Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group trial (NUTRIREA-3)

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Summary

Background

The optimal calorie and protein intakes at the acute phase of severe critical illness remain unknown. We hypothesised that early calorie and protein restriction improved outcomes in these patients, compared with standard calorie and protein targets.

Methods

The pragmatic, randomised, controlled, multicentre, open-label, parallel-group NUTRIREA-3 trial was performed in 61 French intensive care units (ICUs). Adults (≥18 years) receiving invasive mechanical ventilation and vasopressor support for shock were randomly assigned to early nutrition (started within 24 h after intubation) with either low or standard calorie and protein targets (6 kcal/kg per day and 0·2–0·4 g/kg per day protein *vs* 25 kcal/kg per day and 1·0–1·3 g/kg per day protein) during the first 7 ICU days. The two primary endpoints were time to readiness for ICU discharge and day 90 all-cause mortality. Key secondary outcomes included secondary infections, gastrointestinal events, and liver dysfunction. The trial is registered on ClinicalTrials.gov, NCT03573739, and is completed.

Findings

Of 3044 patients randomly assigned between July 5, 2018, and 8 Dec 8, 2020, eight withdrew consent to participation. By day 90, 628 (41·3%) of 1521 patients in the low group and 648 (42·8%) of 1515 patients in the standard group had died (absolute difference –1·5%, 95% CI –5·0 to 2·0; p=0·41). Median time to readiness for ICU discharge was 8·0 days (IQR 5·0–14·0) in the low group and 9·0 days (5·0–17·0) in the standard group (hazard ratio [HR] 1·12, 95% CI 1·02 to 1·22; p=0·015). Proportions of patients with secondary infections did not differ between the groups (HR 0·85, 0·71 to 1·01; p=0·06). The low group had lower proportions of patients with vomiting (HR 0·77, 0·67 to 0·89; p<0·001), diarrhoea (0·83, 0·73 to 0·94; p=0·004), bowel ischaemia (0·50, 0·26 to 0·95; p=0·030), and liver dysfunction (0·92, 0·86–0·99; p=0·032).

Interpretation

Compared with standard calorie and protein targets, early calorie and protein restriction did not decrease mortality but was associated with faster recovery and fewer complications.

Introduction

Critical illness requiring organ support is associated with both mortality and prolonged recovery in survivors. A key period is the acute phase characterised by organ failure, anorexia, metabolic disorders, endocrine dysfunction, and major hypercatabolism with severe muscle wasting.1,2 Nutritional support is crucial at this phase. Greater calorie and protein deficits have been shown to be associated with higher risks of health-care-associated infections, intensive care unit (ICU)-acquired weakness, prolonged invasive mechanical ventilation,

long ICU stays, and death.3,4 International guidelines recommend starting nutritional support within 48 h after ICU admission, via the enteral route if not contraindicated, with targets of 20–25 kcal/kg per day and 1·2–2 g/kg per day of protein at the acute phase.5,6 These targets are rarely achieved in patients with severe critical illnesses, who frequently experience gastroparesis responsible for intolerance to enteral nutrition.7

Data from studies conducted in the past 10 years challenge the appropriateness of these standard calorie and protein targets during the acute phase of critical illness.8,9 In randomised trials, increasing the enteral calorie intake did not improve outcomes.10–12 Adding parenteral nutrition to enteral nutrition to increase intakes was associated with longer ICU stays and higher infection rates.13,14 Higher protein intakes during the acute phase might be linked to greater muscle wasting and ICU-acquired weakness.1,15 Intentionally supplying fewer calories than recommended, even down to 400 kcal per day (trophic feeding), did not adversely affect patient outcomes.16,17 Thus, low calorie and protein intakes might have benefits. A major limitation of available studies of calorie restriction is failure to reach the standard target in the control groups, which decreased the ability to detect a significant difference between groups. Moreover, no studies compared low versus standard protein intakes at the acute phase. Thus, the optimal calorie and protein intakes at the acute phase of severe critical illness remain unknown.9,18,19

We designed the NUTRIREA-3 multicentre randomised trial to evaluate whether, in critically ill patients receiving invasive mechanical ventilation and vasoactive drugs, low-calorie low-protein feeding decreased day 90 mortality or ICU length of stay, or both parameters, compared with standard calorie and protein supplies.

Methods

Study design

NUTRIREA-3 was a 1:1 randomised, controlled, multicentre, open-label, parallel-group, superiority trial. The study protocol was approved by the competent ethics committee (Comité de Protection des Personnes Sud-Méditerranée 2, number 2018-A00424-51). Before each inclusion, the patient or next of kin provided written informed consent. If the patient was unable to receive information and no next of kin could be contacted during screening for the study, trial inclusion was completed as an emergency procedure by the ICU physician, in compliance with French law. The electronic case-record form and database organisation were approved by the appropriate committees as required by French law. The study protocol has been published elsewere.20

Participants

The trial was conducted in the 61 French ICUs listed in the appendix (pp 3–8). Adults (≥18 years) admitted to any of the participating ICUs were eligible if they were receiving invasive mechanical ventilation, with an expected duration of at least 48 h after inclusion and initiation either in the ICU within the past 24 h or before ICU admission having occurred within the past 24 h, concomitantly with vasoactive therapy (adrenaline, dobutamine, or noradrenaline) for shock, and if nutritional support was expected to be started within 24 h after intubation (or within 24 h after ICU admission when intubation occurred before ICU admission). Exclusion criteria were specific nutritional needs, such as pre-existing long-term home enteral or parenteral nutrition for chronic bowel disease; dying patient, not-to-be-resuscitated order, or other treatment-limitation decision at ICU admission; pregnancy, recent delivery, or lactation; adult under guardianship; and correctional facility inmate.

Randomisation and masking

All patients treated with invasive mechanical ventilation and vasoactive drugs for shock within 24 hours after ICU admission were screened for eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a week. Investigators at each centre used a secure, computer-generated, interactive, web-response system to randomly assign consecutive eligible patients in a 1:1 ratio to one of the two early nutritional-support groups defined by low versus standard calorie and protein targets. Randomisation was stratified by centre using permutation blocks of variable sizes. The investigators could not access the randomisation list and were unaware of block size. Given that the volume and delivery of enteral and parenteral feeding preparations cannot be masked, masking of physicians and nurses was not feasible. The electronic case-report form was a secure, interactive, web-response system that was available at each study centre and was provided and managed by the biometrics unit of the Tours University Hospital (CIC INSERM 1415, Tours, France).

Procedures

The calorie and protein targets for the acute phase, defined as the first 7 days after ICU admission, were 6 kcal/kg per day and 0·2–0·4 g/kg per day in the low group versus 25 kcal/kg per day and 1·0–1·3 g/kg per day in the standard group. On day 8, the targets were changed to 30 kcal/kg per day for calories and 1·2–2·0 g/kg per day for protein in both groups. The daily nutritional intake required to meet the assigned calorie target was calculated based on bodyweight. In patients with obesity (BMI >30 kg/m²), the bodyweight yielding a BMI of 30 kg/m² was used. In patients whose BMI was below 18·5 kg/m², we used the corrected bodyweight computed as half the sum of the ideal and actual bodyweights. The calorie to protein ratios of nutrient preparations currently available in French hospitals ensured that the protein intake complied with the assigned target.

In both groups, the assigned feeding strategy was initiated as soon as possible after randomisation and no later than 24 h after intubation (or after ICU admission in patients intubated before ICU admission). It was continued until extubation and withdrawal of vasoactive drugs, death, or end of day 7 from admission, whichever occurred first. Patients who were reintubated within 7 days after inclusion were managed until the end of the acute phase using the feeding strategy they were assigned to initially. Nutritional support was started at the flow rate (mL/h) that achieved the calorie target on day 1 and was delivered continuously over the 24 h cycle, with no interruptions.

During the acute phase, bedside physicians determined the best feeding route each day, according to clinical considerations, to ensure that the calorie target was achieved.21,22 After the acute phase, enteral feeding remained the preferred route in patients without contraindications.5,6 At each centre, the usual blood-glucose control and insulin-therapy protocols were applied. Additional water, electrolytes, vitamins, and trace elements were given intravenously according to the needs of each patient, as assessed by the physician in charge, using the standard preparations and protocols available at each centre.

Additional details of the interventions and protocols for providing nutritional support, including measures designed to evaluate tolerance, have been published previously.20 All participating ICU staff members attended training in the study procedures and protocols for providing nutritional support and managing intolerance to enteral nutrition.20

Outcomes

We assessed two primary outcomes: all-cause day 90 mortality and time to readiness for ICU discharge. Patients were considered ready for ICU discharge as soon as they met all the predefined criteria, regardless of availability of beds on the ward: (1) no longer in need of, or at risk for needing, invasive mechanical ventilation; (2) no longer in need of, or at risk for needing, vasoactive support; (3) no agitation or consciousness alteration requiring close monitoring and management; and (4) no severe acute metabolic or haematological disorder requiring close monitoring and management.13,14 Readiness for ICU discharge was checked daily in all patients

weaned off invasive mechanical ventilation and vasoactive drugs. This evaluation was performed by the bedside physician in charge of the patient.

Secondary outcomes included the Sequential Organ Failure Assessment (SOFA) score; bodyweight; amount of calories and protein delivered; vomiting; prokinetic drug use; diarrhoea and constipation; blood glucose; insulin treatment; blood concentrations of lactate, bilirubin, alanine aminotransferase, and aspartate aminotransferase; antiulcer prophylaxis; antimicrobial treatments; prone positioning; dialysis during the intervention period; day 28 mortality; ICU mortality; hospital mortality; ICU length of stay; acute-care hospital length of stay; days without life-support; ICU-acquired infections; and non-infectious complications. Information on data collection and outcome definitions was previously reported.20

Baseline characteristics were recorded at inclusion. The Simplified Acute Physiology Score (SAPS II) was computed 24 h after ICU admission. After nutritional support initiation, daily recordings were made of nutritional data, treatments, nosocomial infections, abdominal complications, laboratory data, and invasive devices, until hospital discharge or day 90, whichever occurred first. Vital status was recorded at ICU discharge, at hospital discharge, and on days 28 and 90. Bowel ischaemia and ventilator-associated pneumonia were diagnosed according to predefined criteria, as previously reported.20,21 ICU-acquired infections were adjudicated by an independent masked committee, based on all available clinical, radiological, and bacteriological data. All the study data were stored in a logged database that was locked on July 28, 2022, after the site investigators had responded to all the queries made by the database managers.20

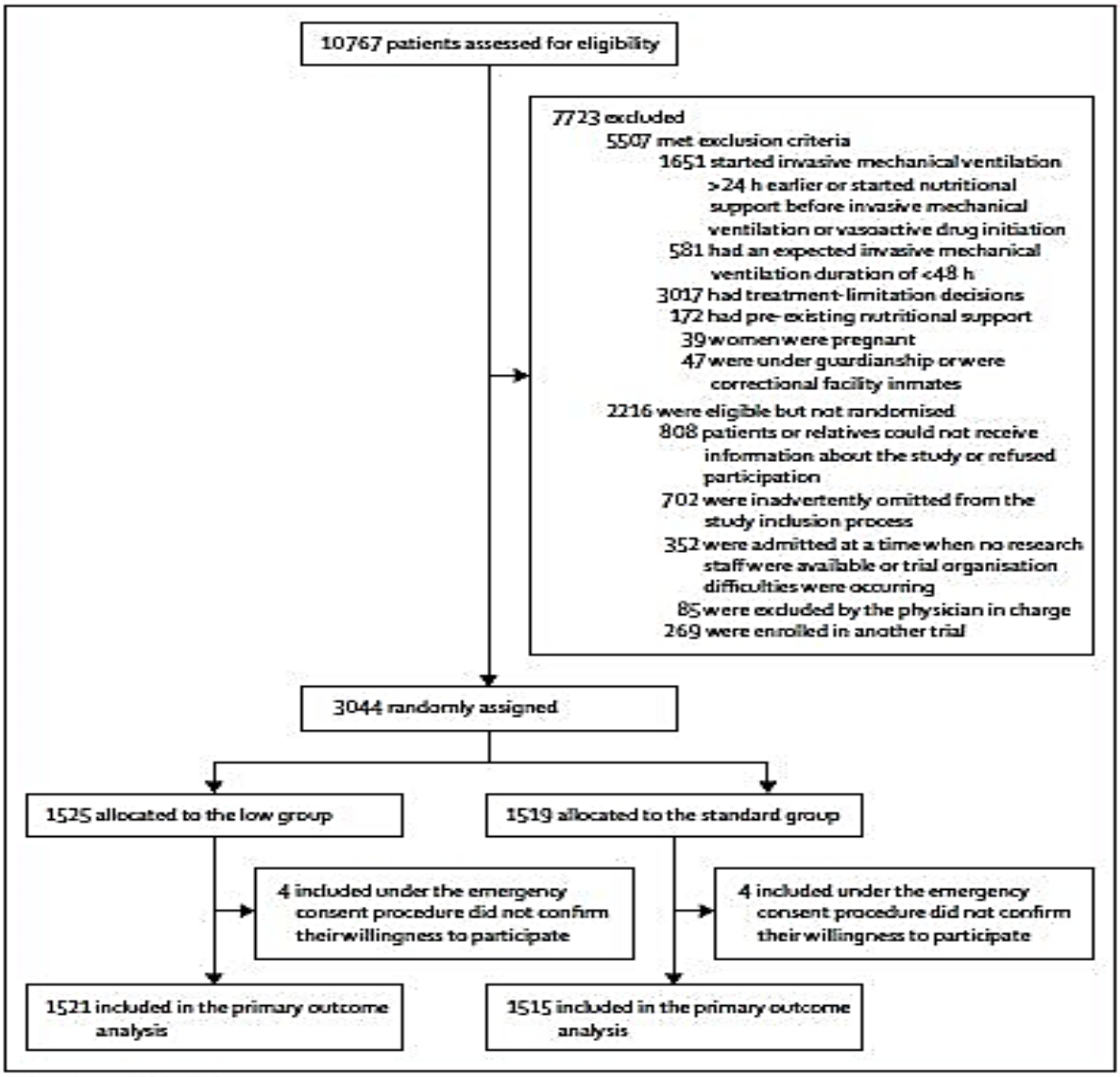


Figure 1: **Trial profile**

	Low group (n=1521)	Standard group (n=1515)
Age, years	66 (13)	66 (13)
Sex		
Men	1010 (66·4%)	1026 (67·7%)
Women	511 (33·6%)	489 (32·3%)
McCabe score		
0—no fatal underlying disease	1051 (69·5%)	1054 (69·7%)
1—death expected within 5 years	389 (25·7%)	378 (25·0%)
2—death expected within 1 year	73 (4·8%)	81 (5·4%)
Pre-existing illness at ICU admission	1059 (70·2%)	1066 (70·9%)
Pre-existing illness at ICU admission		
Chronic renal failure	184 (12·2%)	180 (12·0%)
Liver disease	139 (9·2%)	150 (10·0%)
Cardiovascular disease	292 (19·5%)	298 (19·9%)
Chronic respiratory failure	195 (13·0%)	155 (10·4%)
Neurological disease	209 (13·9%)	192 (12·8%)
Cancer or immune deficiency	395 (26·2%)	407 (27·1%)
Oesophageal, gastric, or duodenal ulcer	116 (7·7%)	99 (6·6%)
Diabetes	374 (24·9%)	384 (25·6%)
Weight, kg	76·5 (65·0–89·5)	77·0 (65·3–90·0)
BMI, kg/m²	26·7 (23·0–31·1)	27·0 (23·0–31·5)
Pre-existing malnutrition*		
None	1362 (90·0%)	1379 (91·2%)
Moderate	64 (4·2%)	62 (4·1%)
Severe	87 (5·8%)	71 (4·7%)
SAPS II†	60 (48–74)	61 (48–74)
SOFA score‡	10 (8–13)	10 (8–13)
Medical diagnosis at admission	1253 (82·8%)	1258 (83·1%)
Acute illness at ICU admission		
Cardiac arrest	185 (12·2%)	209 (13·8%)
Acute heart failure	232 (15·3%)	253 (16·7%)
Acute central nervous system failure	109 (7·2%)	112 (7·4%)
Acute respiratory failure	686 (45·3%)	654 (43·2%)
Trauma	25 (1·7%)	28 (1·8%)
Miscellaneous	278 (18·3%)	258 (17·7%)
Cause of shock		
Cardiac	254 (16·8%)	283 (18·7%)
Sepsis	889 (58·7%)	874 (57·7%)
Other	372 (24·5%)	357 (23·6%)

(Table 1 continues on next page)

	Low group (n=1521)	Standard group (n=1515)
(Continued from previous page)		
Ongoing treatments§		
Prone position	90 (6·0%)	93 (6·1%)
Sedative agents	1368 (90·5%)	1351 (89·3%)
NMBA	483 (32·0%)	497 (32·8%)
Insulin	593 (39·2%)	664 (43·9%)
Antiulcer medication	656 (43·4%)	686 (45·3%)
Prokinetic agents	39 (2·6%)	52 (3·4%)
Antimicrobial treatment	1298 (85·8%)	1290 (85·1%)
Dialysis	161 (10·6%)	183 (12·1%)
Other parameters		
FIO_2	50·0 (40·0–80·0)	60·0 (40·0–90·0)
PEEP, cmH_2O	7·0 (5·0–10·0)	7·0 (5·0–10·0)
Glucose, mmol/L¶	8·8 (6·7–12·0)	9·5 (7·1–12·8)
Serum creatinine, µmol/L‖	128·5 (84·0–215·0)	130·0 (85·0–211·0)
Lactate, mEq/L	2·4 (1·5–4·6)	2·7 (1·6–4·9)
Bilirubin, µmol/L	13·0 (8·0–25·0)	13·0 (8·0–26·0)
C-reactive protein, mg/L	137·0 (42·0–266·0)	144·0 (51·0–273·8)
Pre-albumin, g/L	0·10 (0·06–0·15)	0·11 (0·06–0·17)
Albumin, g/L	25·0 (20·0–29·6)	25·0 (20·0–29·9)
Time from intubation to randomisation, h	14·8 (8·7–20·0)	15·1 (8·8–19·8)

Data are mean (SD), n (%), or median (IQR). Denominators might vary slightly according to missing data. ICU=intensive care unit. SAPS II=Simplified Acute Physiology Score version II. SOFA=Sequential Organ Failure Assessment. NMBA=neuromuscular blocking agent. FIO_2=fractional concentration of oxygen in inspired air. PEEP=positive end-expiratory pressure. *Severe pre-existing malnutrition was defined as BMI <18·5 kg/m^2 or weight loss >10% within the past 6 months and moderate pre-existing malnutrition as BMI 18·5–19·9 kg/m^2 or weight loss >5% within the past 6 months; patients who did not meet these criteria were classified in the none category. †SAPS II values can range from 0 (lowest level of critical illness) to 163 (most severe level of critical illness with 100% predicted mortality); a score of 50 predicts a 46·1% risk of death; the SAPS II was determined 24 h after ICU admission. ‡SOFA scores can range from 0 (no organ failure) to 24 (most severe level of multi-organ failure); the SOFA sub-score values at ICU admission are reported in the appendix (p 18). §Antimicrobial treatments included antibiotics, antiviral drugs, and antifungal drugs; antiulcer treatments included proton-pump inhibitors and histamine-2 receptor antagonists; prokinetic agents were metoclopramide and erythromycin. ¶To convert glucose values to mg/dL, multiply by 18·02. ‖To convert creatinine values to mg/dL, multiply by 0·113.

Table 1: Baseline characteristics of the participants

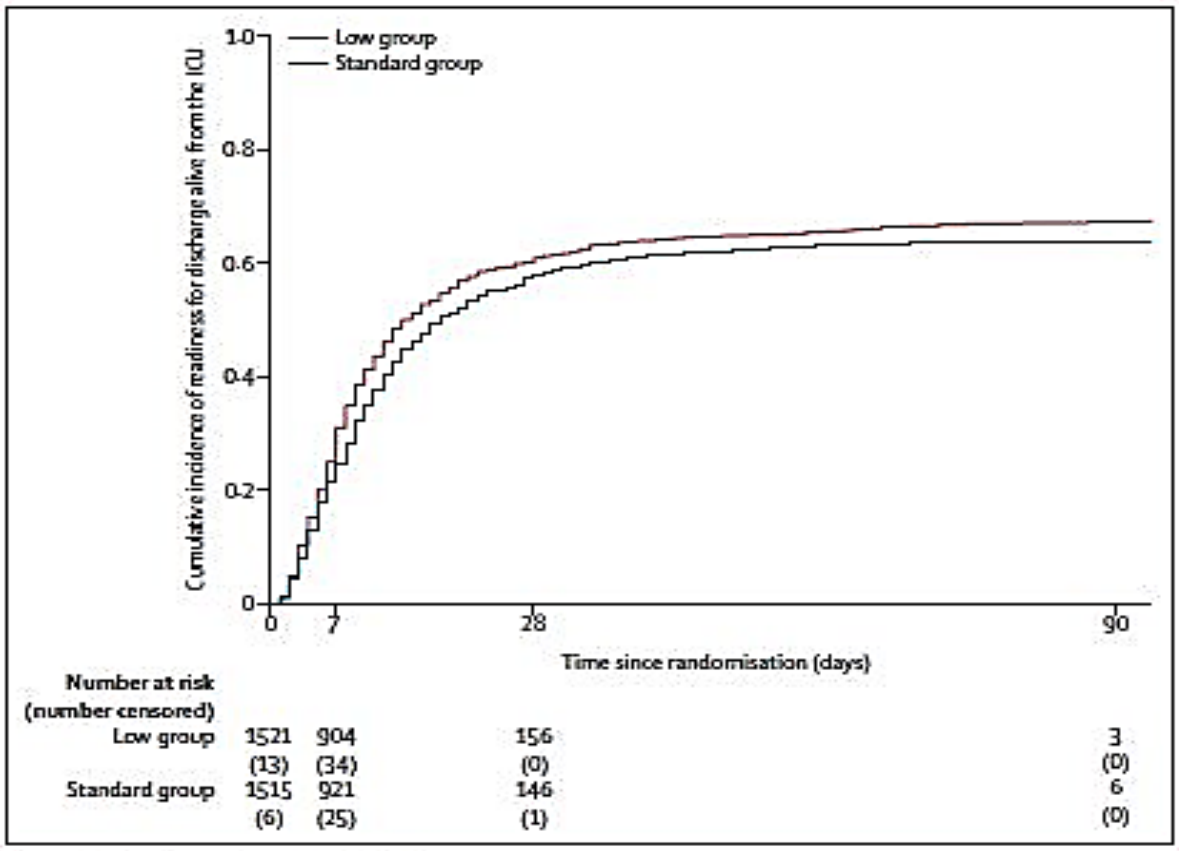


Figure 2: Time to readiness for ICU discharge
Cumulative incidence curves for patients who achieved readiness for ICU discharge. ICU=intensive care unit.

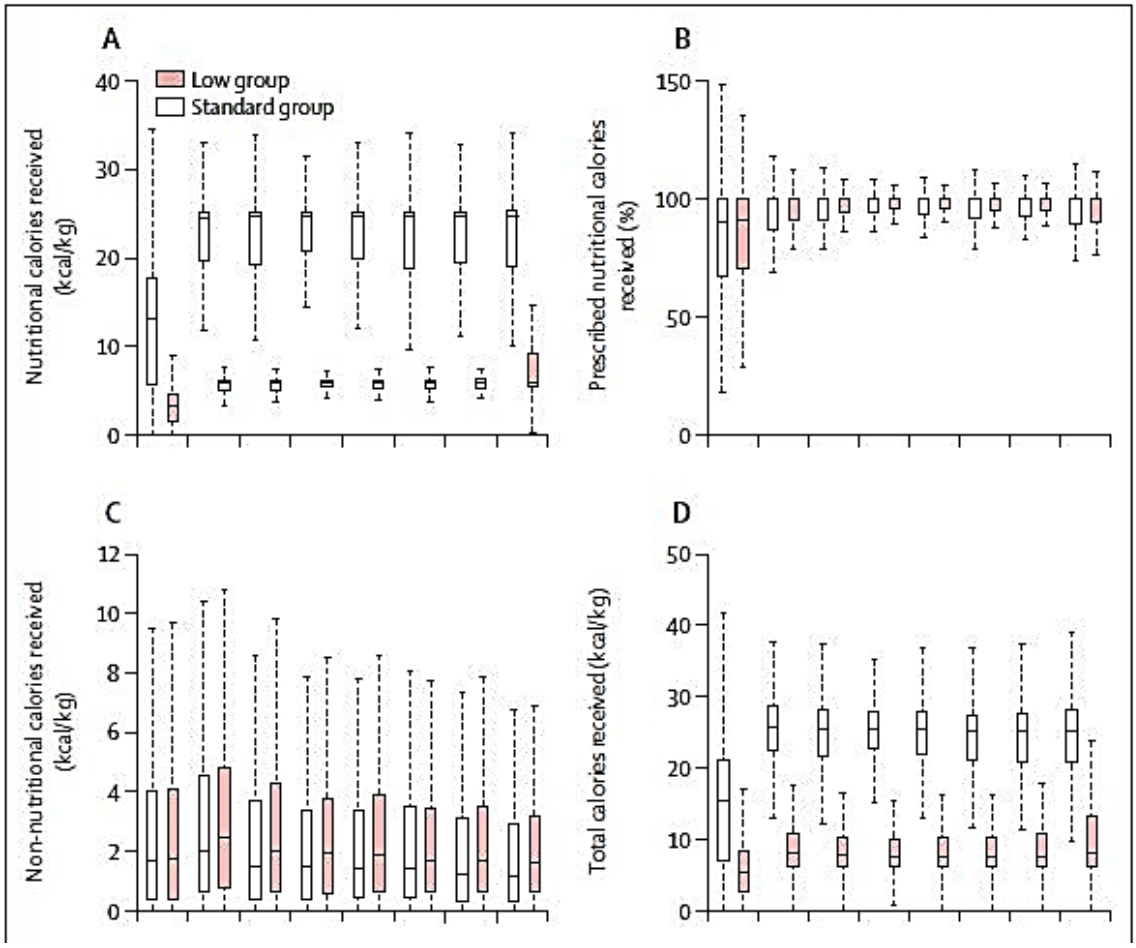
Statistical analysis

Two interim analyses to be performed using the Haybittle-Peto approach were scheduled, after enrolment of 1000 and 2000 patients, respectively. The significance level associated with both interim analyses was 0·001 and the significance level associated with the final analysis was 0·049. With this method, the overall risk of type 1 error was 5%. As shown in the appendix (pp 8), the independent data safety monitoring board was composed of a methodologist and two intensivists not otherwise involved in the trial. For both interim analyses, the board had access to unmasked results on day 90 mortality, time to ICU discharge alive, SOFA score variations from day 0 to day 7, amount of calories and protein received daily from day 0 to day 7, and nosocomial infections. The results of the interim analyses were not disclosed to the investigators.

To estimate the required sample size, we used the mortality rates and mean ICU length of stay recorded in survivors in the NUTRIREA-2 trial, which used similar selection criteria.21 Assuming a 43% day 90 mortality rate in the standard group and a 5% absolute decrease to 38% in the low group, with the α risk set at 4·9% (as two interim analyses were planned) and the β risk at 20%, 1522 patients were needed in each group—ie, 3044 patients in total. This sample size provided 94% power for detecting a 1·5-day difference in readiness to ICU discharge between the two groups (mean 14·5 days in the standard group *vs* 13·0 days in the low group). No corrections were planned for multiple comparisons.
All statistical analyses followed a prespecified statistical analysis plan. Values of p no greater than 0·049 were taken to indicate significance. Categorical variables were described as frequencies and percentages (n[%]) and continuous variables as medians (IQR) or means (SD). No statistical tests were performed to compare baseline characteristics between groups. Patients with missing data on day 90 mortality were assumed to have died.

Day 90 mortality was reported as the point estimate with the 95% CIs in each group. The difference in proportions, with 95% CIs, was also estimated. Day 90 mortality was compared between the two groups using

the χ^2 test. Time to readiness for ICU discharge was evaluated using a Fine-and-Gray model with death in the ICU as a competing risk. Secondary outcomes expressed as proportions were compared between the two groups by applying the χ^2 test. Outcomes reported as cumulative incidences were analysed using the competing-risk approach, with death, ICU discharge, or hospital discharge as the competing event. Changes over time were compared between the two groups by building mixed linear models, after data transformation if necessary. Statistical analyses for secondary endpoints were not adjusted for multiplicity. The findings should therefore be interpreted as exploratory. Continuous data were analysed by applying Wilcoxon's nonparametric test. SAS (version 9.4) and R (version 3.3.1) were used for the statistical analyses. The trial is registered with ClinicalTrials.gov (NCT03573739) under the name NUTRIREA-3.



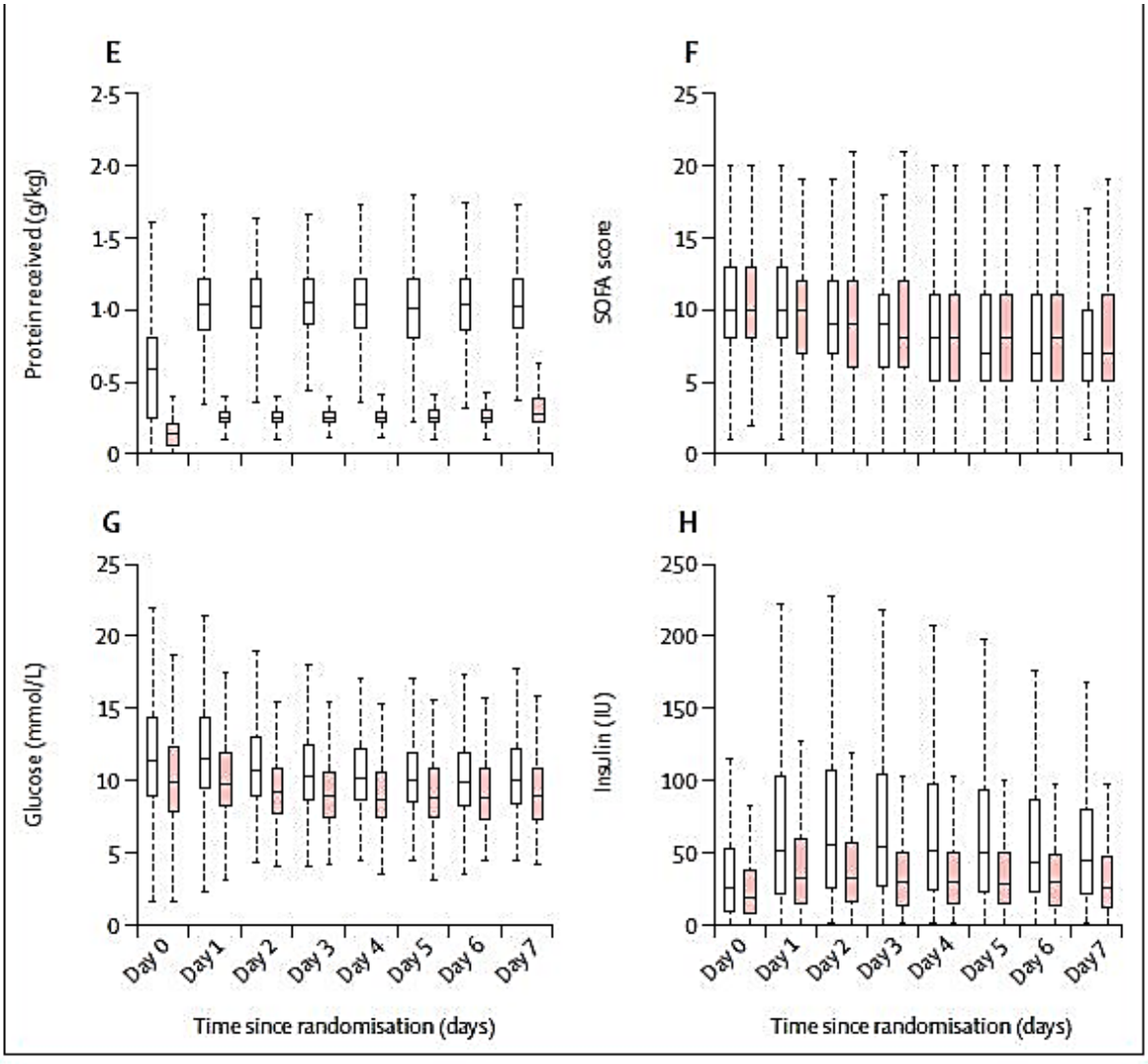


Figure 3: **Daily calorie intake, protein intake, SOFA score, and glucose control during the intervention period (days 0–7)**

Nutritional calories received daily (A), percentages of the calorie targets supplied (B), non-nutritional calories received daily (C), and total calories received daily (D), during the intervention period (from day 0 to day 7), in both groups. (E) Protein amounts administered daily during the intervention period in both groups. Bodyweight measured on admission was used throughout the ICU stay to calculate calorie and protein targets. (F) Differences between the low and standard groups for the SOFA score during the intervention period ; SOFA scores can range from 0 (no organ failure) to 24 (most severe level of multiorgan failure). Differences between the low and standard groups for daily blood glucose concentrations (G) and daily insulin intake (H); box plot represents median (IQR), and the lower whisker represents the 25th percentile minus 1·5 times the IQR and the upper whisker the 75th percentile plus 1·5 times the IQR; if the box plot contains no horizontal line, the median value is the same as the 75th percentile. ICU=intensive care unit. SOFA=Sequential Organ Failure Assessment.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, or data interpretation; writing of the report; or decision to submit for publication.

Results

From July 5, 2018, to Dec 8, 2020, 3044 patients in 61 French ICUs, including 34 (55·7%) in university hospitals (appendix p 18), were randomly assigned to one of the study groups. Four patients were withdrawn in each group, leaving 3036 patients for the analysis: 1521 in the low group and 1515 in the standard group (figure 1). Baseline characteristics were similar between groups (table 1).

By day 90, 628 (41·3%) of 1521 patients in the low group and 648 (42·8%) of 1515 patients in the standard group had died (absolute difference –1·5%, 95% CI –5·0 to 2·0; p=0·41). The results were similar after exclusion of three patients with missing data on day 90 mortality (estimated difference –1·6%; –5·1 to 1·9; p=0·37). Time to readiness for ICU discharge was 8·0 days (IQR 5·0–14·0) in the low group and 9·0 days (5·0–17·0) in the standard group (hazard ratio [HR] 1·12, 95% CI 1·02 to 1·22; p=0·015; figure 2).

Adherence to the protocol was high, with daily calorie and protein intakes close to targets in both groups (figure 3, appendix p 9). Feeding routes were similar between groups, and nearly 60% of patients in both groups received only enteral feeding (table 2, appendix p 20). Median blood glucose concentrations and cumulative incidence of patients receiving insulin were lower in the low group than in the standard group, but there was no difference in the cumulative incidence of patients with hypoglycaemia (table 2; figure 3G, daily blood glucose concentrations 0·01 mmol/L, 95% CI 0·001 to 0·01; p=0·016; figure 3H, daily insulin intake –0·2 IU per day, 95% CI –0·05 to 0·001; p=0·065). Median phosphataemia was lower in the standard group compared with the low group (appendix p 10). There was no between-group difference in blood concentrations of potassium and magnesium or in serum C-reactive protein (appendix p 11, 20). During the intervention period, patients in the low group had lower bodyweight and lower pre-albuminaemia compared with patients in the standard group (appendix p 12, 14). The cumulative incidence of patients treated with prone positioning was lower in the low group than in the standard group (table 2). The low group had a higher cumulative incidence of patients whose blood lactate returned to normal and a faster SOFA score decrease, compared with the standard group (table 2, figure 3F, SOFA mean difference –0·08; 95% CI –0·13 to –0·02; p=0·008).

	Low group (n=1521)	Standard group (n=1515)	Hazard ratio (95% CI)	p value
Clinical management				
Intubation to feeding, h	16·7 (10·6–21·6)	17·0 (10·8–21·8)	–	–
Feeding route				
Patients receiving enteral nutrition only	932 (61·6%)	846 (56·0%)	–	–
Patients receiving parenteral nutrition only	358 (23·7%)	349 (23·1%)	–	–
Patients receiving parenteral nutrition then enteral nutrition	208 (13·8%)	296 (19·6%)	–	–
Neither enteral nutrition nor parenteral nutrition	14 (0·9%)	21 (1·4%)	–	–
Daily intakes				
Calories, kcal/kg per 24 h*	7·4 (5·8–9·5)	22·0 (17·5–24·9)	–	–
Protein, g/kg per day	0·2 (0·2–0·3)	0·9 (0·7–1·0)	–	–
Fluids, L	11·1 (6·1–16·4)	17·2 (9·7–23·4)	–	–
Gastrointestinal events, cumulative incidence				
Vomiting	14·2%	21·3%	0·64 (0·54–0·76)	<0·001
Prokinetic drug therapy	13·1%	20·9%	0·60 (0·51–0·72)	<0·001
Constipation†	23·8%	23·9%	0·99 (0·87–1·13)	0·92
Diarrhoea	19·1%	22·9%	0·81 (0·69–0·95)	0·008
Blood parameters				
Glucose, mmol/L				
Daily highest	11·6 (9·6–14·5)	13·7 (11·2–17·1)	–	<0·001
Daily lowest	4·8 (3·9–5·7)	5·0 (4·1–5·8)	–	0·002
Insulin, cumulative incidence	63·1%	77·7%	0·74 (0·70–0·80)	<0·001
Hypoglycaemia, cumulative incidence‡	6·0%	4·9%	1·24 (0·91–1·69)	0·17
Lactate, daily highest, g/L	2·8 (1·8–5·2)	3·0 (2·0–5·6)	–	0·003
Lactate normalisation, cumulative incidence§	86·5%	84·1%	1·09 (1·02–1·16)	0·01
Bilirubin, daily highest, µmol/L	16·0 (10·0–33·0)	15·0 (10·0–32·0)	–	0·22
ALAT, daily highest, IU/L	65 (33–174)	77 (36–218)	–	0·008
ASAT, daily highest, IU/L	98 (46–288)	110 (50–345)	–	0·016
Hypokalaemia, cumulative incidence¶	58·6%	58·9%	0·97 (0·89–1·06)	0·48
Hypophosphataemia, cumulative incidence‖	53·6%	61·3%	0·83 (0·76–0·91)	<0·001
Other treatments, cumulative incidence				
Prone position	13·4%	17·2%	0·77 (0·64–0·92)	0·005
Dialysis	26·9%	27·2%	0·99 (0·86–1·12)	0·82

Data are median (IQR) or n (%), unless otherwise specified. Denominators might vary slightly according to missing data. SI conversion factors: to convert glucose values to mg/dL, multiply by 18·02; to convert bilirubin values to mg/L, multiply by 0·58. Volume of fluids was the total amount of fluids received from day 0 to day 7 and included in enteral preparations, parenteral preparations, and non-nutritional fluids. The intervention period started with the initiation of nutritional support and ended after day 7 or ICU discharge or death, whichever occurred first. Percentages of patients with each outcome were compared between groups using the χ^2 test and categorical data reported as median (IQR) using Wilcoxon's non-parametric test. Outcomes reported as cumulative incidences were analysed using a competing risk approach, with death and ICU discharge as competing risks. ALAT=alanine aminotransferase. ASAT=aspartate aminotransferase. *Calories in propofol and dextrose solutions were included in the total calorie count. †Defined as no passage of stools from randomisation to day 6 inclusive. ‡Defined as blood glucose concentration lower than 2·3 mmol/L. §Defined as blood lactate lower than 2 mmol/L. ¶Defined as blood potassium concentration lower than 3·5 mmol/L. ‖Defined as blood phosphate concentration lower than 0·81 mmol/L.

Table 2: Clinical management and outcomes during the intervention period (days 0–7)

	Low group (n=1521)	Standard group (n=1515)	Absolute difference (95% CI)	Hazard ratio (95% CI)	p value
Primary outcomes					
Day 90 mortality	628 (41·3%)	648 (42·8%)	−1·5 (−5·0 to 2·0)	..	0·41
Time to readiness for ICU discharge*	8·0 (5·0 to 14·0)	9·0 (5·0 to 17·0)	..	1·12 (1·02 to 1·22)	0·015
Secondary outcomes					
Day 28 mortality	504 (33·2%; n=1519)	533 (35·2%)	−2·0 (−5·4 to 1·4)	..	0·24
ICU mortality, cumulative incidence	29·6%	32·7%	..	0·89 (0·78 to 1·00)	0·051
Hospital mortality, cumulative incidence	32·2%	34·5%	..	0·93 (0·83 to 1·05)	0·24
ICU length of stay, days†	9·0 (5·0 to 15·0)	10·0 (6·0 to 17·0)	..	..	..
Acute-care hospital length of stay, days†	21·0 (12·0 to 38·0)	22·0 (14·0 to 39·0)	..	..	..
Time to weaning from vasopressor support, days	3·0 (2·0 to 4·0)	3·0 (2·0 to 4·0)	..	1·07 (0·99 to 1·15)	0·054
Time to invasive mechanical ventilation weaning, days	5·0 (2·0 to 11·0)	6·0 (3·0 to 12·5)	..	1·12 (1·03 to 1·22)	0·007
Received dialysis, cumulative incidence	30·1%	31·9%	..	0·93 (0·82 to 1·05)	0·25
Infections, cumulative incidence					
ICU infection‡	15·3%	17·5%	..	0·85 (0·71 to 1·01)	0·06
Ventilator-associated pneumonia	11·2%	10·9%	..	0·98 (0·79 to 1·21)	0·82
Bacteraemia	4·0%	5·5%	..	0·73 (0·53 to 1·01)	0·06
Central venous catheter infection	1·5%	1·9%	..	0·81 (0·48 to 1·37)	0·44
Urinary tract infection	0·7%	0·8%	..	1·20 (0·54 to 2·67)	0·66
Soft-tissue infection	7 patients	5 patients	..	..	..
Other infection	1·7%	2·4%	..	0·78 (0·48 to 1·28)	0·33
Gastrointestinal events, cumulative incidence					
Vomiting	20·2%	25·5%	..	0·77 (0·67 to 0·89)	<0·001
Diarrhoea	28·9%	33·3%	..	0·83 (0·73 to 0·94)	0·004
Constipation	27·8%	28·7%	..	0·97 (0·86 to 1·10)	0·64
Bowel ischaemia	0·9%	1·8%	..	0·50 (0·26 to 0·95)	0·030
Acute colonic pseudo-obstruction	8 patients	2 patients	..	..	..
Liver dysfunction, cumulative incidence§	61·7%	65·8%	..	0·92 (0·86 to 0·99)	0·032

Data are %, n (%), or median (IQR), unless otherwise specified. Percentages of patients with each outcome were compared between groups using the χ^2 test and categorical data reported as median (IQR) using Wilcoxon's non-parametric test. Outcomes reported as cumulative incidences were analysed using a competing risk approach, with death and ICU discharge as competing risks; the only exceptions were ICU mortality and hospital mortality, for which competing risks were only ICU discharge and hospital discharge, respectively. ICU=intensive care unit. *Analysed using a competing risks model with death as a competing risk; hazard ratio >1 means that more patients were ready for ICU discharge during follow-up—ie, that time to ICU-discharge readiness was shorter in the low group than in the standard group. †For patients discharged alive. ‡Ventilator-associated pneumonia, bacteraemia, urinary tract infections, catheter-related infections, and other infections acquired in the ICU. §Defined as serum bilirubin >50 μmol/L or elevation to more than three times the upper limit of normal, or both parameters, in one or more liver enzymes (γ-glutamyl transferase, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase).

Table 3: Outcomes

Time to weaning off invasive mechanical ventilation was significantly shorter in the low group than in the standard group (table 3). Adverse gastrointestinal events (including vomiting, diarrhoea, and bowel ischaemia) were significantly less common in the low than in the standard group (table 3). The cumulative incidence of patients with liver dysfunction was lower in the low group compared with the standard group (table 3). The groups were not different for 28 day, ICU, or hospital mortality; vasoactive drug or renal replacement therapy use; frequency of ICU-acquired infections; out-of-bed mobilisation; or Medical Research Council (MRC) score at ICU discharge (table 3; appendix pp 15–17, 22).

Discussion

In this multicentre randomised trial, day 90 all-cause mortality did not differ between low versus standard calorie and protein intakes during the acute phase of critical illness requiring invasive mechanical ventilation and vasoactive support. However, compared with patients receiving standard calorie and protein intakes, those receiving low intakes had a shorter time to readiness for ICU discharge analysed with death as a competing event. The low feeding strategy was associated with a shorter duration of invasive mechanical ventilation and fewer gastrointestinal and hepatic complications.

Compared with standard intakes, low intakes were not associated with adverse outcomes. All-cause mortality was non-significantly lower in the low versus the standard group, in keeping with previous studies.10,16–18 All-cause mortality should be viewed as a marker of the safety of interventions in patients with severe critical illness, and there is no evidence from our trial that low calorie and protein intakes were associated with increased risks. More specifically, infections were not more common. Observational ICU studies suggested an association between calorie deficiency and infections,4 but this finding was not replicated in randomised trials of permissive or trophic underfeeding.16,17 The TARGET trial found no benefits from increasing the enteral calorie supply.10 In the EpaNIC randomised trial of early versus late parenteral nutrition to supplement insufficient enteral intakes, mortality was similar in the two groups, but benefits in the late group included fewer ICU-acquired infections and shorter durations of mechanical ventilation, renal replacement therapy, and ICU stay.13 In our trial, ICU-acquired infections were less common than in EpaNIC despite greater critical illness severity and higher mortality of patients, perhaps because all infections were adjudicated by an independent committee. Despite the lower values for glycaemia and proportion of insulin-treated patients in the low group, the frequency of hypoglycaemia was not different between the two groups. The association of the low strategy with important benefits, without adverse outcomes, supports targets as low as 6 kcal/kg per day for calories and 0·2–0·4 g/kg per day for protein during the acute phase of critical illness.

The mechanisms involved in clinical benefits from calorie and protein restriction are unclear. Anorexia during the acute phase of critical illness is considered an adaptive process with benefits including a heightened immune response and decreases in metabolic disturbances.23 Macronutrient restriction might contribute to preserve the neuroendocrine response in acute critical illness.24 Evidence exists identifying autophagy as a key mechanism for safeguarding cellular integrity, notably in the muscle, and therefore making a major contribution to recovery after severe critical illness.25 Increased macronutrient intakes could suppress autophagy, thereby decreasing the clearance of damaged cell components.25,26 The higher frequencies of gastrointestinal and hepatic complications in our standard group compared with the low group can be ascribable to a greater mismatch between oxygen needs and supply.27 Another possibly relevant finding is the higher blood glucose concentration in the standard group, although the effects of blood glucose control remain controversial.28 Although refeeding syndrome might be considered given the higher proportion of patients with hypophosphataemia in the standard group, any effect would be limited given the absence of between-group differences in blood potassium and magnesium concentrations and in mortality. Finally, the larger fluid intake in the standard group could have contributed to the higher frequency of prone positioning and longer duration of invasive mechanical ventilation. However, two trials investigating intravenous fluid restriction in patients with acute lung injury or septic shock produced conflicting results.29,30 Moreover, two-thirds of our patients received enteral feeding only, and the effect of the enteral fluid intake is unknown.

One limitation of our trial is that neither the patients nor the health-care staff could be masked to the intervention. However, the nutritional protocols were standardised. Moreover, regarding the primary outcomes, day 90 mortality was objective and time to readiness for ICU discharge was determined according to predefined criteria and checked daily by bedside physicians. A similar strategy regarding this endpoint has been used previously in studies on nutrition in the ICU.13,14 We also used pre-established definitions or adjudication for the secondary outcomes. These methodological features reduce any potential biases related to the absence of blinding, bed availability, and variations across ICU physicians in assessing readiness for ICU discharge.

Duration of the intervention was from day 1 to day 7 in all patients except those weaned off invasive mechanical ventilation and vasopressor support before day 7. Duration of the acute phase of critical illness can vary across patients. No clinical or laboratory criteria are available to determine the end of the acute phase, and the first 7 days after ICU admission is a well accepted range used in guidelines.5 Finally, we adjusted for multiplicity in the interim analyses but not for multiple outcomes in the final analysis. Both decreasing mortality and expediting recovery are central goals of critical care medicine. In previous randomised trials, nutritional interventions affected time to readiness for ICU discharge but not mortality.13,14 In the current trial, time to readiness for ICU discharge should be viewed as an efficacy outcome and mortality as a safety outcome. Adjusting for multiple outcomes would have required an even greater number of patients than the large sample included, thus strongly limiting trial feasibility. It is worth noting that the best methods for taking multiple outcomes into account are debated.31

Our trial also has important strengths. The design was pragmatic. More specifically, the feeding route during the acute phase was at the discretion of the bedside physicians, based on previous trials showing no outcome differences between the enteral and parenteral routes.21,22 Standard enteral and parenteral preparations routinely used in ICUs were administered. These preparations ensure that both calorie and protein targets are easily met, as shown by our data. Complements were not given, except for electrolytes and micronutrients when required. These conditions, combined with the large number of participating centres, support the external validity of our findings. NUTRIREA-3 shows the benefits of limiting both calorie and protein intakes versus standard calorie and protein targets during acute critical illness. Previous studies assessed restriction of either only calories or only protein. Of note, the calorie and protein targets differed markedly between our two trial groups. The standard group complied with guidelines and the restricted group with the hypothesis that intakes seen in individuals with anorexia might provide benefits. The trial procedures were rigorously followed and, in both groups, the calorie and protein intakes were near the targets. From day 8 onwards, the observed total calorie intakes were below 30 kcal/kg per day, indicating that overfeeding did not occur. Last, we included a well defined and representative population of critically ill patients who required at least invasive mechanical ventilation and vasoactive drugs and who were at high risk for death or protracted recovery and, therefore, likely to benefit from improved early nutritional support.

In conclusion, for the nutritional support of patients at the acute phase of severe critical illness, calorie and protein restriction was superior to standard calorie and protein intake, with fewer complications and a faster recovery.

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Contributors

JR, GPl, J-BL, and ALG designed the study. JR, GPl, J-PM, LA, PA, NA, JB, N-VB, LB, H-NB, DC, LC, AC, CC, MDa, VD, MDe, AD, JD, L-MD, OG, SG, LG, BG, YH, SJ, FL, CL, PL, BM, JM, OM, FM, VM, EM, M-AN, SN, JO, WP, GPi, J-PQ, FR, AR, JR, J-PR, FS, DS, MS, BS, FTa, NT, DT, GT, NT-R, J-FT, FTi, PT, TV, IV, CV, SV, and J-BL approved the design of the study, coordinated individual sites, participated in the inclusion of study participants and collected the data. JR and ALG directly accessed and verified all the data reported in the manuscript. ALG did the statistical analysis. JR wrote the first draft of the manuscript with input from J-BL and ALG. All authors had full access to the study data, revised the manuscript, and read and approved the final version before submission. All authors accept responsibility for submitting the final manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The datasets generated for this study will not be publicly available owing to the limitations of participant consent and approvals in place regarding data sharing between organisations involved in the study. The data will be held in the Nantes University Hospital, Nantes, France, and will be used internally for secondary purposes. Any applications for potential data sharing or collaboration should be made to the corresponding author and will be considered. Study tools, including the protocol, consent forms, statistical analysis plan, definition of outcomes, training materials, and regulatory documents are available upon request.

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