Role of timing and dose of energy received in patients with acute lung injury on mortality in the Intensive Nutrition in Acute Lung Injury Trial (INTACT): a post hoc analysis[1,2]

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ABSTRACT

Background: Our trial INTACT (Intensive Nutrition in Acute Lung Injury Trial) was designed to compare the impact of feeding from acute lung injury (ALI) diagnosis to hospital discharge, an interval that, to our knowledge, has not yet been explored. It was stopped early because participants who were randomly assigned to energy intakes at nationally recommended amounts via intensive medical nutrition therapy experienced significantly higher mortality hazards than did those assigned to standard nutrition support care that provided energy at 55% of recommended concentrations.

Objective: We assessed the influence of dose and timing of feeding on hospital mortality.

Design: Participants (n = 78) were dichotomized as died or discharged alive. Associations between the energy and protein received overall, early (days 1–7), and late (days ≥8) and the hazards of hospital mortality were evaluated between groups with multivariable analysis methods.

Results: Higher overall energy intake predicted significantly higher mortality (OR: 1.14, 95% CI: 1.02, 1.27). Among participants enrolled for ≥8 d (n = 66), higher early energy intake significantly increased the HR for mortality (HR: 1.17, 95% CI: 1.07, 1.28), whereas higher late energy intake was significantly protective (HR: 0.91, 95% CI: 0.83, 1.0). Results were similar for early but not late protein (grams per kilogram) exposure (early-exposure HR: 8.9, 95% CI: 2.3, 34.3; late-exposure HR: 0.15, 95% CI: 0.02, 1.1). Threshold analyses indicated early mean intakes ≥18 kcal/kg significantly increased subsequent mortality.

Conclusions: Providing kilocalories per kilogram or grams of protein per kilogram early post-ALI diagnosis at recommended levels was associated with significantly higher hazards for mortality, whereas higher late energy intakes reduced mortality hazards. This time-varying effect violated the Cox proportionality assumption, indicating that feeding trials in similar populations should extend beyond 7 d and use time-varying statistical methods. Future trials are required for corroboration. INTACT was registered at clinicaltrials.gov as NCT01921101. *Am J Clin Nutr* 2017;105:411–6.

Keywords: post hoc secondary analysis, medical nutrition therapy, randomized clinical trial, energy requirement, critical care, acute lung injury, energy dose and timing, threshold effect

INTRODUCTION

The impact of nonvolitional nutrition support on clinical outcomes in the critically ill has been a focus of research for >3 decades. Despite this long duration, large randomized clinical trials designed to detect the influence of providing enteral nutrition (EN)[8] and/or parenteral nutrition (PN) in this population have been conducted in the past 7 y. The results of the 11 clinical trials in intensive care unit (ICU) patients that have investigated the impact of nutrition support on clinical outcomes within the past 5 y have varied (1–11). The groups randomly assigned to higher energy intake had improved outcomes in 2 trials (8, 9), no difference in 5 (1, 5–7, 10), and worse outcomes in 4 (2–4, 11) than those randomly assigned to a lower intake. The 2 trials that found fewer infections with greater energy intake had problems with unintended imbalanced randomization that led to considerably greater numbers of patients prone to infection in the hypocaloric group (9) or issues regarding outcome reporting (8) that have raised questions about how these results should be interpreted (12). We suspect the remaining equivocal findings reflect variations in the timing and dose of feedings received.

Our recent clinical trial INTACT (Intensive Nutrition in Acute Lung Injury Trial) (NCT01921101) (3) explored the impact of providing intensive medical nutrition therapy (IMNT) from acute lung injury (ALI) diagnosis to hospital discharge on clinical outcomes. IMNT provided 30 kcal/kg, per the 2009 national guideline recommendations (13), and was compared with those who received

[1] Supported by NIH grant R01 HL093142.

[2] Supplemental Table 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[8] Abbreviations used: ALI, acute lung injury; EN, enteral nutrition; ETC, electron transport chain; ICU, intensive care unit; IMNT, intensive medical nutrition therapy; INTACT, Intensive Nutrition in Acute Lung Injury Trial; PN, parenteral nutrition; SNSC, standard nutrition support care; SOFA, Sequential Organ Failure Assessment.

Received July 26, 2016. Accepted for publication November 11, 2016.

First published online December 14, 2016; doi: 10.3945/ajcn.116.140764.

standard nutrition support care (SNSC). SNSC was directed by the physician and historically has provided 40–60% of prescribed feedings (14, 15). Participants were severely ill, and 45% were categorized as malnourished by subjective global assessment. The study was stopped early ($n = 78$) because of greater mortality among participants randomly assigned to IMNT than those assigned to SNSC (40% compared with 16%, respectively; $P < 0.02$).

It is biologically feasible that the influence of exogenous nutrition received during the most catabolic phase of illness on mortality differs substantially from feedings provided later in the disease process. Early acute illness is characterized by elevated concentrations of catabolic hormones and cytokines, which along with bed rest induce muscle wasting. Exogenous nutrients received at this time attenuate but do not reverse this process (16, 17). Repletion is not attainable until the disease-associated catabolism resolves. All of the trials reported since 2011 (except INTACT), to our knowledge, have restricted their interventions to this early acute illness interval. INTACT was designed to provide optimal nutrient intake from ALI diagnosis through hospital discharge; thus, it enables post hoc assessment regarding the timing and dose of energy received throughout this interval on mortality, an area that heretofore has been virtually unexplored. Therefore, the purpose of this secondary analysis was to compare INTACT participants who died with those who survived and to determine whether the timing and/or dose of the energy or protein received influenced the hazards of mortality while hospitalized.

METHODS

The study design, methodology, patient population, intervention, and results of INTACT have been previously reported (3). Briefly, this single-center randomized controlled trial conducted at an urban university hospital was designed to discern the influence of IMNT [i.e., 30 kcal/kg and 1.5 g protein/kg (13)] compared with SNSC (standard physician-directed EN and ad libitum feeding) from ALI diagnosis through hospital discharge. The primary outcome was postrandomization infections; secondary outcomes included days on mechanical ventilation, hospital and ICU length of stay, and mortality. Energy and protein needs were based on admission weight or obesity-adjusted ideal body weight. Energy and protein intake were assessed by physician orders and nursing graphics of the EN and/or PN received. The EN data included the formula name and volume received. The PN prescription ordered and received (volume and percentage of carbohydrates, protein, and fat) was recorded. The caloric contribution of lipid-based sedatives and/or dextrose-containing intravenous fluids and medications were also recorded. When oral diets were initiated, research personnel obtained daily calorie counts with the use of the 24-h multiple-pass approach. To facilitate this process, menus were saved and reviewed with all participants and/or family members daily. The energy and caloric intake of hospital foods was assessed with the use of a food and nutrition services nutrient analysis system. Foods consumed that were not from the institution were assessed with the use of the University of Minnesota Nutrient Data System for Research. Ethical approval was granted by the medical center and university's institutional review boards.

Our original analyses indicated that the study groups were similar in terms of age, severity of illness, sex, ethnicity, and baseline concentrations of C-reactive protein, white blood cell count, or glucose. By design, the IMNT group received a significantly greater percentage of estimated energy (85% compared with 55%; $P < 0.001$) and protein (82% compared with 60%; $P < 0.001$) needs from enrollment through discharge than the SNSC group. Recruitment was terminated when 39% (78 participants) of the recruiting goal (200 participants) had been reached because of a significantly higher mortality in the IMNT than SNSC groups (16/40 compared with 6/38, respectively; $P < 0.02$). Cox proportional hazards models indicated that the hazards of death in those randomly assigned to IMNT was 5.67 times higher than those assigned to SNSC ($P = 0.001$).

Characterization of hospital survivors and nonsurvivors

Participants ($n = 78$) were dichotomized as died or discharged alive, and between-group comparisons for descriptive characteristics, days from ICU admission to study enrollment, and energy and protein received from the first day after being randomly assigned to death or hospital discharge were assessed with standard univariate and multivariable analyses. Binary logistic regression with forward stepwise variable selection was used to discern the best model for characterizing patients who died compared with those who were discharged alive.

Associations between timing of energy and protein exposure on hazards of mortality

The impact of the timing of kilocalories per kilogram or grams of protein per kilogram received from the first day after being randomly assigned to death or hospital discharge on overall mortality, regardless of treatment, was explored with the use of logistic multiple regression. Models were designed to explore the effect of early nutrients received on the likelihood of subsequent death and how varying the length of time used to define early feeding influenced the effect of nutrients received on the likelihood of subsequent death or being discharged alive. The number of full feeding days after patients were randomly assigned was explored by increasing the intervals by 1 d (i.e., days 1–2, 1–3, 1–4, etc.). For each interval, patients who died or were discharged during the interval were excluded, and the impact of the nutrients received during the interval was assessed only for those who died compared with those who were discharged alive after the interval. The interval that best captured the effect of early feeding was used to inform the choice of interval for piecewise Cox models and to explore a caloric threshold effect.

Impact of early energy and protein exposure (days 1–7) compared with late exposure (days ≥8) on hazards of mortality

Cox proportional hazards multiple regression was used to fit models for death during days 1–7 and ≥8 for all patients still enrolled on day 8. Models were adjusted for significant baseline covariates [age, sex, baseline Sequential Organ Failure Assessment (SOFA) score] and a time-dependent variable for mean feeding received during days 1–7 and ≥8. Additional time-dependent variables explored in these models included the number of days that kilocalories per kilogram or grams of protein per kilogram received was greater than estimated needs, mean insulin received, and number of days any insulin was received.

Defining the energy exposure threshold (i.e., the lowest energy intake) associated with mortality

Logistic multiple regression models adjusted for baseline covariates were used to explore kilocalorie per kilogram exposure thresholds during days 1–7 for subsequent death. SAS version 9.4 (SAS Institute) was used for all analyses.

RESULTS

Effect of energy and protein received on mortality over entire enrollment

Demographic, nutritional status, severity of injury, kilocalories per kilogram and grams of protein per kilogram received, and other disease profiles of INTACT participants categorized into those who died compared with those who were discharged alive are presented in **Table 1**. The causes of death included terminally extubated (n = 18), septic shock or bradycardia (n = 3), and cardiac arrest (n = 1). Participants who died were significantly older, more malnourished, and had higher SOFA scores than those who were discharged alive. No differences between the groups in mean kilocalories per kilogram and grams of protein per kilogram received, PN, and/or lipid exposure were found.

Effect of early days of feeding on subsequent outcomes

Binary logistic regression findings comparing participants who died with those who were discharged from the hospital are presented in **Table 2**. Forward stepwise variable selection chose age, sex, and SOFA score as significant baseline predictors. Other baseline variables considered [BMI (in kg/m^2), PN, and/or intravenous lipids; Acute Physiology and Chronic Health Evaluation II score; subjective global assessment score; days from ICU admission to enrollment] were not significant at $\alpha = 0.05$ when adjusted for the selected variables. Separate models were constructed to avoid problems with multicollinearity for energy and protein received because of their significant correlation ($r = 0.681$; $P < 0.0001$). Participants who died were significantly older, more likely to be women, and had higher baseline SOFA scores than patients who were discharged alive. Adjusting for these factors, patients who died received significantly higher mean daily kilocalories per kilogram across the entire enrollment period ($P = 0.02$). The mean daily grams of protein per kilogram received did not differ between participants who died compared with those who were discharged alive ($P = 0.22$).

Detailed results for the logistic multiple regression models that examined the impact of kilocalories per kilogram and grams of protein per kilogram received during progressive intervals of feeding days on subsequent outcomes (i.e., death or discharged) are provided in **Supplemental Table 1**. The mean kilocalories per kilogram received significantly predicted subsequent death as early as day 3, and the strongest association occurred during days 1–7. The effects of early grams of protein per kilogram received did not significantly predict subsequent outcome, although its strongest effects also occurred during days 1–7 ($P = 0.08$).

Cox proportional hazards multiple regression was used to fit models for the hazard of death during postrandomization days 1–7 as a function of significant baseline covariates (age, sex, baseline SOFA score) and the time-varying mean daily kilocalories per kilogram or grams of protein per kilogram received so far. Patients still alive on day 8 were right-censored at day 8

TABLE 1
Baseline characteristics of INTACT participants who died compared with those who were discharged alive[1]

Variables	Died (n = 22)	Discharged alive (n = 56)	P
Age, y	64.3 ± 14	52.2 ± 16.8	0.004
Women, n (%)	14 (64)	24 (43)	0.07
BMI, kg/m^2	29.5 ± 9.1	30.3 ± 9.2	0.70
SGA, n (%)			0.05
Normal	10 (45)	39 (70)	
Moderate or severe	12 (55)	17 (30)	
Admitting diagnosis, n (%)			—
Respiratory failure	15 (68)	39 (70)	
Sepsis	3 (14)	6 (11)	
Pneumonia	2 (9)	5 (9)	
Fever	2 (9)	1 (2)	
Gastrointestinal bleed	0	1 (2)	
Seizure	0	1 (2)	
Overdose	0	1 (2)	
Other	0	2 (4)	
ICU days before study enrollment	4.8 ± 2.8	4.2 ± 3.6	0.46
Total enrollment days	11.3 ± 7.3	17.9 ± 12.4	0.005
ICU admit APACHE II	27.5 ± 8.8	24.7 ± 8.9	0.21
SOFA enrollment	12.2 ± 3.5	8.2 ± 3.0	<0.0001
History of diabetes, n (%)	4 (18.2)	12 (21.4)	0.70
Mean kcal/kg received overall	21.0 ± 7.4	20.8 ± 7.7	0.97
Mean g protein/kg received overall	0.79 ± 0.30	0.91 ± 0.38	0.16

[1] All values are means ± SDs unless otherwise indicated. P values were generated from Student's t and chi-square tests. APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; INTACT, Intensive Nutrition in Acute Lung Injury Trial; SGA, subjective global assessment; SOFA, Sequential Organ Failure Assessment.

TABLE 2
Multiple logistic regression model for INTACT participants who died compared with those who were discharged alive[1]

Independent variables	β Hat	SE	P	OR (95% CI)
Model 1				
Age[2]	0.083	0.028	0.003	1.09 (1.03, 1.2)
Women compared with men	1.808	0.759	0.017	6.1 (1.38, 27.0)
Baseline SOFA[3]	0.569	0.156	0.0003	1.77 (1.32, 4.0)
Mean daily kcal/kg received over entire enrollment period[4]	0.130	0.056	0.02	1.14 (1.02, 1.27)
Model 2				
Age[2]	0.070	0.027	0.008	1.07 (1.02, 1.13)
Women compared with men	1.958	0.789	0.013	7.08 (1.5, 33.3)
Baseline SOFA[3]	0.485	0.137	0.0004	1.62 (1.24, 2.12)
Mean daily g protein/kg received over entire enrollment period[5]	0.017	0.014	0.223	1.02 (0.99, 1.05)

[1] n = 78 (22 died; 56 discharged alive). INTACT, Intensive Nutrition in Acute Lung Injury Trial; SOFA, Sequential Organ Failure Assessment.
[2] Mean increase of 1 y.
[3] Mean increase of 1 unit.
[4] Mean increase of 1 kcal/kg.
[5] Mean increase of 1 g/kg.

for this model. The time-varying kilocalories per kilogram or the grams of protein per kilogram received during this interval did not significantly affect the hazard of death during postrandomization days 1–7, likely reflecting the few deaths that had occurred.

Table 3 depicts Cox proportional hazards results for all participants still enrolled on or after day 8 (n = 66) as a function of significant baseline covariates (age, sex, baseline SOFA score) and the mean kilocalories per kilogram or grams of protein per kilogram received during postrandomization days 1–7. The time-dependent variables explored included the mean daily kilocalories per kilogram and grams of protein per kilogram received starting with day 8, number of days since day 8 that kilocalories per kilogram or grams of protein per kilogram received were greater than estimated needs, mean insulin received, and number of days any insulin was received. After day 8, the hazards for subsequent death were significantly increased by higher mean daily kilocalories per kilogram received during early postrandomization days 1–7 (HR: 1.17; 95% CI: 1.07, 1.28 for every 1-kcal increase/kg; $P < 0.0004$) or grams of protein per kilogram (HR: 8.87; 95% CI: 2.29, 34.3 for each 1-g protein increase/kg; P = 0.002), and significantly reduced by the time-varying kilocalories per kilogram received on and after day 8 (HR: 0.91; 95% CI: 0.83, 1.0; P = 0.04); late grams of protein per kilogram received was not significant (HR: 0.15; 95% CI: 0.02, 1.17; P = 0.04). No other time-dependent variables were significant.

The threshold of detection for lowest energy intake (kilocalories per kilogram) on days 1–7 that was associated with a significantly greater likelihood of subsequent death was assessed with logistic multiple regression models that were adjusted for age, sex, and baseline SOFA score. Instead of treating mean daily kilocalories per kilogram as a continuous variable as in previous models, the effects of binary indicators for mean intake above a range of different thresholds were estimated and compared. A mean intake of ≥18 kcal/kg on postrandomization days 1–7 was the lowest energy threshold that predicted significantly higher mortality on days ≥8 (P = 0.02), whereas a mean intake of ≥23 kcal/kg was the strongest (P = 0.01) predictor of subsequent death.

DISCUSSION

Findings from this post hoc analysis of INTACT indicate the hazards of mortality were significantly affected by the dose and timing of feeding exposure. We hypothesize 3 unique aspects of

TABLE 3
Proportional hazards multiple regression models for hazard of death on or after 8 d for INTACT participants[1]

Independent variable	β Hat	SE	P	HR (95% CI)
Model 1				
Mean kcal/kg received during days 1–7[2]	0.1575	0.0441	0.0004	1.17 (1.07, 1.28)
Time-dependent mean daily kcal/kg received during days 1–7 and after day 8[2]	−0.0967	0.0471	0.04	0.91 (0.83, 1.0)
Model 2				
Mean daily g protein/kg received during days 1–7[3]	2.18	0.69	0.002	8.87 (2.3, 34.3)
Time-dependent mean daily g protein/kg received during days 1–7 and after day 8[3]	−1.89	1.00	0.06	0.15 (0.02, 1.07)

[1] Models were adjusted for age, sex, and baseline SOFA score, n = 66 (15 deaths). INTACT, Intensive Nutrition in Acute Lung Injury Trial; SOFA, Sequential Organ Failure Assessment.
[2] Mean increase of 1 kcal/kg.
[3] Mean increase of 1 g/kg.

our trial enabled the detection of these findings. First, participants in the intervention group received a mean intake of 25 kcal/kg (the nationally recommended energy intake) early and throughout the trial, providing an adequate number of "exposed" participants for detecting its effect. Second, the trial began when ALI was diagnosed rather than on a prespecified ICU day, improving the homogeneity of the catabolic phase of illness between participants. Finally, because energy intake was assessed from ICU enrollment through hospital discharge, detecting the time-varying impact of feeding exposure that occurred through this interval was possible.

Of the clinical trials reported since 2011 that have explored caloric exposure in critically ill patients, 10 to our knowledge have compared hypocaloric with full feeding either through supplemental PN to enhance intake (4, 6, 8, 9) or manipulation of EN support to intentionally reduce intake (1–3, 5, 10, 11). The heterogeneity in kilocalories per kilogram received in these studies limits the interpretation of their findings. Only 3 of these trials (3, 4, 11) successfully delivered randomized energy intake at the nationally recommended estimated concentration or measured resting energy expenditure (18) early in ICU stay. These 3 trials all were conducted in severely ill patients, initiated nutrition support within 24 h of ICU admission (4, 11) or upon ALI diagnosis (3), and had worse outcomes in the group that received higher energy intake. Specifically, higher mortality occurred in INTACT (3), a lower likelihood of early alive discharge from the ICU was reported in the large multicenter Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients study (4), and longer ICU stays and time on mechanical ventilation were found in Singer et al. (11). Interestingly, the EDEN trial (n = 1000) conducted in patients with ALI that began at admission to the ICU found no difference between trophic (400 kcal/d; ∼5-kcal/kg enrollment weight) or full (1300 kcal/d; ∼15-kcal/kg enrollment weight) feedings on 60-d mortality rates (10). We speculate that the difference observed between our findings and those from EDEN reflects the overall low energy exposure in the EDEN participants. Of note, EDEN has been cited in support of the current national recommendations for either full or trophic feedings in patients with ALI (18, 19) despite an intake among its participants that was 36–80% below the guidelines for full feeding at 25–30 kcal/kg.

The post hoc analysis of 2 other clinical trials that explored the influence of energy exposure at recommended concentrations early in the ICU stay found results similar to ours (20, 21). The Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients post hoc study (20) compared the impact of higher energy intake in patients categorized by severity of illness, BMI, and nutrition risk and found no benefits from the reduction in calorie deficits via early feedings from either EN or PN in any of these subgroups. Overall, participants in the lowest quintile for kilocalories per kilogram received (i.e., 13–18 kcal/kg) had the highest likelihood of early alive discharge than all other quintiles independent of the route of feeding (PN or EN). Furthermore, a subgroup analysis of participants with contraindications for EN (n = 517) showed that those randomly assigned to late PN (n = 261) had significantly lower infection rates and were 20% more likely to be discharged alive earlier from the ICU (HR: 1.20; 95% CI: 1.0, 1.4) than those randomly assigned to early PN (n = 256). The post hoc analysis of the 2008 trial by Arabi et al. (21) explored the impact of the caloric intake during days 1–7 on subsequent morbidity and mortality. They found that providing >65% of the energy intake goal (∼20 kcal/kg) for the first 7 d was associated with significantly higher hospital mortality than patients who received <33% of estimated energy requirements. The consistency of the findings from randomized trials and post hoc studies of trials that met the recommended energy intake early in severely ill populations indicate caution in broadly implementing the current national guidelines of 25–30 kcal/kg early in ICU patients.

To our knowledge, INTACT is the only clinical trial that has assessed the impact of energy and protein exposure from all sources from ICU enrollment to hospital discharge. This design enabled exploration of the time-varying impact of early (days 1–7) compared with late (days ≥8) energy and protein intake on outcomes. Among participants who remained in the trial for ≥8 d (n = 66), energy exposure had a crossover effect on mortality. Specifically, higher early intake significantly increased the mortality hazards, whereas higher late energy intake significantly reduced mortality hazards. The metabolic response to critical illness has been known for decades (22). Feeding during the early phase of critical illness does not mitigate the catabolic response or enhance the repletion of lean body mass (17, 23, 24). Our findings suggest the amount of early energy intake should be <18 kcal/kg and increased as the catabolic response resolves, when anabolism is possible. These findings also indicate the need for trials in critically ill populations to extend beyond the first week of ICU stay and include statistical analyses that address the time-varying response to energy intake. The Cox proportional hazards model is frequently used to explore survival time as a function of multiple prognostic factors. This model assumes proportionality of the hazards (i.e., the factors investigated have a constant impact on the hazard over time). Our finding of a time-varying effect of energy exposure indicates that the assumption of proportionality is violated. Future feeding studies in ICU populations that use the Cox model should verify that the proportionality assumption is met and, if the assumption is violated, take steps to address the issue.

The mechanisms of harm through which feeding may induce worse clinical outcomes in critically ill patients is a current area of research focus (25–28). Proinflammatory states, achieved by increasing nitric oxide production, are known to increase reactive oxygen species production within the mitochondrial electron transport chain (ETC) in response to nutrient substrate. Furthermore, nitric oxide generates reactive species that impair the enzyme systems in place to manage the increased oxidative stress. We are currently investigating whether providing nutrition support at the nationally recommended concentrations during this time of redox vulnerability increases oxidative stress, leading to diminished mitochondrial function and causing decreased ATP productive capacity, cell death, and multiple organ failure. This theory is further supported by human and animal studies that have shown calorie exposure to be deleteriously associated with attenuations in both autophagy (28) and the low T3 syndrome (26). We hypothesize that low T3 prevents the forced ATP production from suboptimal ETCs, whereas autophagy increases the percentage of optimal ETCs by recycling damaged mitochondria. Attenuating these processes through excessive exogenous nutrition would be expected to increase reactive oxygen species production and further mitochondrial damage, leading to increased cell death and worse clinical outcomes.

Our study has several limitations. The findings are based on a posteriori associations of the impact of kilocalories per kilogram

or grams of protein per kilogram received in participants who died compared with those who survived in INTACT. Thus, all results are associations and hypothesis-generating rather than causal. This was a small single-center study restricted to adult patients with ALI, limiting generalizability and requiring further corroboration. Selection bias and incomplete assessment of the exposure and outcomes of interest are generally of concern in observational studies. It is unlikely that our study suffers from these issues because *1*) participants were restricted to those enrolled in a randomized trial, minimizing risks for selection bias, and *2*) both the outcome (mortality) and the exposure of interest (energy and protein intake) were identically assessed for all participants from enrollment through hospital discharge, minimizing the bias for incomplete data acquisition.

In conclusion, caloric and protein intake at current nationally recommended concentrations of 25–30 kcal/kg (18, 19) early in the ICU stay during the most acute phase of illness was associated with higher hazards of mortality, whereas higher energy exposure later in the hospitalization was associated with lower mortality hazards. Overall, these findings suggest that early feedings in severely ill adults with ALI at current recommended concentrations (19) are harmful, whereas optimizing nutrient intake later, when repletion can be achieved, is beneficial. Future studies are needed to test and substantiate this hypothesis.

The authors' responsibilities were as follows—CLB, SF, PMS, DG, and GF: designed the research; PMS, SJP, SGP, LM, OL, and DG: conducted the research; SF: analyzed the data and performed the statistical analysis; CLB, SF, PMS, SJP, LM, and GF: wrote the manuscript; CLB: had primary responsibility for the final content; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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