirect calorimetry protocol for measurement of resting energy expenditure in mechanically ventilated and spontaneously breathing critically ill patients. Intensive Care Med. 2001;27:1164 -8.

554 35. Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and
555 clinical outcomes in critically ill patients: results of an international multicenter observational
556 study. Intensive Care Med. 2009;35:1728-37.
557 36. Chapple LS, Deane AM, Williams L, et al. Longitudinal changes in anthropometrics
558 and impact on self-reported physical function after traumatic brain injury. Critical Care and
559 Resuscitation. 2017;19:29-36.
560 37. Earthman CP. Body Composition Tools for Assessment of Adult Malnutrition at the
561 Bedside. JPEN J Parenter Enteral Nutr. 2015;39:787-822.
562 38. Kuchnia A, Earthman C, Teigen L, et al. Evaluation of Bioelectrical Impedance
563 Analysis in Critically Ill Patients: Results of a Multicenter Prospective Study. JPEN J Parenter
564 Enteral Nutr. 2017;41:1131-8.
565 39. Baldwin CE, Paratz JD, Bersten AD. Body composition analysis in critically ill
566 survivors: a comparison of bioelectrical impedance spectroscopy devices. JPEN J Parenter
567 Enteral Nutr. 2012;36:306-15.
568 40. Hough CL, Lieu BK, Caldwell ES. Manual muscle strength testing of critically ill
569 patients: feasibility and interobserver agreement. Crit Care. 2011;15:R43.
570 41. Parry SM, Berney S, Granger CL, et al. A new two-tier strength assessment approach
571 to the diagnosis of weakness in intensive care: an observational study. Critical Care.
572 2015;19:52-61.
573 42. Denehy L, De Morton NA, Skinner EH, et al. A Physical Function Test for Use in the
574 Intensive Care Unit: Validity, Responsiveness, and Predictive Utility of the Physical Function
575 in Intensive Care Test (Scored). Physical Therapy. 2013;93:1636-45.
576 43. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis Acquired in the Intensive
577 Care Unit: A Prospective Multicenter Study. JAMA. 2002;288:2859-67.
578 44. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS
579 International Sepsis Definitions Conference. Crit Care Med. 2003;31:1250-6.
580 45. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat
581 Methods Med Res. 1999;8:135-60.
582 46. Heyland DK, Cahill N, Day AG. Optimal amount of calories for critically ill patients:
583 depends on how you slice the cake! Crit Care Med. 2011;39:2619-26.
584 47. Peake SL, Davies AR, Deane AM, et al. Use of a concentrated enteral nutrition
585 solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical
586 trial. Am J Clin Nutr. 2014;100:616-25.
587 48. Yeh DD, Fuentes E, Quraishi SA, et al. Adequate Nutrition May Get You Home:
588 Effect of Caloric/Protein Deficits on the Discharge Destination of Critically Ill Surgical Patients.
589 JPEN J Parenter Enteral Nutr. 2016;40:37-44.
590 49. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and
591 energy balance on clinical outcome in ICU patients. Clin Nutr. 2005;24:502-9.
592 50. De Waele E, Nguyen D, De Bondt K, et al. The CoCoS trial: Caloric Control in
593 Cardiac Surgery patients promotes survival, an interventional trial with retrospective control.
594 Clin Nutr. 2018;37:864-9.

51. Lambell KJ, King SJ, Forsyth AK, et al. Association of Energy and Protein Delivery on Skeletal Muscle Mass Changes in Critically Ill Adults: A Systematic Review. JPEN J Parenter Enteral Nutr. 2018;42:1112-22.
52. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: A randomized controlled trial. JAMA. 2013;309:2130-8.
53. Casaer MP, Mesotten D, Hermans G, et al. Early versus Late Parenteral Nutrition in Critically Ill Adults. N Engl J Med. 2011;365:506-17.
54. Casaer MP, Langouche L, Coudyzer W, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med. 2013;41:2298-309.
55. Braunschweig CA, Sheean PM, Peterson SJ, et al. Exploitation of diagnostic computed tomography scans to assess the impact of nutrition support on body composition changes in respiratory failure patients. JPEN J Parenter Enteral Nutr. 2014;38:880-5.
56. Reid C, Campbell IT, Little RA. Muscle wasting and energy balance in critical illness. Clin Nutr. 2004;23:273-80.
57. Hermans G, Casaer MP, Clerckx B, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013;1:621-9.
58. Needham DM, Dinglas VD, Bienvenu OJ, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. BMJ. 2013;346:f1532.

Figure1. Consort Diagram

Abbreviations: Eligible – patients who met all inclusion criteria at the time of screening, exclusion criteria = unable to mobilise - included major trauma necessitating a period of immobilisation; new neurological insults; and poor pre-morbid mobility (unable to mobilise independently with or without a gait aid). ICU – intensive care unit, not an Australian citizen –non citizens were excluded as they are ineligible for Medicare should their participation in the study result in the need for additional medical care. MEE – measured energy expenditure.

Table 1. Participant demographic and clinical characteristics

Abbreviations: BMI; Body Mass Index, Kg; kilograms, m^2; meters squared, APACHE II; Acute Physiology And Chronic Health Evaluation II, NUTRIC Score; The Nutrition Risk in Critically ill, IQR; interquartile range, SD; Standard deviation, ICU-AW; Intensive care acquired weakness, LOS; Length of stay and MV; Mechanical ventilation. Values are presented as median [interquartile range] unless stated.

Table 2. Nutrition Provision

Abbreviations: EN; Enteral Nutrition, PN; Parenteral Nutrition, NBM; Nil by Mouth, NS; nutrition support, SD; standard deviation, values are presented as median [interquartile range] unless stated.

Table 3. Nutritional outcomes

Abbreviations: Kg; Kilograms, BIS; Bioimpedance spectroscopy, FFM; Fat Free Mass, MUAC; Mid Upper Arm Circumference, g/L; grams per litre. The mean difference was determined using a paired t-test.

Figure 2. Daily energy deficit from nutrition support using estimated prescribed energy targets and measured energy expenditure

Abbreviations: MEE; Measured energy expenditure, error bars indicate interquartile range.

Table 4. Cumulative nutritional energy deficit and associated outcomes

Abbreviations: BMI; Body Mass Index centered at 30 kg/m^2, Age centered at 60 years, APACHE II; Acute Physiology And Chronic Health Evaluation II, centred at 25, FFM; Fat free Mass. Logistic regression analysis models were used for ICU-Acquired weakness and Malnutrition. Linear regression analysis models were used for fat free mass and physical function.

Table 1. Participant demographic and clinical characteristics

Age years, mean (SD)	58 (16)
Gender male, n (%)	33 (55)
BMI kg/m^2, median [IQR]	28 [24-31]
APACHE II score, mean (SD)	23 (7.5)
NUTRIC Score, (n=49), mean (SD)	4.6 (2.1)
Admission category, n (%)	Medical: 34 (57) Emergency Surgery: 21 (35) Elective Surgery: 5 (8)
Admission Diagnosis, n (%)	Cardiac arrest: 14 (23) Respiratory failure: 8 (13) Trauma: 7 (12) Cardiovascular surgery: 7 (12) Gastrointestinal surgery: 7 (12) Gastrointestinal non-surgery: 6 (10) Sepsis: 4 (7) Endocarditis: 2 (3) Other: 5 (8)
ICU-AW diagnosis (awakening), n (%)	23 (38)
ICU LOS, days	7.0 [4.0-12.0]
Hospital LOS, days	19.0 [13.0-30.8]
Length of MV, days	4.0 [3.0-8.0]
Sedation duration, days	3.5 [2-7.0]
Sepsis duration, days	3.0 [0-6.8]
28 day mortality, n (%)	13 (22)
Discharge destination of survivors, n (%) Home Rehabilitation Other (including residential care)	 29 (48) 14 (23) 4 (7)

Abbreviations: BMI; Body Mass Index, Kg; kilograms, m^2; meters squared, APACHE II; Acute Physiology And Chronic Health Evaluation II, NUTRIC Score; The Nutrition Risk in Critically ill, IQR; interquartile range, SD; Standard deviation, ICU-AW; Intensive care acquired weakness, LOS; Length of stay and MV; Mechanical ventilation. Values are presented as median [interquartile range] unless stated.

Table 2. Nutrition Provision

EN provided, n (%)	58 (97)
PN provided n (%)	11 (18)
Days of EN	5.0 [3.0 - 8.8]
Days of PN (when provided)	6.0 [5.0-9.3]
Days NBM	1 [0-1]
Days on oral intake	2 [0-3]
Time from admission to initiating NS, hours, mean (SD)	20 (13)
Duration of NS interruption, hours	16 [6.0 - 31]
Duration of NS interruption, days	2 [1-3]
Prescribed estimated energy, kcal/day	1950 [1763 – 2160]
Energy delivered, kcal/day	1182 (443)
Energy delivered, kcal/kg/day	16 (6.1)
Energy adequacy, % of prescribed, mean (SD)	64 (22)
Estimated protein requirements, g/kg/day	1.3 [1.2-1.3]
Protein provided, g/kg/day, mean (SD)	0.58 (0.25)
Protein adequacy, % of estimate, median [IQR]	61 [44-69]

Abbreviations: EN; Enteral Nutrition, PN; Parenteral Nutrition, NBM; Nil by Mouth, NS; nutrition support, SD; standard deviation, values are presented as median [interquartile range] unless stated.

Table 3. Nutritional outcomes

Weight, kg	45	85 (22)	82 (19)	-3.0 (-5.2 to - 0.7)	0.01
BIS FFM, kg	45	69 (19)	62 (19)	-7.7 (-10 to -5.0)	<0.001
MUAC, cm	49	34 (5.3)	32 (5.3)	-1.9 (-2.3 to -1.4)	<0.005
Transthyretin millig/L	32	108 (35)	153 (17)	46 (11 to 81)	0.01
Albumin g/L	50	27 (5.2)	26 (4.6)	-0.73 (-2.3 to 0.7)	0.31

Abbreviations: Kg; Kilograms, BIS; Bioimpedance spectroscopy, FFM; Fat Free Mass, MUAC; Mid Upper Arm Circumference, g/L; grams per litre. The mean difference was determined using a paired t-test.

Table 4. Cumulative nutritional energy deficit and associated outcomes

Variable	Univariate analysis			Multivariable Sensitivity analysis		
	OR	95% CI	P value	OR	95% CI	P value
Calorie deficit (per 1000kcal)	2.2	1.3- 3.7	<0.01	2.1	1.4-3.3	0.001
BMI (≥30kg/m^2)	6.2	1.1- 35	0.04	3.6	0.9- 5.2	0.08
Age (> 60 years)	1.0	0.2- 4.6	1.0	2.0	0.5- 8.2	0.35
APACHE II (> 25)	0.62	0.1 -3.5	0.59	5.0	1.1- 23	0.04

Variable	Univariate analysis adjusted for baseline malnutrition diagnosis			Multivariable analysis adjusted for all variables		
	OR	95% CI	P value	OR	95% CI	P value
Calorie deficit (per 1000kcal)	1.6	1.1-2.4	0.01	1.9	1.1- 3.2	0.02
BMI (≥ 30kg/m^2)	0.55	0.10 - 2.9	0.48	0.31	0.03 - 3.4	0.34
Age (> 60 years)	2.	0.50- 17	0.23	2.4	0.32- 18	0.40
APACHE II (> 25)	1.1	0.21-5.8	0.10	2.9	0.34- 26	0.33

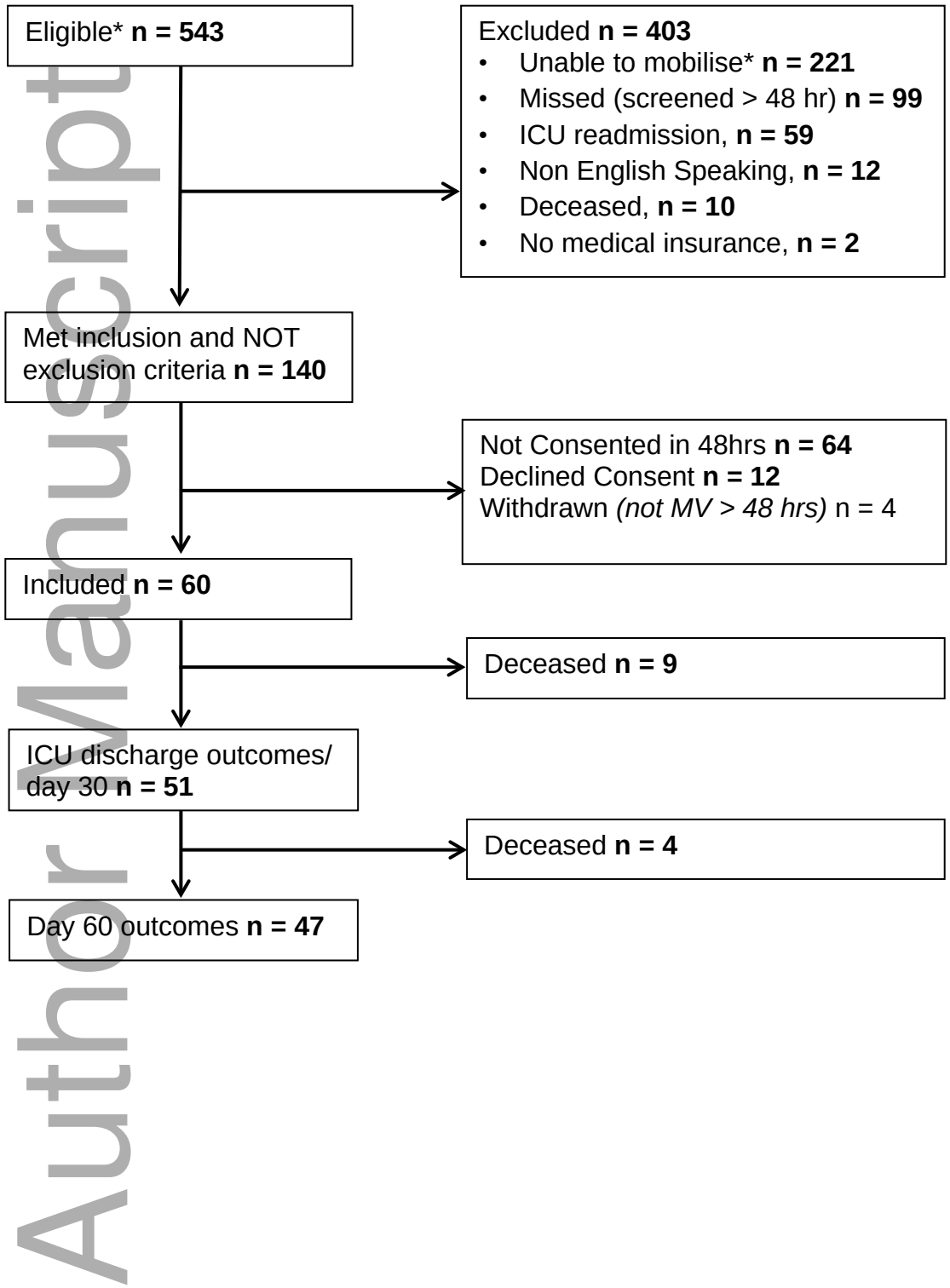
Variable	Univariate analysis adjusted for Baseline FFM			Multivariable analysis adjusted for all variables		
	effect	95% CI	P value	effect	95% CI	P value
FFM (Baseline), kg	0.93	0.80 to 1.1	<0.001	0.91	0.8 to 1.1	<0.001
Calorie deficit (per 1000kcal)	-1.1	-2.2 to -0.08	0.04	-1.3	-2.4 to -0.21	0.02
BMI (≥ 30kg/m^2)	2.2	-4.1 to 8.5	0.49	2.1	-4.1 to 8.1	0.51
Age (> 60 years)	-0.71	-6.2 to 4.7	0.80	0.24	-5.1 to 5.5	0.91
APACHE II (> 25)	-2.5	-11 to 9.8	0.38	-4.0	-9.5 to 1.6	0.15

Variable	Univariate analysis			Multivariable analysis adjusted for all variables		
	effect	95% CI	P value	effect	95% CI	P value
Calorie deficit (per 1000kcal)	-0.6	-0.9 to -0.2	0.002	-0.59	-0.92 to -0.26	0.001
BMI (≥ 30kg/m^2)	-1.9	-3.7 to -0.15	0.03	-2.0	-3.5 to -0.38	0.02
Age (> 60 years)	-1.1	-2.9 to 0.71	0.23	-1.2	-2.7 to 0.38	0.14

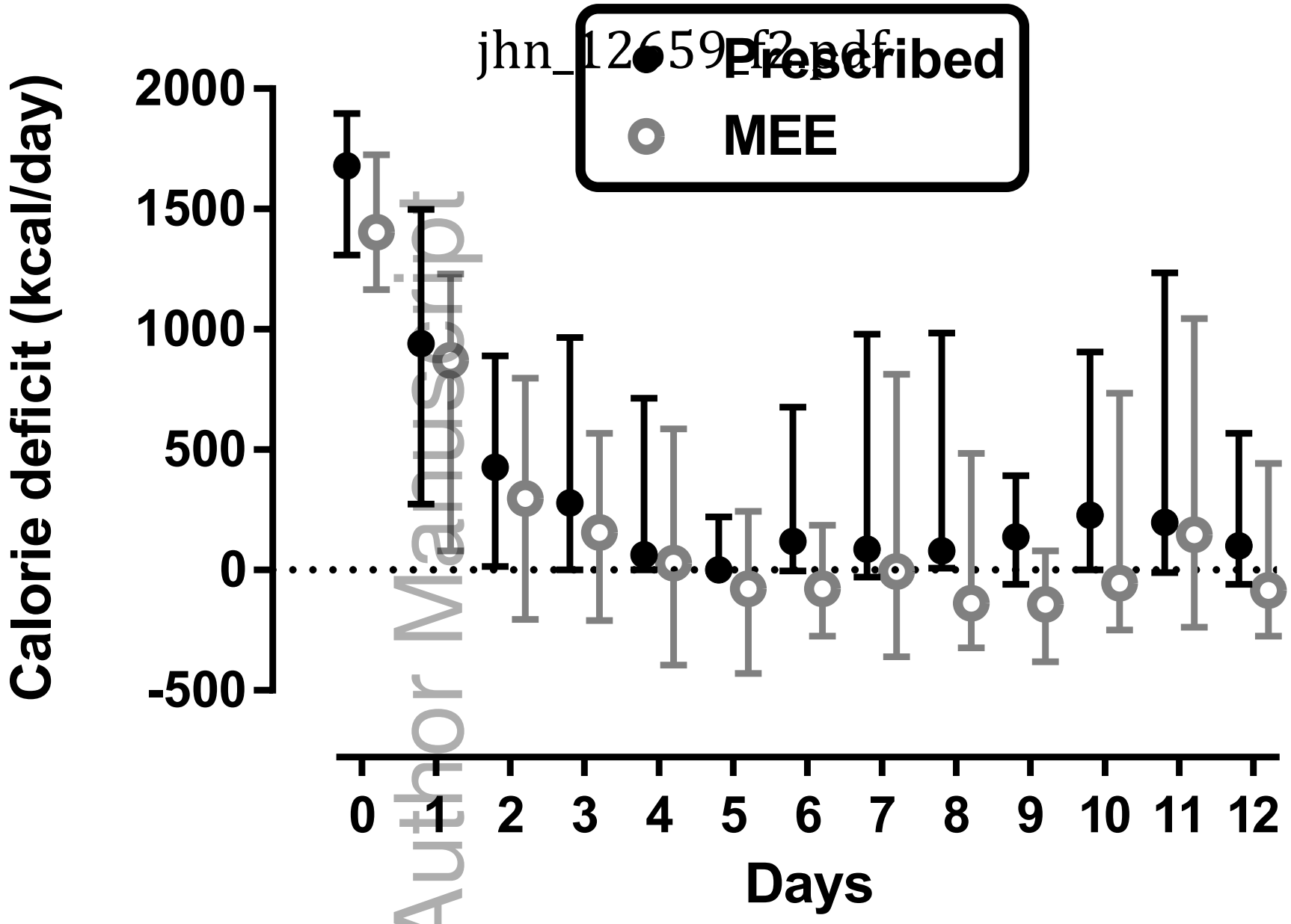
APACHE II (> 25)	-0.31	-2.2 to 1.6	0.75	-1.1	-2.8 to 0.54	0.18

Abbreviations: BMI; Body Mass Index centered at 30 kg/m^2, Age centered at 60 years, APACHE II; Acute Physiology And Chronic Health Evaluation II, centred at 25, FFM; Fat free Mass. Logistic regression analysis models were used for ICU-Acquired weakness and Malnutrition. Linear regression analysis models were used for fat free mass and physical function.

Figure1. Consort Diagram



Abbreviations: Eligible – patients who met all inclusion criteria at the time of screening, exclusion criteria = unable to mobilise - included major trauma necessitating a period of immobilisation; new neurological insults; and poor pre-morbid mobility (unable to mobilise independently with or without a gait aid). ICU – intensive care unit, not an Australian citizen –non citizens were excluded as they are ineligible for Medicare should their participation in the study result in the need for additional medical care. MEE – measured energy expenditure.



Prescribed (n)	41	60	59	52	44	35	30	23	20	17	15	12	11
Measured (n)	30	43	42	39	33	28	24	19	17	14	14	12	11