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Prescribed hypocaloric nutrition support for critically-ill adults (Review)

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TABLE OF CONTENTS

[Intervention Review]

Prescribed hypocaloric nutrition support for critically-ill adults

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ABSTRACT

Background

There are controversies about the amount of calories and the type of nutritional support that should be given to critically-ill people. Several authors advocate the potential benefits of hypocaloric nutrition support, but the evidence is inconclusive.

Objectives

To assess the effects of prescribed hypocaloric nutrition support in comparison with standard nutrition support for critically-ill adults

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library), MEDLINE, Embase and LILACS (from inception to 20 June 2017) with a specific strategy for each database. We also assessed three websites, conference proceedings and reference lists, and contacted leaders in the field and the pharmaceutical industry for undetected/unpublished studies. There was no restriction by date, language or publication status.

Selection criteria

We included randomized and quasi-randomized controlled trials comparing hypocaloric nutrition support to normo- or hypercaloric nutrition support or no nutrition support (e.g. fasting) in adults hospitalized in intensive care units (ICUs).

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We meta-analysed data for comparisons in which clinical heterogeneity was low. We conducted prespecified subgroup and sensitivity analyses, and post hoc analyses, including meta-regression. Our primary outcomes were: mortality (death occurred during the ICU and hospital stay, or 28- to 30-day all-cause mortality); length of stay (days stayed in the ICU and in the hospital); and Infectious complications. Secondary outcomes included: length of mechanical ventilation. We assessed the quality of evidence with GRADE.

Main results

We identified 15 trials, with a total of 3129 ICU participants from university-associated hospitals in the USA, Colombia, Saudi Arabia, Canada, Greece, Germany and Iran. There are two ongoing studies. Participants suffered from medical and surgical conditions, with a

variety of inclusion criteria. Four studies used parenteral nutrition and nine studies used only enteral nutrition; it was unclear whether the remaining two used parenteral nutrition. Most of them could not achieve the proposed caloric targets, resulting in small differences in the administered calories between intervention and control groups. Most studies were funded by the US government or non-governmental associations, but three studies received funding from industry. Five studies did not specify their funding sources.

The included studies suffered from important clinical and statistical heterogeneity. This heterogeneity did not allow us to report pooled estimates of the primary and secondary outcomes, so we have described them narratively.

When comparing hypocaloric nutrition support with a control nutrition support, for hospital mortality (9 studies, 1775 participants), the risk ratios ranged from 0.23 to 5.54; for ICU mortality (4 studies, 1291 participants) the risk ratios ranged from 0.81 to 5.54, and for mortality at 30 days (7 studies, 2611 participants) the risk ratios ranged from 0.79 to 3.00. Most of these estimates included the null value. The quality of the evidence was very low due to unclear or high risk of bias, inconsistency and imprecision.

Participants who received hypocaloric nutrition support compared to control nutrition support had a range of mean hospital lengths of stay of 15.70 days lower to 10.70 days higher (10 studies, 1677 participants), a range of mean ICU lengths of stay 11.00 days lower to 5.40 days higher (11 studies, 2942 participants) and a range of mean lengths of mechanical ventilation of 13.20 days lower to 8.36 days higher (12 studies, 3000 participants). The quality of the evidence for this outcome was very low due to unclear or high risk of bias in most studies, inconsistency and imprecision.

The risk ratios for infectious complications (10 studies, 2804 participants) of each individual study ranged from 0.54 to 2.54. The quality of the evidence for this outcome was very low due to unclear or high risk of bias, inconsistency and imprecision

We were not able to explain the causes of the observed heterogeneity using subgroup and sensitivity analyses or meta-regression.

Authors' conclusions

The included studies had substantial clinical heterogeneity. We found very low-quality evidence about the effects of prescribed hypocaloric nutrition support on mortality in hospital, in the ICU and at 30 days, as well as in length of hospital and ICU stay, infectious complications and the length of mechanical ventilation. For these outcomes there is uncertainty about the effects of prescribed hypocaloric nutrition, since the range of estimates includes both appreciable benefits and harms.

Given these limitations, results must be interpreted with caution in the clinical field, considering the unclear balance of the risks and harms of this intervention. Future research addressing the clinical heterogeneity of participants and interventions, study limitations and sample size could clarify the effects of this intervention.

PLAIN LANGUAGE SUMMARY

Does the prescription of low-calorie (hypocaloric) nutrition support improve the recovery of critically-ill adult patients?

Review question

Does low-calorie nutrition delivered into the stomach or small intestine (enteral), or into a vein (parenteral) improve clinical outcomes in critically-ill adults admitted to an intensive care unit (ICU), when compared with standard calorie nutrition support?

The main outcomes were death (in the hospital, in the ICU and at 30 days); length of ICU and hospital stay; infectious complications and length of time the person was mechanically ventilated (a machine used in ICU to help a person breath) .

Background

Critically-ill people experience major metabolic changes (one chemical is transformed through a series of steps into another chemical) during injury or sepsis (a life-threatening condition in which the body's response to infection causes injury to its own organs). They receive nutritional support to prevent or minimize some adverse effects. Nevertheless, both overfeeding and starvation can be harmful.

There is currently no agreement about the amount of calories we should give to these critically-ill people. Normal caloric feeding provides the estimated caloric needs. Hypocaloric feeding provides an intentionally lower amount of calories.

Study characteristics

We included 15 trials with 3129 ICU surgical or medical participants from academic hospitals. Four studies used parenteral nutrition and nine studies used only enteral nutrition. The route was unclear in the remaining two studies. While the studies planned to give different amounts of calories in the experimental and control groups, the actual difference in calories was small. Most studies were funded by the US government or non-governmental associations, but three studies received funding from the industry. Five studies did not state how they were funded.

Key results

The differences in the type of nutrition and type of participants across studies did not allow us to combine study results, so we describe the range of results across the individual studies.

The number of deaths at the hospital, in the ICU and at 30 days in those who received low-calorie nutrition was similar to those in the control group. The length of hospital and ICU stay and the length of mechanical ventilation varied across studies, sometimes shorter and sometimes longer when compared to the control group. The number of infections also varied across studies. We tried to analyse subgroups of participants in order to clarify this variation, but the results were not consistent.

Quality of evidence

The overall quality of evidence for each outcome according to GRADE classification varied from very low to low. This was due to problems in the design and conduct of the studies, the variation in the study results (inconsistency between studies) and the wide range of possible results (imprecision).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Hypocaloric nutrition compared to control for critically-ill adults

Hypocaloric nutrition compared to control for critically-ill adults

Patient or population: critically-ill adults
Settings: Hospitals (intensive care units), eight in USA, two in Colombia, one in Saudi Arabia and Canada, and one each in Saudi Arabia, Germany, Greece and Iran
Intervention: hypocaloric nutrition

Comparison: control nutritional support with a higher caloric intake than the 'intervention' group

Outcomes	Effect estimate (range of results of individual studies)	N of Participants (studies)	Quality of the evidence (GRADE)
Mortality in hospital: death occurring during the hospital stay	Range of risk ratios from 0.23 to 5.54[a]	1775 (9 studies)	⊕⊕⊖⊖ **very low**[b,c,d]
Mortality in ICU: death occurred during the ICU stay	Range of risk ratios from 0.81 to 5.54[a]	1291 (4 studies)	⊕⊕⊖⊖ **very low**[b,c,d]
Mortality at 30 days: 28 to 30 days all-cause mortality	Range of risk ratios from 0.79 to 3.00[a]	2611 (7 studies)	⊕⊕⊖⊖ **very low**[b,c,d]
Length of hospital stay: days stayed in the hospital	Range of length of hospital stay from 15.70 days lower to 10.70 days higher[a]	1677 (10 studies)	⊕⊖⊖⊖ **very low**[b,c,e]
Length of ICU stay: days stayed in the ICU	Range of length of ICU stay from 11.00 days lower to 5.40 days higher[a]	2942 (11 studies)	⊕⊖⊖⊖ **very low**[b,c,e]
Infectious complications: events of any type of infectious complications occurred during the hospital stay, registered by the study authors according to their diagnostic criteria of infections.	Range of risk ratios from 0.54 to 2.54[a]	2804 (10 studies)	⊕⊖⊖⊖ **very low**[b,c,e]
Length of mechanical ventilation: days on mechanical ventilation during ICU stay	Range of mean differences: 13.20 days lower to 8.36 days higher[a]	3000 (12 studies)	⊕⊖⊖⊖ **very low**[b,c,e]

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Results were not combined due to clinical heterogeneity.
[b]Downgraded one level due to risk of bias: most studies had unclear or high risk of bias.
[c]Downgraded one level due to imprecision issues: very wide confidence intervals.
[d]Downgraded one level due to inconsistency: wide variance of point estimates across studies.
[e]Downgraded one level due to inconsistency: high statistical heterogeneity $I^2 > 50\%$.

BACKGROUND

Description of the condition

Most critically-ill people treated for injury or sepsis have some degree of hypermetabolism and hypercatabolism and are also unable to feed themselves. For these reasons, it was recommended to provide them with nutrition support by enteral or parenteral routes, in order to prevent or minimize depletion of protein and caloric stores; to enhance protein synthesis; and to avoid deficiencies in essential and semi-essential nutrients (Cerra 1997). However, there are several aspects of nutrition support for the critically-ill that are still under debate, such as: the time at which to initiate nutrition support; the route (enteral, parenteral or combined); the caloric and protein requirements; the amount and type of protein to give; the composition of lipids; the supplementation of some amino acids and micronutrients; and the occurrence and type of some complications. Several of these topics were recently discussed (Berger 2012; Biolo 2002; Bost 2014; Heyland 2003; Kreymann 2006;Preiser 2015; Wischmeyer 2012; Wischmeyer 2013), and some of these aspects are included in Cochrane Reviews on adults (Alkhawaja 2015; Allingstrup 2015; Fuentes Padilla 2016; Lewis 2016; Tao 2014), and children (Joffe 2016), as well as in a Cochrane protocol (Dushianthan 2016). This current review focuses on the prescription of hypocaloric versus normocaloric feeding debate in nutrition support for critically-ill adults.

During the 1970s, the proposed goal of nutrition support was to provide sufficient calories to match the measured increased resting energy expenditure (hypermetabolism) in order to prevent protein depletion. As indirect calorimetry (the gold standard) is not available in most intensive care units (ICUs) or it is not possible to perform it in certain patients, it is usual to estimate the daily caloric requirements using formulae. For years the most frequently used one was the Long equation (resting metabolic expenditure calculated by the Harris-Benedict equation with the addition of an injury factor and an activity factor; Long 1979). This approach often led to overestimation of caloric requirements (compared with the values obtained by indirect calorimetry), mainly in ventilated and sedated patients (McClave 1992). It also induced some degree of overfeeding with nutrition support, which was associated with several metabolic complications (Klein 1998), such as hypertriglyceridaemia, increased production of CO_2, hepatic steatosis and hyperglycaemia, which also behaves as an independent factor for increased mortality in critically-ill patients (Badawi 2012; Krinsley 2003).

It is currently known that the caloric requirements for nutrition support of a critically-ill person could differ from the estimated resting or total energy expenditure (Reid 2004). We must take into account variability due to several factors: the presence of injury or sepsis (type, severity and metabolic response of the host) (Hoffer 2003); the time course of the disease or the elapsed time in the ICU (Monk 1996; Uehara 1999); current ICU care and treatments (Boulanger 1994); the nutrition state or the fat-free mass (Zauner 2006); the complications and some factors associated with the disease states (Magnuson 2011; Stahel 2010), and comorbidities. This variability contributes to the difficulty in estimating energy needs for the nutrition support of these patients (Frankenfield 2011). The use of predictive equations (Cooney 2012) could be one of the causes of underfeeding or overfeeding in some critically-ill people (Reid 2006).

There is consensus about some aspects of caloric and protein requirements for nutrition support of the critically-ill ventilated person:
a) the degree of hypermetabolism due to injury or sepsis is lower than that reported at the beginning of the 1970s (Liggett 1990), particularly during the first days in the ICU (Biolo 2002; Heyland 2003; Kreymann 2006);
b) positive or neutral energy balance failed to decrease the protein catabolic rate or nitrogen loss and did not prevent negative nitrogen balance and protein depletion (Frankenfield 1997; Plank 2003);
c) positive energy balance is associated with increased fat mass, without changes in lean body mass (Hart 2002; Streat 1987);
d) the main determinant of a positive, or less negative, nitrogen balance during nutrition support seems to be the nitrogen intake (Iapichino 1984; Weijs 2013);
e) nutrition support did not modify the rate of protein catabolism, but was able to preserve some nitrogen loss (less negative nitrogen balance) by promoting whole-body protein synthesis, with protein intake of up to 1.5 g/kg/day (Shaw 1987).

The well-known clinical guidelines for the nutrition support of critically-ill people (ASPEN / SCCM guidelines 2016; ASPEN / SCCM guidelines 2009; ESPEN guidelines 2009) sometimes disagreed with each other, and in the literature there are some open debates. For example, when and how to initiate the nutrition support; when to begin lipid administration by the parenteral route and the type of lipids to be used; the role and timing for supplemental parenteral nutrition; the amount of protein or the non-protein calories/nitrogen ratio to prescribe; the dose and type of supplemental trace elements and antioxidant vitamins; the best way to estimate the caloric requirements; if caloric provision should be optimized to prevent a caloric deficit during the first days of ICU in order to minimize the initial or delayed complications associated with undernutrition (Dvir 2006; Heidegger 2013; Rubinson 2004; Wischmeyer 2013), or if it is better to give hypocaloric nutrition during the first days of intense inflammatory response (and metabolic changes) induced by injury or sepsis (Berger 2007; Berger 2012; Casaer 2014; Cooney 2012; Dickerson 2011; Kreymann 2012; Singer 2010; Weijs 2013; Wischmeyer 2012). This review focuses only on the clinical results of providing hypocaloric nutrition support compared to normocaloric nutrition to critically-ill adults.

Description of the intervention

More than 20 years ago, Zaloga 1994 proposed a short period of dietary restriction during the first few days of acute injury or sepsis, originally designated "permissive underfeeding" and later "hypocaloric nutrition support" (Patiño 1999). The provision of hypocaloric nutrition support with high-protein content was successfully used in a group of obese stressed patients (Dickerson 1986). This approach was first reviewed (Kushner 2011), suggested by a group of experts for critically-ill people (McClave 2011), and recommended in some clinical guidelines (ASPEN guidelines 2013; ASPEN / SCCM guidelines 2016). The use of hypocaloric nutrition support in critically-ill people, mainly during the first days of ICU stay, has been frequently mentioned in the literature; some evidence and opinions were reported in several narrative reviews (Boitano 2006; Berger 2007; Jeejeebhoy 2004; Malone 2007; Stapleton 2007).

How the intervention might work

Severely critically-ill people experiencing major metabolic changes during the acute phase of systemic inflammatory response induced by injury or sepsis could benefit from this approach. This may be explained by: avoidance of the well-known deleterious effects of overfeeding or the consequences of starvation; diminishing metabolic disturbances, especially hyperglycaemia, and the level of inflammatory cytokines. In certain animal models, hypocaloric nutrition during acute stress seemed to lower morbidity and mortality. This could also be possible in critically-ill people, but the available data are not conclusive about the potential benefits of hypocaloric feeding. On the contrary, there is some evidence that underfeeding could be associated with complications and worse outcomes for critically-ill people (Dvir 2006; Villet 2005), and that the effect of hypocaloric nutrition support could be different in malnourished and well-nourished people (Braunschweig 2001). The possible role of starvation-induced autophagy is currently under consideration (Marik 2016a).

Why it is important to do this review

We do not so far have conclusive evidence for how many calories we should give to critically-ill people in order to improve outcomes and diminish complications. However, today we certainly know that caloric requirements are rather less than that proposed in the 1970s or 1980s (Krishnan 2003; Rubinson 2004). Currently, in several countries there are intensive care or nutrition support specialists providing hypocaloric nutrition support to most of their critically-ill patients during the first few days of illness, or tolerating the administration of less than prescribed enteral nutrition (fewer calories than the estimated ones) for their patients. This is based more on observational evidence or expert opinions than on scientific data.

Several authors consider it important to optimize the energy provision, targeting measured or estimated requirements, in order to avoid caloric deficits ("caloric debt") during the first days of ICU stay (Faysy 2008; Singer 2010; Singer 2011; Wischmeyer 2013; Wischmeyer 2015), or, even more importantly, to also target the protein supply (Weijs 2012; Weijs 2014; Hoffer 2012; Nicolo 2016), or give some supplementary protein (Alberda 2009).

Due to these unanswered questions, the controversial data and the different interpretations of it, it is necessary to perform systematic reviews of each contentious topic and to analyse the clinical significance of each nutritional approach. We have therefore conducted this systematic review to explore the effects of prescribed hypocaloric enteral or parenteral nutrition on clinical and metabolic outcomes in critically-ill adults.

OBJECTIVES

To assess the effects of prescribed hypocaloric nutrition support in comparison with standard nutrition support for critically-ill adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and quasi-randomized controlled trials. We considered the inclusion of quasi-randomized controlled trials in order to enlarge the evidence about the efficacy and safety of hypocaloric nutrition support (Schneider 2007; Shadish 2002).

Types of participants

We included all adult participants (aged 18 years or more) hospitalized for different diseases and severity at medical, surgical or disease-specific (burns, trauma, neurological, etc.) intensive care units (ICUs) and requiring any type of nutrition support.

Exclusion criteria: none.

Types of interventions

The experimental intervention evaluated was: hypocaloric nutrition support with fewer total calories than measured resting energy expenditure (REE) by indirect calorimetry or, if not measured, less than 25 kcal/kg/day. This could be done through restricted doses of carbohydrates or lipids, or both, with either normal or increased protein dose. The control intervention was:

1. Normo- or hypercaloric nutrition support: equal to or more than the measured REE or than 25 kcal/kg/day (with the same characteristics as above); or
2. No nutrition support at all: fasting or dextrose solutions.

We evaluated the results of trials designed to compare prescribed hypocaloric enteral or parenteral nutrition support (or permissive underfeeding) with standard nutrition support, or with no nutrition, even if those trials did not reach their caloric goals in the intervention or control groups (intention-to-treat analysis). Furthermore, we did not include trials that planned to provide full nutrition support but resulted in unintended hypocaloric provision (for any reason).

Types of outcome measures

Primary outcomes

The primary outcomes were the following clinical outcomes:

1. Mortality. Death occurring during the ICU and hospital stay, or 28- to 30-day all-cause mortality.
2. Length of stay. Days stayed in the ICU and in the hospital.
3. Infectious complications. Events of any type of infectious complications occurring during the hospital stay, registered by the study authors according to their diagnostic criteria of infections.

Secondary outcomes

The secondary outcomes were one or more of the following outcomes:

1. Length of mechanical ventilation. Days on mechanical ventilation during ICU stay.
2. Non-infectious complications. Events of any non-infectious complication during the hospital stay, potentially associated with the nutrition status or the nutrition support, according the criteria of the study authors (for example: wound dehiscence, decubitus ulcers, etc.)
3. Carbohydrate metabolic outcomes. Events of hyperglycaemia (glycaemia higher than 150 mg/dl) during ICU stay. Events of hypoglycaemia (glycaemia lower than 70 mg/dl) during ICU stay.

4. Lipid metabolic outcomes. Events of hypertriglyceridaemia (higher than 200 mg/dl) or any lipid metabolic complication associated with the nutrition support according to the criteria of the study authors.
5. Protein metabolic outcomes. Nitrogen balance (positive or negative in grams/day) or any protein metabolic complication associated with the nutrition support according to the criteria of the study authors.
6. Nutrition status or clinical condition at ICU discharge. Nutrition or functional evaluation, made at the time of ICU discharge with any method of assessment used by the study authors.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 5, 2017); MEDLINE/Ovid (1946 to 20 June 2017); Embase (1980 to 20 June 2017), and LILACS (1992 to 20 June 2017). We developed a specific strategy for each database (see Appendix 1 for CENTRAL, Appendix 2 for MEDLINE, Appendix 3 for Embase and Appendix 4 for LILACS).

We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy phases one and two, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The filter used to identify randomized controlled trials (RCTs) in the search strategy for MEDLINE was from Glanville 2006. For Embase we applied the trial filter for therapy maximizing sensitivity developed by Health Information Research Unit (HIRU) at McMaster University: hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx).

We did not apply restrictions by language or by publication status.

We also searched (up to 20 June 2017) for relevant ongoing trials in specific trial registries:

1. ClinicalTrials.Gov: clinicaltrials.gov/
2. International Clinical Trials Registry Platform: apps.who.int/trialsearch/
3. ISRCTN Registry: www.isrctn.com/

Searching other resources

We searched the Conference Proceedings of the annual congresses of the following four societies, as published in their respective journals, in order to find papers presented at different meetings:

1. American Society for Parenteral and Enteral Nutrition (ASPEN), through the Journal of Parenteral and Enteral Nutrition (1990 to 30 June 2017).
2. European Society for Clinical Nutrition and Metabolism (ESPEN), through the journal Clinical Nutrition (1990 to 30 June 2017).
3. Society of Critical Care Medicine (SCCM), through the journal Critical Care Medicine (1990 to 30 June 2017).
4. European Society of Intensive Care Medicine (ESICM), through the journal Intensive Care Medicine (1997 to 30 June 2017).

We also handsearched the original papers published in the following journals:

1. Journal of Parenteral and Enteral Nutrition (1990 to 30 June, 2017).
2. Clinical Nutrition (1990 to 30 June 2017).
3. Nutrition (1990 to 30 June 2017).
4. Nutrition Clinique et Métabolisme (1994 to 30 June 2017).

We also checked the reference list and citations of the relevant articles and reviews related to hypocaloric feeding and to caloric and protein requirements of critically-ill people (1970 to 30 June 2017).

Correspondence

We contacted main authors of relevant trials and reviews to identify any additional studies, and relevant pharmaceutical companies for published and unpublished reports.

Data collection and analysis

Selection of studies

Three review authors (MP, ACr and CL) independently scanned the titles and abstracts of reports identified by electronic searching, manual searching, snowballing and by contacts with clinical experts and the pharmaceutical industry. We retrieved and evaluated potentially relevant studies, chosen by at least one review author, in full-text versions. These review authors independently selected trials that met the inclusion criteria using a checklist designed in advance for that purpose. We resolved any disagreement through consultation with a fourth review author (GP). We rejected articles at the initial screening only if we could determine from the title and abstract that the study was not a report of a randomized or quasi-randomized controlled trial; or that it did not address enteral and/or parenteral nutrition in critically-ill adults. When we could not reject a study with certainty, we obtained the full text of the article for further evaluation.

Data extraction and management

Two review authors (ACr and CL) independently extracted data using a standardized checklist. We registered it in the data extraction form. We resolved any disagreement through consultation with a third review author (MP).

Assessment of risk of bias in included studies

Two review authors (GP and CL) independently assessed risks of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement through discussion and consultation with a third assessor (ACi).

(1) Sequence generation (checking for possible selection bias)

We looked for the description of methods used in each included study to generate the allocation sequence, and assessed if they were adequate to produce comparable groups (unbiased selection). We classified methods as being at low, high or unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We looked for the description of methods used in each included study to conceal the allocation sequence and assessed if they were adequate to avoid the intervention allocation being foreseen or changed. We classified methods as being at low, high or unclear risk of bias.

(3) Blinding (checking for possible performance bias)

We looked for the description of methods used, if any, in each included study to blind study participants and personnel from knowledge of which intervention a participant received. We also considered partial blinding (e.g. where it had not been feasible to blind participants but outcome assessment was carried out without knowledge of group assignment). Where blinding was not possible we assessed whether the lack of blinding was likely to have introduced bias. We classified methods as being at low, high or unclear risk of bias.

We also assessed any information about whether the intended blinding was effective.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We looked for the completeness of outcome data in each included study, for each main outcome, including attrition and exclusions from the analysis. We assessed whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition/exclusion, and any re-inclusions in analyses. We classified methods as being at low, high or unclear risk of bias.

(5) Selective reporting bias

We assessed this by comparing the study protocol, when available, and all of the study's pre-specified outcomes that are of interest in the review. We classified methods as being at low, high or unclear risk of bias.

(6) Other sources of bias

We looked for any important concerns about other possible sources of bias in each included study. For example, was there a potential source of bias related to the specific study design? Was the trial stopped early due to some data-dependent process? Was there extreme baseline imbalance? Has the study been claimed to be fraudulent? Has the researcher gained sponsorship from agencies with a vested interest in the findings? We assessed whether each study was free of other problems that could put it at risk of bias. We classified methods as being at low, high or unclear risk of bias.

(7) Overall risk of bias

We made an explicit judgement about whether studies were at an overall high, low or unclear risk of bias, according to the following criteria: low risk if all six 'Risk of bias' domains were rated low for that study; unclear risk if at least one domain was rated at unclear risk; high risk if at least one domain was rated at high risk of bias.

We assessed the likely magnitude and direction of identified risks of bias, and whether we considered this could have a significant effect on the findings. We explored the impact of the level of bias through sensitivity analyses.

Measures of treatment effect

For dichotomous outcomes we calculated risk ratios (RRs) and 95% confidence intervals (95% CIs). We calculated the mean difference (MD) for continuous outcomes measured using the same scales, or the standardized mean difference (SMD) if they used different scales.

Unit of analysis issues

The unit of analysis was the participant in each trial arm. All included studies had a parallel-group design, so there was no need for adjustment for a cluster or cross-over design.

Dealing with missing data

We obtained missing data from study authors, if feasible, and performed intention-to-treat analyses if data were available; otherwise, we performed available-case analyses. We investigated attrition rates, such as dropouts, losses to follow-up and withdrawals, and we critically appraised issues of missing data. We did not impute missing data.

We contacted by email the first authors of the following included and ongoing trials:

1. Ahrens 2005. The first author sent the estimates of continuous outcomes as means and standard deviations for length of hospital and ICU stay and for length of mechanical ventilation.
2. Arabi 2015 The first author sent us the length of hospital and ICU stay and of mechanical ventilation in means and standard deviation.
3. Charles 2014 The first author sent us mean and standard deviation of days on mechanical ventilation, and additional information to complete the 'Risk of bias' table.
4. NHLBI 2012 and Rice 2011 The corresponding author sent us all the information required to render their data compatible, and also some additional unpublished results: length of hospital stay, ICU and mechanical ventilation in means and standard deviations, number of participants with infections and hyperglycaemic episodes, and amount of calories received by participants in both groups.
5. Ochoa 2017 We contacted the lead author. He replied that he would try to recover and send the requested study results, but we have not received them yet.
6. Petros 2016. The study was initially published only in abstract form. The first author sent us all the information we required from its finished but unpublished pilot study. The full paper of the pilot trial was recently published (Petros 2016).
7. Rugeles 2013 We initially identified the study before publication. The first author sent us the full paper ready to be published in advance of publication, and some additional considerations to better assess the risk of bias and the number of participants with hyperglycaemia.
8. Rugeles 2016 The first author sent us the full paper of this clinical trial before it was indexed in MEDLINE (It was registered in clinicaltrials.gov as NCT02577211). The second author gave us the means and standard deviations for length of ICU stay and of mechanical ventilation, and also some additional information to complete the 'Risk of bias' table.
9. Theodorakopoulou 2016 We did not received an answer to several questions about the abstract of the trial.

Assessment of heterogeneity

In cases of statistical heterogeneity, i.e. a Chi^2 test with a P value less than 0.10 or an I^2 greater than 30% (Higgins 2002), we examined the potential causes of the heterogeneity by prespecified subgroup and sensitivity analyses. We followed the suggestions in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*

and interpreted and rated heterogeneity according to the I^2 value as follows: 'not important' if 40% or less, 'moderate' with I^2 between 30% and 60%, 'substantial' with I^2 between 50% and 90%, and 'considerable' if I^2 is higher than 75% (see Data synthesis section for levels of I^2 that allowed us to report numerical results or not) (Higgins 2002).

We assessed clinical heterogeneity by considering different parameters of clinical practice. We considered the objectives and methodology of the trials, the type/severity of the participants (surgical, medical and others), and several aspects of the nutrition support, such as time to initiation, route, duration and amount of calories and protein received by the intervention and the control groups. The most important parameters of this pragmatic and subjective assessment were the amount of calories received by each group of participants, and the difference in calories received by the intervention and control groups. We defined clinical heterogeneity as 'low', 'moderate' or 'important', according to a clinical judgement about the possibility of comparing trials with small, moderate or important differences according to the above parameters.

Some of the parameters we used to define clinical heterogeneity were also used for subgroup and sensitivity analyses, to investigate the heterogeneity (Subgroup analysis and investigation of heterogeneity). In addition, where we identified important statistical or clinical heterogeneity we performed meta-regression in order to explore the possible causes.

Assessment of reporting biases

The search strategy included consultation with leaders in the field, the pharmaceutical industry, conference and congress proceedings and snowballing techniques to maximize the possibility of finding unpublished studies. We performed funnel plot analyses when eight or more studies were included in each outcome analysis.

Data synthesis

We first reviewed the data from included studies qualitatively. Then, if possible, we combined them quantitatively by population, intervention and outcome, using Cochrane statistical software (Review Manager 2014). We based the quantitative analyses of outcomes on intention-to-treat (ITT) results.

In case of unimportant statistical heterogeneity between studies (I^2 of 30% or less), we performed meta-analyses using the fixed-effect model. In case of I^2 between 30% and 50%, we used a random-effects model to produce more conservative confidence intervals. If the I^2 was above 50%, we did not report pooled estimates of the meta-analysis. In cases of important clinical heterogeneity we did not report pooled estimates of the meta-analyses, even in the absence of statistical heterogeneity.

In the subgroup analyses we reported results using a random-effects model if one or more of the subgroups had an I^2 between 30% and 50%, for a more conservative analysis. If the total statistical heterogeneity test showed I^2 above 50% or if the clinical heterogeneity was important, we did not report summary estimates of the meta-analysis.

In all cases where it was not possible to perform or report total or subtotal analyses, we produced a short descriptive comment about the results of the studies for each outcome.

Subgroup analysis and investigation of heterogeneity

The prespecified possible causes of heterogeneity were the following:

1. Age: 18 to 65 years old, 66 to 75 years old, and more than 75 years old.
2. Primary disease of the participants: major surgery, trauma, sepsis, medical diseases.
3. Disease severity with or without organ failure: acute physiology and chronic health evaluation II (APACHE II); simplified acute physiology score II (SAPS II); sequential organ failure assessment (SOFA); multiple organ dysfunction score (MODS); logistic organ dysfunction system (LODS), other scores.
4. With or without comorbidities: assessed by the Charlson score or similar.
5. Nutrition status: obese, malnourished or well-nourished.
6. Level of inflammation (by determination of plasma level of C reactive protein or other acute phase reactants) or hypermetabolism (by indirect calorimetry) or hypercatabolism (by measured or estimated total urinary nitrogen).
7. Amount of calories in the intervention group: low versus very low amount of calories.

After retrieval of studies, we acknowledged that there were important differences among them that we should consider in the assessment of clinical heterogeneity. We therefore added other non-prespecified explorations of heterogeneity:

1. Subgroup analysis by route of nutrition support: enteral or parenteral nutrition.
2. Meta-regressions (using STATA 14.1; Stata), to explore the effect of the following variables on the main outcomes: type of participants, the calories received, and the difference in calories received by the intervention and control groups.

To investigate differences between two or more subgroups we used the test for heterogeneity across subgroup results rather than across individual study results. We also calculated an I^2 statistic for subgroup differences (Higgins 2011). We considered a P value less than 0.05 as statistically significant.

Sensitivity analysis

1. Trial design: we performed three prespecified sensitivity analyses: 1) excluding the quasi-randomized trials: 2) excluding those studies with at least one high 'Risk of bias' criterion; and 3) in all the outcomes performed with the fixed-effect model, we also conducted the analysis with the random-effects model.
2. We undertook two more non-prespecified sensitivity analyses, excluding trials with a primary goal different from prescribed hypocaloric enteral or parenteral nutrition.

'Summary of findings' table and GRADE

We present the overall quality of the evidence for selected outcomes using the GRADE approach (Schünemann 2011). This approach takes into account five criteria:

1. Risk of bias
2. Inconsistency
3. Imprecision
4. Directness
5. Publication bias

For each comparison, two review authors (JVAF, ACi) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low', using GRADEpro GDT software. We resolved any discrepancies by consensus, or, if needed, by arbitration by a third review author (MP).

We present the results for the comparison of hypocaloric nutrition versus control for the following outcomes:

1. Mortality in hospital
2. Mortality in ICU
3. Mortality at 30 days
4. Length of hospital stay (days)
5. Length of ICU stay (days)
6. Infectious complications
7. Length of mechanical ventilation (days)

Since meta-analysis was not possible in most cases due to both statistical and clinical heterogeneity, we present the range of effect estimates of the individual studies along with the number of participants, number of included studies and confidence in the effect estimates (Guyatt 2011; Schünemann 2011).

RESULTS

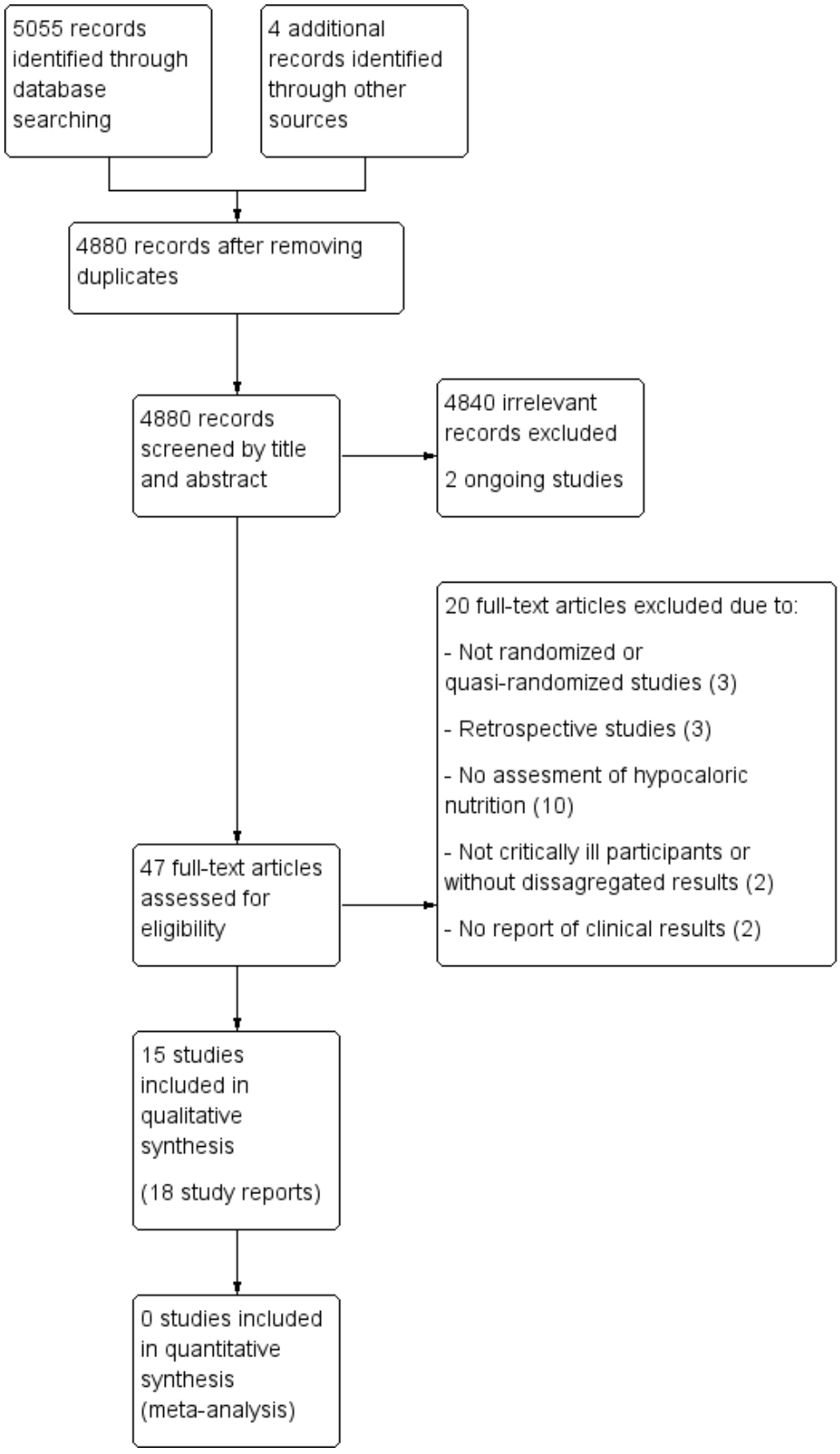
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The search strategy from electronic databases, updated to 20 June 2017, retrieved 5055 records. We found four more studies by handsearching. One full paper was sent by the first author before it was indexed in MEDLINE (original reference in clinicaltrials.gov, with the identifier NCT02577211). After removing duplicates we screened the remaining 4880 records. After title and abstract evaluation, we eliminated 4840 records as irrelevant. We found two ongoing trials. We assessed 47 full-text reports for eligibility and excluded 20 of them for different reasons (see Characteristics of excluded studies). We therefore included the remaining 15 studies (18 reports, Characteristics of included studies). See the updated flow diagram of the studies in Figure 1.

Figure 1. Updated study flow diagram, 20 June 2017



Included studies

Fifteen studies fulfilled the inclusion criteria (Ahrens 2005; Arabi 2011; Arabi 2015; Battistella 1997; Charles 2014; Choban 1997; Ibrahim 2002; McCowen 2000; NHLBI 2012; Norouzy 2013; Petros 2016; Rice 2011; Rugeles 2013; Rugeles 2016; Theodorakopoulou 2016). Two studies (Norouzy 2013; Theodorakopoulou 2016), were available as abstract only, so some of the study characteristics are missing.

Sample sizes

The total number of ICU participants included was 3129. The range of number of ICU participants included in the trials varied from 13 to 1000.

Setting

Eight included studies were performed in the USA, two in Colombia, one in Saudi Arabia and Canada, and one in each of the following countries: Saudi Arabia, Greece, Germany and Iran. Fourteen of the included studies were RCTs and one was a quasi-randomized trial (Ibrahim 2002). The setting was mostly university-associated hospitals.

Participants

Two studies (Ahrens 2005; Choban 1997), reported data of participants in the ICU and on a regular patient care floor. In those studies we only included the data of the ICU participants. The rest of the trials only included ICU participants. The type of ICU was reported in the studies as medical, medical-surgical or trauma ICU, but after evaluating the reported diagnoses of the included participants, we considered only two categories: surgical participants in five trials (Ahrens 2005; Battistella 1997; Charles 2014; Choban 1997; McCowen 2000;), and medical participants in 10 trials (Arabi 2011; Arabi 2015, Ibrahim 2002; NHLBI 2012; Norouzy 2013; Petros 2016; Rice 2011; Rugeles 2013; Rugeles 2016; Theodorakopoulou 2016). Some inclusion criteria considered participants with specific conditions, such as hyperglycaemia (Arabi 20111), obesity (Choban 1997), sepsis (Theodorakopoulou 2016), or mechanical ventilation for at least 24 hours (Ibrahim 2002; Rice 2011). In four studies the participants received parenteral nutrition (Ahrens 2005; Battistella 1997; Choban 1997; McCowen 2000). Nine studies used only enteral nutrition (Arabi 2011; Arabi 2015; Ibrahim 2002; NHLBI 2012; Norouzy 2013; Rice 2011; Rugeles 2013; Rugeles 2016; Theodorakopoulou 2016). In two studies the indication was enteral nutrition, but if this was not possible they used parenteral nutrition (Petros 2016; Charles 2014), (see Table 1).

Interventions and study design

All studies had a parallel-group design, except for two (Arabi 2011; NHLBI 2012) which had a factorial design. These also evaluated, respectively, intensive insulin treatment versus standard insulin treatment, and a nutritional supplement containing omega-3 fatty acids and antioxidants versus an isocaloric formula. The 15 included studies had a control group with prescribed normocaloric nutrition support. None of the included studies had fasting or only hydration as a comparator. See Table 1; Table 2. Most of the included studies did not achieve the proposed caloric target, with a difference in calories between the intervention and control groups in the range of 2 to 14 kcal/kg/day.

Outcomes

For full details of the reported outcomes see Table 3 and Characteristics of included studies.

Funding

Studies were funded by non-governmental associations or foundations (Arabi 2015; Choban 1997; Ibrahim 2002), or by the US government (Battistella 1997; Charles 2014; NHLBI 2012; Rice 2011). Three studies received funding from the industry (Arabi 2011; Rugeles 2013; Rugeles 2016), and five studies did not specified their sources of funding (Ahrens 2005; McCowen 2000; Norouzy 2013; Petros 2016; Theodorakopoulou 2016).

Excluded studies

Out of the 47 full papers we initially assessed for eligibility, we finally excluded 20 for the following reasons:

1. Three were not randomized or quasi-randomized controlled trials (Alberda 2009; Arabi 2010; Müller 1995).
2. Three were retrospective studies (Casadei 2006; Dickerson 2002; Lau 2010).
3. Ten studies did not assess hypocaloric nutrition (Desachy 2008; Dissanaike 2007; Doig 2013; Fiaccadori 2005; Garrel 1995; Mackenzie 2005; Moses 2009; Rodríguez 2005; Esterle 2010; Wewalka 2010).
4. Two studies did not include critically-ill participants or only some of them without disaggregated results (Owais 2014; Schricker 2005).
5. Two studies did not report clinical results (Berg 2013; Iapichino 1990).

Refer to the Characteristics of excluded studies for further details.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

There are two ongoing studies.

We identified one study (NCT01665664) through clinical trial registries. It is set in Israel, and plans to include adult participants with mechanical ventilation and to compare hypocaloric nutrition to normocaloric nutrition. The study outcomes include all-cause mortality, ICU mortality, hospital mortality, length of stay (hospital and ICU), length of mechanical ventilation, rate of infections, ventilator-free days and rate of ventilator-associated pneumonia. This study was last verified in 2012 in ClinicalTrials.gov and was "not recruiting". We were unsuccessful in contacting the study author.

We identified the second ongoing study in a conference proceeding (Ochoa 2017). This multicentre RCT includes adult, obese, critically-ill and mechanically ventilated participants requiring enteral nutrition, and compares hypocaloric versus normocaloric enteral nutrition support. The study outcomes include events of hyperglycaemia and hypoglycaemia. Since the abstract included limited information about a preliminary interim analysis we contacted the study author for further information. This study is funded by Nestlé Health Science.

Refer to the Characteristics of ongoing studies

Risk of bias in included studies

We assessed seven domains of possible biases, according to prespecified criteria. Details for each included study are provided in their corresponding 'Risk of bias' table in the Characteristics of included studies. A graphical summary can be seen in Figure 2 and Figure 3 (showing overall percentages of risk level for each domain, and levels of risk of bias for each study, respectively).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias domain presented as percentages across all included studies.

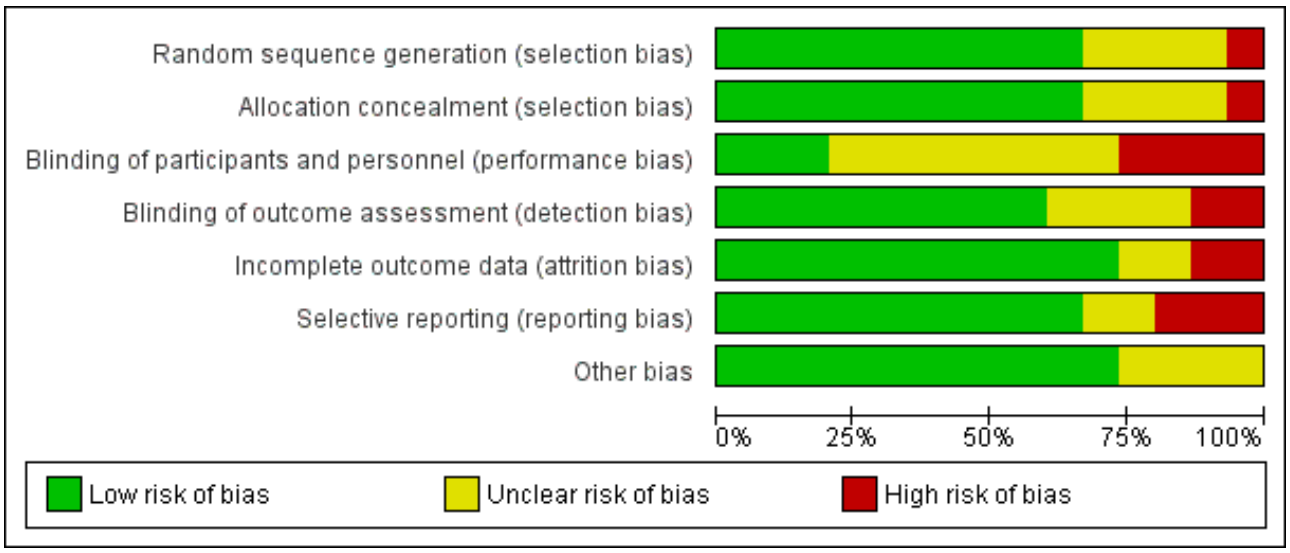
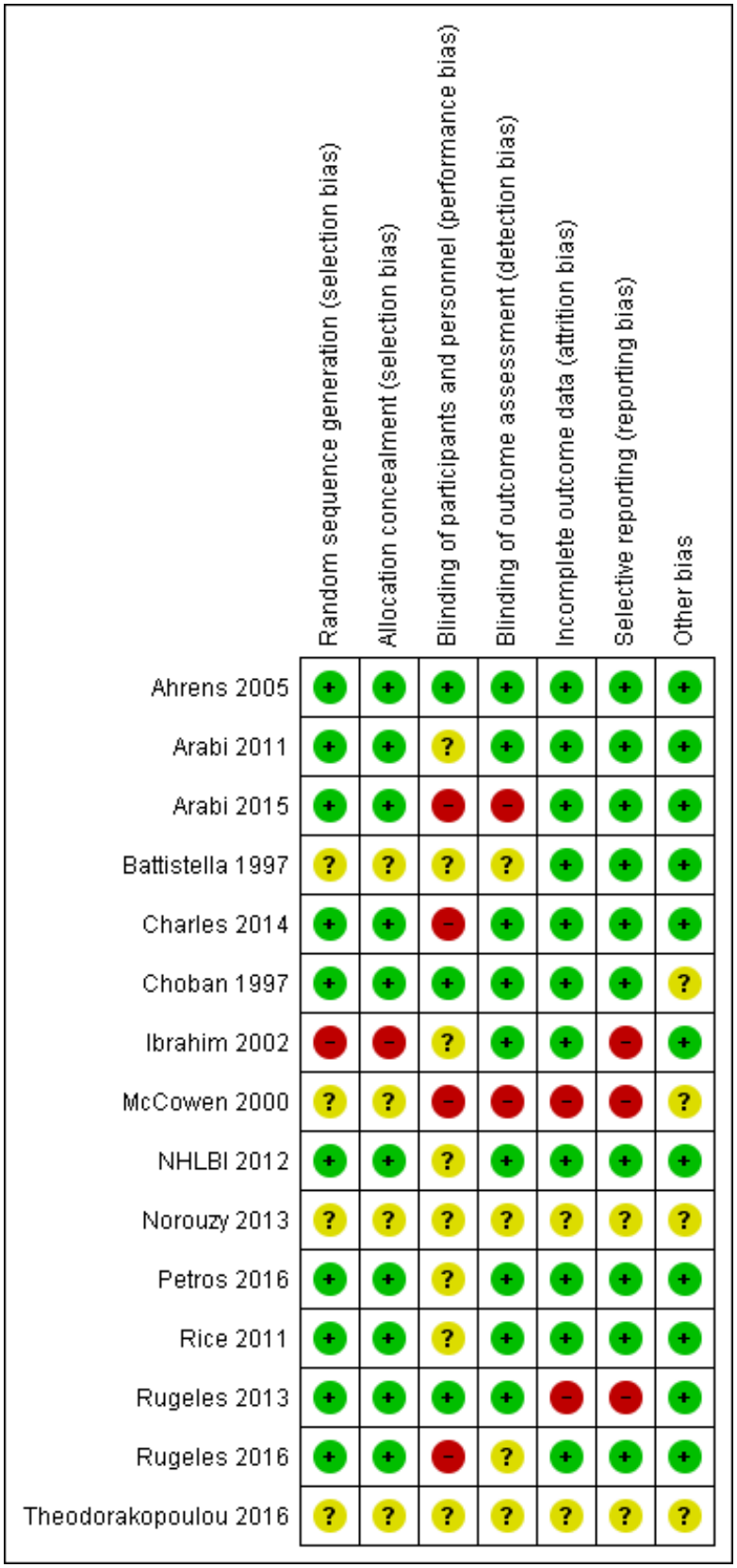


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias domain for each included study. Red colour represents high risk of bias; green, low risk of bias; and yellow, unclear risk of bias.



Overall, only one study had low risk of bias in all the evaluated domains (Ahrens 2005). Six studies had at least one high 'Risk of bias' criterion (Arabi 2015; Charles 2014; Ibrahim 2002; McCowen 2000; Rugeles 2013; Rugeles 2016). The eight remaining studies had at least one unclear 'Risk of bias' criterion. In six of them (Arabi 2011; Battistella 1997, NHLBI 2012; Norouzy 2013; Petros 2016; Rice 2011), this was attributable to an unblinded study design. In these cases, although most outcomes were objective or well-defined with low risk of detection bias, the descriptions of the processes of care by clinical personnel did not have enough detail to assess whether this could have led to a performance bias.

For publication bias, the funnel plots for the outcomes with at least eight trials did not show significant asymmetry.

Allocation

The random sequence generation and the allocation concealment were appropriately performed in 10 studies (Ahrens 2005; Arabi 2011; Arabi 2015; Charles 2014; Choban 1997; NHLBI 2012; Petros 2016; Rice 2011; Rugeles 2013; Rugeles 2016). One study was quasi-randomized (Ibrahim 2002), and therefore had a high risk of bias. Four studies (Battistella 1997; McCowen 2000; Norouzy 2013; Theodorakopoulou 2016) did not clearly describe these processes, and we classified them as being at unclear risk of bias.

Blinding

Lack of blinding (open-label or blinding only participants) was the main driver of the high or unclear risks of bias in most studies (Arabi 2011; Arabi 2015; Battistella 1997; Charles 2014; Ibrahim 2002; McCowen 2000; NHLBI 2012; Petros 2016; Rice 2011; Norouzy 2013; Rugeles 2016; Theodorakopoulou 2016). The inherent difficulty of blinding a nutrition support strategy in critically-ill people explains the fact that 80% of the studies could not blind the healthcare personnel. Nevertheless, three studies managed to do it (Ahrens 2005; Choban 1997; Rugeles 2013).

Incomplete outcome data

Only two studies had a high risk of attrition bias (McCowen 2000; Rugeles 2013). They excluded participants because they did not fulfil the prespecified follow-up criteria. Nevertheless, they should have reported all included participants in an intention-to-treat analysis. We classified two studies as being at unclear risk, due to a lack of information in these trials which were only published as conference abstracts (Norouzy 2013; Theodorakopoulou 2016). The other 11 studies reported outcomes for all included participants .

Selective reporting

Three studies had a high risk of reporting bias (Ibrahim 2002; McCowen 2000; Rugeles 2013). For Ibrahim 2002, some prespecified secondary outcomes (duration of mechanical ventilation, need for gastrostomy tube) were not reported. For McCowen 2000, "nitrogen balance was only measured in 12 participants (57%) in the hypocaloric and 10 (53%) of the control group, usually because of an error during collection". Rugeles 2013 did not report mortality. The authors justified this by explaining that they excluded participants who did not fulfil the 96 hours of enteral nutrition requirement. They therefore did not report mortality because this result would have been biased (they only measured mortality in participants who completed the 96 hours). A better approach would have been to perform an intention-to-treat analysis and also to report premature deaths. In Norouzy 2013 and Theodorakopoulou 2016, the information was not provided, so we classified them as being at unclear risk. We rated all the other studies at low risk of reporting bias.

Other potential sources of bias

Choban 1997 was partially funded by a corporation. Since we could not guarantee that this sponsorship had no material interest in the findings of the study, we classified it as being at unclear risk of bias.

The lack of detail in the description of the methods section of McCowen 2000 could not warrant a 'low risk' rating for Other sources of bias. We therefore classified it as being at unclear risk of bias. Due to the lack of information in the abstracts of Norouzy 2013 and Theodorakopoulou 2016 we also classified them as being at unclear risk of Other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Hypocaloric nutrition compared to control for critically-ill adults

The 15 included studies showed significant clinical heterogeneity between them, mainly related to the amount of calories provided to the intervention and control groups (Table 2)**,** and also to some differences in trials methodology, the target participants and the feeding strategies. As stated in Assessment of heterogeneity and in Data synthesis, the degree of clinical or statistical heterogeneity precluded us from reporting the numerical summary results of the meta-analysis for all the primary and secondary outcomes (Analysis 1.1 to Analysis 1.11). We used similar criteria to report the sensitivity or subgroup analyses.

When we could not report results due to clinical or statistical heterogeneity or both, we did a qualitative synthesis of the trial results. We also reported trial results of the included studies in tabular form: percentages and means of the hypocaloric and the control group of the seven main outcomes (Table 3).

Primary outcomes

1.1 Mortality in hospital

For this outcome we found nine relevant trials (1775 participants) (Arabi 2011; Arabi 2015; Battistella 1997; Charles 2014; Choban 1997; Ibrahim 2002; McCowen 2000; Petros 2016; Rice 2011). We found no statistical heterogeneity (I^2 = 0%) but important clinical heterogeneity due to the differences in the underlying diagnoses of the medical or surgical ICU participants and the route/characteristics of administration of enteral or parenteral nutrition or both, but mainly to the wide differences in calories and protein received by the participants in the included trials (Table 1; Table 2). We therefore did not pool the point estimates in meta-analysis (Analysis 1.1). There were 210 deaths in the 881 participants who received hypocaloric nutrition, and 235 deaths in the 894 participants who received the control intervention. All studies suffered from imprecision and their confidence intervals included the null value (Analysis 1.1). The central estimates of risk ratios for hospital mortality of each individual studies ranged from 0.23 to 5.54. When we excluded Battistella 1997, the range of risk ratio estimates was narrower, since this study has a more extreme estimate due to small sample size and zero events in the control group. The quality of the evidence for this outcome was very low, due to high risk of attrition bias, imprecision and inconsistency

(wide variance of point estimates across studies) (Summary of findings table 1).

1.2 Mortality in the intensive care unit (ICU)

We found four relevant trials for this outcome (1291 participants) (Arabi 2011; Arabi 2015; Battistella 1997; Petros 2016). We found no statistical heterogeneity (I^2 = 0%) but important clinical heterogeneity due to the type of participants, the nutrition methodology and the amount of calories received by the participants (Table 1; Table 2). We therefore have not pooled the point estimates (Analysis 1.2). There were 105 deaths in the 641 participants who received hypocaloric nutrition, and 123 deaths in the 650 participants who received the control intervention. All studies suffered from imprecision and their confidence intervals included the null value (Analysis 1.2). The central estimates of risk ratios for ICU mortality of each individual studies ranged from 0.81 to 5.54. When we excluded Battistella 1997, the range of risk ratio estimates was narrower, since this study has a more extreme estimate due to small sample size and zero events in the control group. The quality of the evidence for this outcome was very low, due to a high risk of attrition bias, imprecision and inconsistency (wide variance of point estimates across studies) (Summary of findings table 1).

1.3 Mortality at 30 days

For this outcome we found seven relevant trials (2611 participants) (Arabi 2011; Arabi 2015; NHLBI 2012; Norouzy 2013; Petros 2016; Rice 2011; Rugeles 2016). We found the abstract of an additional trial (Theodorakopoulou 2016), with mortality reported narratively for 38 participants. We found no statistical heterogeneity (I^2 = 0%) but important clinical heterogeneity due to participants' diagnoses, type and characteristics of the nutrition support, the amount of calories and the differences in calories received by the participants of both groups in the analysed trials (Table 1; Table 2). We therefore did not pool the point estimates (Analysis 1.3). There were 275 deaths in the 1309 participants who received hypocaloric nutrition, and 275 deaths in the 1302 participants who received the control intervention. All studies suffered from imprecision and their confidence intervals included the null value (Analysis 1.3). The central estimates of risk ratios for mortality at 30 days of the individual studies ranged from 0.79 to 3.00. The quality of the evidence for this outcome was very low, due to a high risk of attrition bias, imprecision and inconsistency (wide variance of point estimates across studies) (Summary of findings table 1).

2. 1 Length of hospital stay (days)

We found 10 relevant trials for this outcome (1677 participants) (Ahrens 2005; Arabi 2011; Arabi 2015; Battistella 1997; Charles 2014; Choban 1997; Ibrahim 2002; McCowen 2000; Norouzy 2013; Petros 2016). We found considerable statistical heterogeneity (I^2 = 78%) and important clinical heterogeneity due to differences in participants, nutrition methodology, and calories received by the participants of the intervention and control groups (Table 1; Table 2). We therefore did not pool the estimates (Analysis 1.4). Participants who received hypocaloric nutrition support had a mean length of stay of 15.70 days lower to 10.70 days higher compared to those with normocaloric nutrition support. The quality of the evidence for this outcome was very low, due to unclear or high risk of bias in most studies, inconsistency and imprecision (Summary of findings table 1).

2. 2 Length of ICU stay (days)

For this outcome we found 11 relevant trials (2942 participants) (Ahrens 2005; Arabi 2011; Arabi 2015; Battistella 1997; Charles 2014; Ibrahim 2002; NHLBI 2012; Petros 2016; Rice 2011; Rugeles 2013; Rugeles 2016). We found considerable statistical heterogeneity (I^2 = 81%) and important clinical heterogeneity due to differences in the type of participants, nutrition methodology and the differences in total amount of calories and protein received by the participants, as well as the caloric difference between the groups in each trial (Table 1; Table 2). We therefore have not pooled the effect estimates (Analysis 1.5). Participants who received hypocaloric nutrition support had a mean length of stay 11.00 days lower to 5.40 days higher compared to those with normocaloric nutrition support. The quality of the evidence for this outcome was very low, due to unclear or high risk of bias in most studies, inconsistency and imprecision (Summary of findings table 1).

3. Infectious complications. Events of any type of infectious complications occurring during the hospital stay, registered by the study authors according to their diagnostic criteria of infections

Ten studies reported this outcome (2804 participants) (Ahrens 2005; Arabi 2011; Arabi 2015; Battistella 1997; Charles 2014; Ibrahim 2002; McCowen 2000; NHLBI 2012; Petros 2016; Rice 2011). We found moderate statistical heterogeneity (I^2 = 49%) and important clinical heterogeneity due to the type of participants, study methodology and amount of calories and protein received by the participants (Table 1; Table 2). We therefore have not pooled the estimates. There were 423 participants with infections in the 1404 participants who received hypocaloric nutrition, and 438 infections in the 1400 participants who received the control intervention. Most studies suffered from imprecision and their confidence intervals included the null value (Analysis 1.6). The range of the central estimate of risk ratios for infectious complications of the individual studies ranged from 0.54 to 2.54. The quality of the evidence for this outcome was very low, due to unclear or high risk of bias, inconsistency and imprecision (Summary of findings table 1).

Secondary outcomes

1. Length of mechanical ventilation. Days on mechanical ventilation during ICU stay

For this outcome we found 12 relevant trials (3000 participants) (Ahrens 2005; Arabi 2011; Arabi 2015; Battistella 1997; Charles 2014; Ibrahim 2002; NHLBI 2012; Norouzy 2013; Petros 2016; Rice 2011; Rugeles 2013; Rugeles 2016). We found substantial statistical heterogeneity (I^2 = 69%) and important clinical heterogeneity due to the type of participants, nutrition methodology and the differences in the amount of calories and protein received by the participants, as well as the caloric difference between the groups in each trial (Table 1; Table 2). We therefore did not pool the effect estimates. Participants who received hypocaloric nutrition support had a mean length of mechanical ventilation of 13.20 days lower to 8.36 days higher compared with those with normocaloric nutrition support. The quality of the evidence for this outcome was very low, due to unclear or high risk of bias in most studies, inconsistency and imprecision (Analysis 1.7; Summary of findings for the main comparison).

2. Non-infectious complications. Events of any non-infectious complication during the hospital stay, potentially associated

with the nutrition status or the nutrition support, according to the criteria of the study authors (diarrhoea)

Three studies reported this outcome (1994 participants) (Arabi 2015; NHLBI 2012; Petros 2016). We found considerable statistical heterogeneity (I^2 = 76%) and important clinical heterogeneity due to the type of participants, nutrition methodology and the differences in the amount of calories and protein received by the participants, as well as the caloric difference between the groups in each trial (Table 1, Table 2). We therefore did not pool the effect estimates. There were 187 participants with non-infectious complications (diarrhoea) in the 1002 participants who received hypocaloric nutrition, and 242 participants with non-infectious complications in the 992 participants who received the control intervention. Most studies suffered from imprecision and their confidence intervals included the null value. The range of the central estimate of risk ratios for non-infectious complications of the individual studies ranged from 0.32 to 0.85. The quality of the evidence for this outcome was very low, due to unclear or high risk of bias, inconsistency and imprecision (Analysis 1.8).

3.1 Carbohydrate metabolic outcomes: hyperglycaemia (glycaemia higher than 150 mg/dl) during ICU stay

For this outcome we found six relevant trials (1380 participants) (Ahrens 2005; McCowen 2000; NHLBI 2012; Petros 2016; Rugeles 2013; Rugeles 2016). We found substantial statistical heterogeneity (I^2 = 62%) with moderate clinical heterogeneity due to the type of participants, nutrition methodology and the differences in the amount of calories and protein received by the participants, as well as the caloric difference between the groups in each trial (Table 1; Table 2). We therefore did not pool the effect estimates. There were 205 participants who suffered hyperglycaemia in the 695 participants who received hypocaloric nutrition, and 279 participants who suffered hyperglycaemia in the 685 participants who received the control intervention. Most studies suffered from imprecision and their confidence intervals included the null value. The central estimate of risk ratios for hyperglycaemia of the individual studies ranged from 0.36 to 0.93. The quality of the evidence for this outcome was very low, due to unclear or high risk of bias, inconsistency and imprecision (Analysis 1.9).

3.2 Carbohydrate metabolic outcomes: events of hypoglycaemia (glycaemia lower than 70 mg/dl) during ICU stay

We found five relevant trials for this outcome (1394 participants) (Ahrens 2005; Arabi 2011; Arabi 2015; Petros 2016; Rugeles 2016). We found no statistical heterogeneity (I^2 = 0%) but important clinical heterogeneity due to the type of participants, nutrition methodology and the differences in the amount of calories and protein received by the participants , as well as the caloric difference between the groups in each trial (Table 1; Table 2). We therefore did not pool the effect estimates. There were 46 participants who suffered hypoglycaemia in the 694 participants who received hypocaloric nutrition, and 38 participants who suffered hypoglycaemia in the 700 participants who received the control intervention. Most studies suffered from imprecision and their confidence intervals included the null value. The central estimate of risk ratios for hypoglycaemia of the individual studies ranged from 0.85 to 1.76. In Rugeles 2016, a risk ratio was not estimable due to no events in either group. The quality of the evidence for this outcome was low, due to unclear or high risk of bias and imprecision (Analysis 1.10).

4. Lipid metabolic outcomes. Events of hypertriglyceridaemia (higher than 200 mg/dl) or any lipid metabolic complication associated with the nutrition support according to the criteria of the study authors

None of the included trials reported this outcome

5. Protein metabolic outcomes: nitrogen balance

For this outcome we found three relevant trials (92 participants) (Battistella 1997; Choban 1997; McCowen 2000). We found substantial statistical heterogeneity (I^2 = 72%) with moderate clinical heterogeneity due to the type of participants, nutrition methodology and the differences in the amount of calories and protein received by the participants, as well as the caloric difference between the groups in each trial (Table 1; Table 2). We therefore did not pool the effect estimates (Analysis 1.11). Participants who received hypocaloric nutrition support had a mean nitrogen balance of −7.70 g/day to +2.00 g/day compared to those with normocaloric nutrition support. The quality of the evidence for this outcome was very low, due to unclear or high risk of bias in most studies, inconsistency and imprecision (Analysis 1.11).

6. Nutrition status or clinical condition at ICU discharge. Nutrition or functional evaluation, made at the time of ICU discharge with any method of assessment used by the study authors.

None of the included trials reported this outcome

Subgroup analyses

We focused our subgroup analyses on the seven outcomes reported in Summary of findings for the main comparison. Out of these seven outcomes only four had considerable statistical heterogeneity: length of hospital and ICU stay, infectious complications and length of mechanical ventilation. We explored sources of statistical heterogeneity and assessed whether meta-analysis was possible, considering clinical heterogeneity in the predefined subgroups.

Due to insufficient information available, we were unable to perform subgroup analysis by: age, disease severity, presence of comorbidities, nutrition status (malnourished or well-nourished), level of inflammation, hypermetabolism or hypercatabolism. It was only possible to perform prespecified subgroup analyses by: obesity status (as a condition of nutrition status), type of underlying medical condition (surgical or medical), amount of calories actually received by participants in the intervention and control groups. During the process of data extraction we realized that the included trials had several methodological differences between them. At this time (before any analysis of results), we decided to perform two additional analyses not prespecified in the protocol (Subgroup analysis and investigation of heterogeneity): subgroup analysis by route of nutrition support (enteral or parenteral) and meta-regression (see below). The I^2 values for these subgroup analyses are shown in Table 4. Most of the subgroup analyses were unable to explain the statistical heterogeneity of the results across studies:

1. In the **subgroup analysis by nutrition status**, limited to obesity, we did not observe subgroup differences in length of hospital stay.
2. In the **subgroup analysis by route of nutrition support** we found considerable subgroup differences in length of stay in ICU and in duration of mechanical ventilation.

3. In the **subgroup analysis by the type of participant** we did not find subgroup differences between the surgical or medical participants in any of the outcomes analysed
4. In the **subgroup analysis by the amount of calories received by each study group** we found considerable subgroup differences in length of hospital stay and in duration of mechanical ventilation.

Sensitivity analyses

1. **Excluding quasi-randomized trials.** The sensitivity analysis after excluding the only quasi-randomized trial (Ibrahim 2002) did not show major changes in the overall results for the outcomes of mortality in hospital, length of hospital stay, length of ICU stay and infectious complications. We only observed a change in the outcome of duration of mechanical ventilation. After excluding this trial, the statistically significant difference in favour of the hypocaloric group disappeared. However, this result should be interpreted with caution due to the substantial statistical heterogeneity (I^2 = 69%) and important clinical heterogeneity.
2. **Excluding trials with at least one high 'Risk of bias' criterion**. The sensitivity analysis after excluding the six trials with at least one high 'Risk of bias' criterion (Arabi 2015; Charles 2014; Ibrahim 2002; McCowen 2000; Rugeles 2013; Rugeles 2016) did not show major changes in the results of the primary and secondary outcomes analysed, nor in the subgroup analyses. We only observed some minor changes in the statistical heterogeneity of several subgroups analysed.
3. **By fixed-effect or random-effects models.** We analysed the primary and secondary outcomes by fixed-effect or random-effects models according to the value of I^2, as stated in Data synthesis. In all the analyses where the pooled estimates were done with the fixed-effect model, we conducted a sensitivity analysis with the random-effects model to explore the robustness of results. No primary or secondary outcomes or subgroup analyses showed a major change in their statistical significance or heterogeneity.
4. **By different primary goal of enteral nutrition trials**. We performed a post hoc sensitivity analysis (see Sensitivity analysis), excluding the three studies (Ibrahim 2002; NHLBI 2012; Rice 2011) with a primary goal to assess the effects of early initiation of trophic (hypocaloric) enteral nutrition or standard (normocaloric) enteral feeding from the beginning. We did not find major differences in the primary or secondary outcomes, except for minor changes in two unreported outcomes due to the heterogeneity: length of mechanical ventilation and hyperglycaemia.
5. **By different primary goal of parenteral nutrition trial**. Another post hoc sensitivity analysis was the exclusion of the Battistella 1997 trial, because its primary goal was the evaluation of parenteral nutrition with or without lipids (equivalent to normocaloric or hypocaloric nutrition, respectively). After excluding this trial, we did not see major changes in the primary and secondary outcomes evaluated, with the exception of the length of mechanical ventilation: loss of statistical significance in favour of the hypocaloric group (result not reported due to the substantial statistical heterogeneity).

Meta-regression

Considering that we found high levels of clinical and statistical heterogeneity, we performed non-prespecified meta-regressions using STATA 14.1 to explore the effect of covariates for which we had data (Table 2; Table 3):

1. Type of participants (medical or surgical participants)
2. The calories received in the hypocaloric group, based on the three aforementioned categories (see *Subgroup analysis by the amount of calories received by each study group*): normo-hypercaloric, hypocaloric or very low hypocaloric.
3. The difference in calories received between study groups (control minus intervention groups).

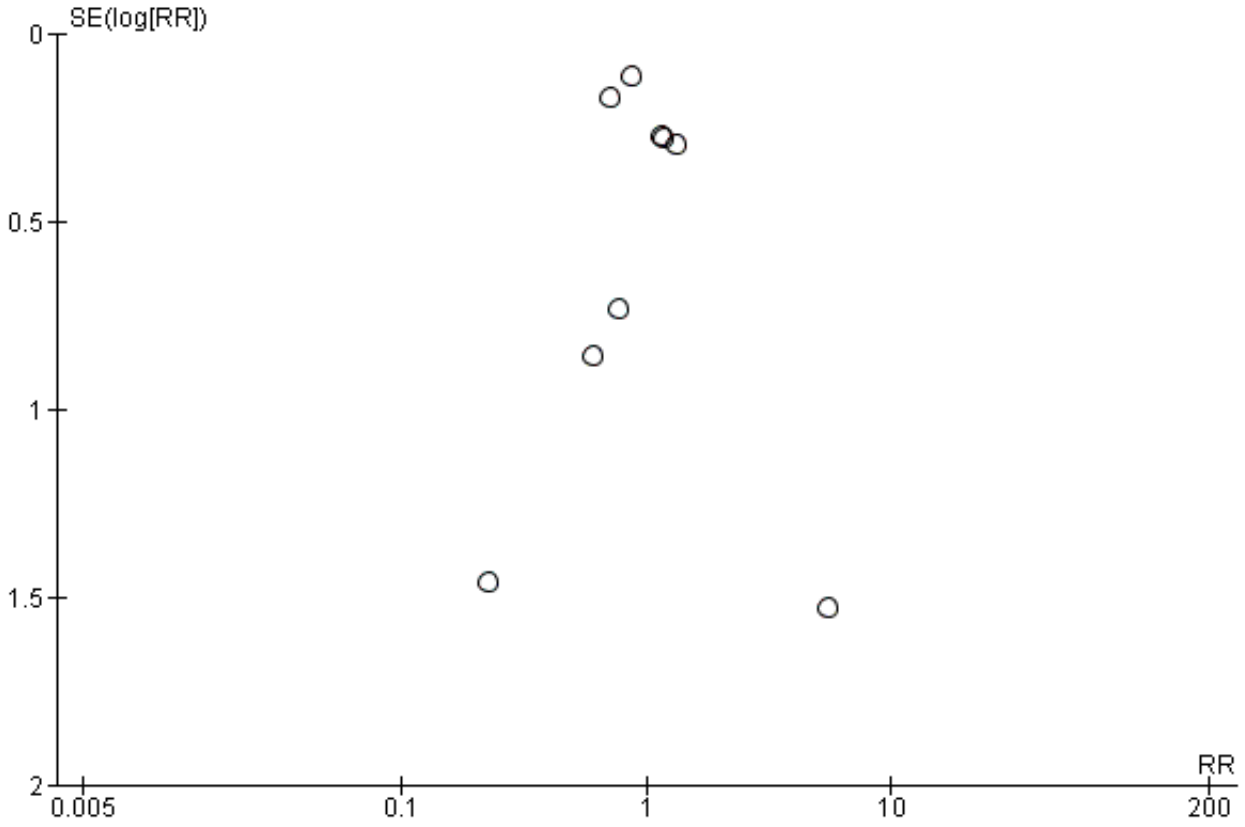
We performed meta-regression on the primary outcomes with results of nine or more trials: hospital mortality, infectious complications, hospital length of stay and ICU length of stay. We did not find significant results explaining sources of heterogeneity using this analysis. None of the analysed explanatory variables influenced the size of the intervention effect of the outcome variables. The details on the definition of variables, dataset and outcome measures are available in Appendix 5 and Appendix 6.

Table 3: In order to show some aspects of the heterogeneous results, in Table 3 we present crude results of the primary outcomes and of length of mechanical ventilation for the 15 included studies. The files of the table were ordered from top to bottom by the difference in the amount of calories receive by the control groups minus those received by the hypocaloric groups (second column from the left).

Assessment of reporting bias

We performed a funnel plot for the outcomes with more than eight included studies (Analysis 1.1; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7). We did not see important asymmetries in the funnel plots, suggesting publication bias (we give one example in Figure 4).

Figure 4. Funnel plot of comparison: 1 Hypocaloric nutrition (intervention) vs. Control, outcome: 1.1 Mortality in hospital.



DISCUSSION

Summary of main results

We identified 15 trials including a total of 3129 ICU participants. The included trials had different objectives, participant characteristics and methodology for the administration of the nutrition support. The consequence of this was important methodological diversity between the included trials (Table 1). Due to the high clinical and statistical heterogeneity, we did not report summary estimates for the primary and secondary outcome analyses. Of all the causes of clinical heterogeneity, the most relevant ones precluding the report of summary estimates were the disparity in the amount of calories/protein received by the intervention and control groups, and the disparity in the differences in the calories received between the study groups in the included trials (Table 2; Table 3). For the same reason, we did not report total estimates of subgroup analyses (See Table 4).

In a descriptive analysis of the results of the included trials for the main outcomes (See Summary of findings for the main comparison), we can summarize the following:

1. We found very low-quality evidence for the outcomes related to **mortality** (in hospital, in ICU and at 30 days), with no statistical but important clinical heterogeneity. Most studies did not find differences in the incidence of mortality between hypocaloric and control groups. The reasons for downgrading the evidence were unclear or high risk of bias in the included studies, inconsistency and imprecision.
2. We found very low-quality evidence for the outcome **length of hospital and ICU stay**, with both clinical and statistical heterogeneity. In smaller studies, there was a tendency towards a shorter length of stay in participants in the hypocaloric group, but the results across studies were inconsistent, some favouring hypocaloric nutrition support and some control. The reasons for downgrading the evidence were unclear or high risk of bias in the included studies, inconsistency and imprecision.
3. We found very low-quality evidence for the outcome **infectious complications**, with moderate statistical and important clinical heterogeneity. The results across studies were inconsistent, some favouring hypocaloric nutrition support and some control. The reasons for downgrading the evidence were unclear or high risk of bias in the included studies, inconsistency and imprecision.
4. We found very low-quality evidence for the outcome **length of mechanical ventilation**, with both clinical and statistical heterogeneity. The results across studies were inconsistent, some favouring hypocaloric nutrition support and some control. The reasons for downgrading the evidence were unclear or high risk of bias in the included studies, inconsistency and imprecision.

Other outcomes

1. For **diarrhoea (non-infectious complications)** the statistical heterogeneity was considerable and the clinical heterogeneity important. The central estimates of the individual studies favoured hypocaloric nutrition support, but the quality of this evidence was very low, due to unclear or high risk of bias in the included studies, inconsistency and imprecision.
2. For **hyperglycaemia** the statistical heterogeneity was substantial and the clinical heterogeneity moderate. The central estimates of the individual studies favoured hypocaloric nutrition support, but the quality of this evidence was very low, due to unclear or high risk of bias in the included studies, inconsistency and imprecision.
3. For **hypoglycaemia**, the clinical heterogeneity was important, but with no statistical heterogeneity. The individual studies did not find differences in the incidence of hypoglycaemia between hypocaloric and control groups, but the quality of this evidence was low, due to unclear or high risk of bias in the included studies and imprecision.
4. For **nitrogen balance**, the statistical heterogeneity was substantial and the clinical heterogeneity moderate. The results were inconsistent, some favouring hypocaloric nutrition support and some control; the quality of evidence was very low, due to unclear or high risk of bias in the included studies, inconsistency and imprecision.

We did not find data to perform several of the subgroup analyses proposed in the review protocol. We performed subgroup analyses for the main outcomes, but these could not comprehensively explain the statistical heterogeneity (See Table 4).

In the three prespecified **sensitivity analyses** (excluding the quasi-randomized trial; the three trials with at least one high 'Risk of bias' domain; or the change of results from fixed-effect to random-effects model) we did not see major changes in the results, nor in the post hoc sensitivity analysis excluding three studies with a primary goal to assess hypocaloric trophic enteral nutrition versus standard enteral feeding. In the other post hoc sensitivity analysis excluding Battistella 1997, in the primary and secondary outcomes we only observed the loss of an unreported significant difference in length of mechanical ventilation.

As we established in the subgroup and sensitivity analyses, Ahrens 2005 and Battistella 1997 had very dissimilar results compared to the other included studies. In both trials, the control groups received a high caloric dose, a median 37 total kcal/kg/day in Ahrens 2005, and 34.4 total kcal/kg ideal body weight/day in Battistella 1997. Moreover, in Ahrens 2005, the control participants not only received hypercaloric parenteral nutrition but also more dextrose than currently recommended for critically-ill participants (ASPEN / SCCM guidelines 2009; ESPEN guidelines 2009), with a median (interquartile (IQ) range) of 4.9 (4.79 to 5.07) mg dextrose/kg/min. (The authors also reported that the administration of more dextrose than 4 mg/kg/min behaved as a predictor of hyperglycaemia). Finally, It is also important to remember that Battistella 1997 compared parenteral nutrition with and without lipid emulsions. It is therefore difficult to discriminate whether the observed results were due to the amount of calories administered, to the withholding of soy-derived lipid emulsions in the parenteral nutrition, or both.

In order to evaluate causes of heterogeneity or to formulate hypotheses about them, we performed a non-prespecified **meta-regression** with the available covariates for the primary outcomes with nine or more trials. We did not find significant results explaining sources of heterogeneity (Appendix 5; Appendix 6). However, the results of the meta-regression should be considered cautiously, due to the fact of post hoc analysis, and to the limited number of studies for the number of covariates in the model.

Overall completeness and applicability of evidence

The research strategy was comprehensive and inclusive. Given the scarcity of evidence, it sought to include all possible trials with a design and goal to evaluate hypocaloric versus normocaloric nutrition support in critically-ill people. This is why we also included quasi-randomized controlled trials, different types of ICU settings (medical, surgical, mixed), types of participants (age, medical condition, etc.), administration routes (enteral, parenteral or both), and also considered trials with a different primary goal or methodology to achieve prescribed hypocaloric feeding. We therefore believe that the included studies represent a complete set of up-to-date evidence on hypocaloric nutrition support in critically-ill adults.

Nevertheless, breadth of scope was at the expense of clinical and statistical heterogeneity. Some of these differences in participants, interventions and outcomes of the included trials can be seen in Table 1 and Table 2. In addition, all studies were performed at university-associated or teaching hospitals, which are probably different from other clinical settings. It is therefore arguable whether our results could be generalized. The clinical and statistical heterogeneity precluded a quantitative synthesis of all the outcomes and most of the subgroup analyses. In the clinical field, the results should be interpreted with caution, considering all these issues.

When we analyse the amount of calories actually received by the groups in each trial (many of them different from those prespecified in their study protocols), we find that most of the included studies did not really evaluate the administration of hypocaloric versus normocaloric nutrition support, but a wide range of calories administered (Table 2). Moreover, the difference in calories received by the control minus the hypocaloric group was quite small in some of the included trials (Table 3). Both factors not only contributed to the clinical heterogeneity, but could also have been associated with the lack of statistically significant differences (if any) between the study groups.

Most of the included trials did not analyse the role of protein administration in the outcomes evaluation. The amount of protein administered to the intervention and control groups was reported in 12 trials: quite diverse in three of them, rather similar in four, and more or less the same in the other five (Table 2). There is wide consensus that obese critically-ill people should receive hyperproteic hypocaloric feeding (ASPEN / SCCM guidelines 2016; Choban 2013; Dickerson 1986), but there is a current debate about the best protein dose for the non-obese people: higher doses of proteins seemed to be associated with better outcomes in the critically-ill people (Dickerson 2012; Weijs 2012; Weijs 2013; Van Zanten 2016). The different daily protein administered to the study groups in the included trials should be considered as another component of the clinical heterogeneity.

Even though our results did not find conclusive significant evidence in favour of the hypocaloric nutrition support, it is also interesting to note that we did not find high-quality evidence for harms. This is in contrast to two observational studies that reported some poorer clinical outcomes or complications when certain levels of calories were not achieved (Rubinson 2004; Villet 2005).

Quality of the evidence

According to GRADE, the quality of evidence for the primary outcomes was very low (see Summary of findings for the main comparison).

Six out of 15 included studies presented one or more high 'Risk of bias' criteria and eight studies had one or more unclear 'Risk of bias' criteria. Given the complexity of nutrition support in critically-ill people, blinding the personnel (the major driver for high risk of bias in this systematic review) is challenging, although some studies were able to do it. Only one included trial (Ahrens 2005) had low risk of bias in all predefined criteria (Figure 3). The quality of evidence according to GRADE was low to very low for all the primary outcomes.

Another reason for downgrading the quality of evidence was inconsistency. We explored the qualitative characteristics that could explain inconsistency, but we were unable to identify them in subgroup analyses (Table 4), sensitivity analyses and meta-regression. Inconsistency was also evident in the wide variance of point estimates for mortality.

Imprecision affected the quality of all main outcomes, especially mortality, due to the low number of events. The confidence intervals were wide and we could not improve precision by pooling results in most cases, due to the clinical heterogeneity.

For publication bias, the funnel plots for the outcomes with at least eight trials did not show significant asymmetry.

Potential biases in the review process

We followed the procedures of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), in order to minimize biases in the review process. The search strategy was defined by a senior librarian and evaluated by another independent expert. Our search strategy was comprehensive, including consultation with opinion leaders, the pharmaceutical industry, conference and congress proceedings and snowballing techniques to maximize the chances of retrieving all existing studies, published or unpublished. Three review authors independently screened the trials, and data extraction and assessment of risks of bias were also done by two independent review authors. We resolved any disagreement through consultation with a third review author.

We strictly followed the inclusion-exclusion criteria of our protocol (Perman 2009). Our included trials are non-homogeneous, with different objectives and methodologies. The main differences related to the type and conditions of the participants and the methodology for the administration of the nutrition support (goals, time of initiation, route, strategy of delivery and calories administered, among others) (Table 1). This clinical and methodological heterogeneity added complexity to the analysis of data and the interpretation of results. It was not possible to report summary estimates due to the clinical or statistical heterogeneity or both.

We acknowledge that the multiplicity of subgroup analyses and post hoc analyses could have yielded false positive results. We added these post hoc analyses in order to explore the clinical heterogeneity found in the included studies. We tried to reduce the risk of false-positive results by restricting the exploration of subgroups to those outcomes in which we found statistical heterogeneity, as we had defined in our protocol.

Agreements and disagreements with other studies or reviews

There are eight previous systematic reviews and meta-analyses directly or indirectly related to the topic of this review. They have similar purposes, but different review questions and inclusion criteria.

The first review (Jiang 2011), evaluated randomized controlled trials comparing hypocaloric parenteral nutrition (≤ 20 non-protein kcal/kg/day) versus standard or high-energy parenteral nutrition (≥ 25 or > 30 non-protein kcal/kg/day, respectively) in surgical or trauma participants. According to their inclusion-exclusion criteria, they included five trials, two of which (Ahrens 2005; Battistella 1997) we also include. The other three studies (in the Chinese language) were trials of postoperative, not critically-ill participants (according to the titles and one abstract of the studies) (Jiang 2003; Mao 2015; Zhan 2007). They reported a statistically significant reduction in infectious complications and length of hospital stay, with moderate heterogeneity, in the surgical participants receiving hypocaloric parenteral nutrition. Those results were more consistent and with less heterogeneity when they excluded the small-sample size trials. The calories administered to the participants seemed to be more homogeneous, but the authors did the analysis with administered non-protein calories. If we add the caloric content of the administered protein, the intervention group received an average of 24.0 (range 20.5 to 27.0) total kcal/kg/day and the control group 34.5 (range 32.5 to 36.0) total kcal/kg/day. This means that the study compared almost normocaloric versus normo- to hypercaloric parenteral nutrition. The favourable effects of the lower-caloric parenteral nutrition on infectious complications and length of hospital stay reported in this meta-analysis should therefore be limited to surgical participants receiving parenteral nutrition with higher than recommended caloric dose. In our subgroup analyses we observed similar results with the analyses of Ahrens 2005 and Battistella 1997.

In 2015 the Canadian Critical Care Nutrition Clinical Practice Guidelines Committee updated the Canadian Clinical Practice Guidelines for nutrition support for critically-ill adults. They produced three different but related systematic reviews and meta-analyses, with the following titles: *Intentional Underfeeding: Trophic Feeds vs. Full Feeds* (Canadian Guideline 3.3a 2015); *Intentional Underfeeding: Hypocaloric Enteral Nutrition* (Canadian Guideline 3.3b 2015); and *Strategies to Optimize Parenteral Nutrition and Minimize Risks: Dose of PN* (Canadian Guideline 10.1 2015). This approach was guidelines-oriented, but also served to diminish the clinical heterogeneity of the included trials and the statistical heterogeneity in some analyses.

For the evaluation of trophic (hypocaloric) versus full (normocaloric) feeding (Canadian Guideline 3.3a 2015), the Canadian group evaluated two studies, also included in our review (NHLBI 2012; Rice 2011), but they did not include a quasi-randomized trial with a similar goal and methodology (Ibrahim

2002). The meta-analysis did not show statistical differences in mortality or ventilator-associated pneumonia between the study groups. They did not report results of length of hospital stay, of ICU stay or of mechanical ventilation, due to the way the data were reported in the trials. However, we could analyse these results after receiving the information from the first author of each trial. We did not find statistically significant differences between the study groups.

To update the 2015 guideline *Intentional Underfeeding: Hypocaloric Enteral Nutrition* (Canadian Guideline 3.3b 2015), the Canadian Committee included four trials in the meta-analysis. We included all four of them in our review (Arabi 2011; Arabi 2015; Charles 2014; Petros 2016). They found that hypocaloric enteral nutrition was associated with a trend towards lower hospital and ICU mortality, and a statistically significant reduction in the length of mechanical ventilation. They did not find significant differences for infectious complications or length of hospital and ICU stay. In the enteral nutrition subgroup analysis we were prevented from reporting summary estimates of the six outcomes evaluated, due to the high clinical or statistical heterogeneity. When we did the same analysis as they did, the results were almost the same (some minor numerical differences).

The Canadian group included four trials in their meta-analysis of parenteral nutrition (Canadian Guideline 10.1 2015), which we also included in our review (Ahrens 2005; Battistella 1997; Choban 1997; McCowen 2000). (They included results from an "unpublished Ahrens 2003" trial, which were the same as our included Ahrens 2005 trial). They did not find statistically significant differences between the intervention and control groups for hospital mortality or infectious complications. In our subgroup analysis of parenteral nutrition, we found some minor numerical differences from the Canadian Guideline in the same two outcomes, but the results were essentially the same. They also reported some additional results (sensitivity analysis and results of individual studies), but not significant ones.

Another systematic review and meta-analysis (Choi 2015), compared the effect of initial enteral nutrition with an underfeeding dose versus initial full-feeding dose of enteral nutrition in critically-ill adults. They included four trials, three of which we also included in our review (Arabi 2011; NHLBI 2012; Rice 2011), and one which we excluded due to a different primary objective (Desachy 2008). They did not find significant differences in overall mortality and other clinical outcomes between the underfeeding and the full-feeding groups. In the subgroup analysis, the underfeeding subgroup that received 33.3% or more of the standard caloric requirement showed a significantly lower overall mortality, compared with the full-feeding group. This was not seen in the underfeeding subgroup that received less than a 33.3% dose of enteral nutrition. This suggests the possibility that a moderate underfeeding enteral nutrition, but not a minimal intake, could be associated with a better prognosis. Nevertheless, the included trials showed clinical heterogeneity, as well as our subgroup analysis of enteral nutrition, where we did not see differences in hospital mortality.

The Tian 2015 meta-analysis included eight randomized trials showing significantly different calories administered by the enteral route. We included four of these trials in our review (Arabi 2011; Charles 2014; NHLBI 2012; Rice 2011). They did not find significant differences between the low- and high-energy groups for mortality; infectious complications; pneumonia; gastrointestinal intolerance and the length of hospital stay, of ICU stay and of mechanical ventilation. In the subgroup analysis, the low-energy groups who received between 33.3% and 66.6% of the caloric goal had a significantly lower mortality compared with the high-energy group. In the subgroup analysis with different amount of protein administration, they found that high protein administration (more than 0.85 g/kg/day) plus high energy could decrease the rate of infectious complication. In our subgroup analysis with three categories of calories administered, we did not find any significant result, but it is necessary to keep in mind the results of the Choi 2015 and Tian 2015 meta-analyses for the dose of calories with enteral nutrition, as well as the dose of protein (Tian 2015).

The Marik 2016b systematic review and meta-analysis compared normocaloric (80% to 100% of daily energy expenditure) with intentional hypocaloric enteral nutrition, dividing it into two different strategies: 'permissive underfeeding' (less than 70% of daily energy expenditure) and 'trophic' (20% of the dose during the first week). They included six trials, which we also include in our review, but analysed them separately in the subgroup 'trophic' (NHLBI 2012; Rice 2011), and 'permissive underfeeding' (Arabi 2011; Arabi 2015; Charles 2014; Petros 2016). In the meta-analysis the statistical heterogeneity was low and they did not find significant differences between the study groups for infectious complications, length of ICU stay and hospital mortality (only a trend towards a lower mortality in the permissive underfeeding subgroup) and ventilator-free days. In line with our protocol, we performed different subgroup and sensitivity analyses, with conceptually similar results. However, their subgroups approach should be considered in future systematic reviews.

In a second systematic review and meta-analysis (Tian 2017), the authors included 11 studies comparing low- and high-energy enteral nutrition (in two studies also enteral plus supplemental parenteral nutrition), administered to adults who were critically-ill but not malnourished. We also included five of these studies (Arabi 2011; Arabi 2015; Charles 2014; NHLBI 2012; Rice 2011). In the meta-analysis, they did not find statistically significant differences between low- and high-energy groups for mortality, infectious complications, pneumonia, length of hospital and ICU stay, and length of mechanical ventilation. They found significantly less gastrointestinal intolerance in the low-energy group. In the subgroup analysis for mortality, they observed significantly less mortality in the low-energy group but only within the range of 33.3% to 66.6% of the goal calories. In another subgroup analysis, the incidence of infectious complications was significantly lower in the high-energy group, but only when the enteral nutrition also provided higher amounts of protein. Even though one might question their decision to perform meta-analysis with such high clinical heterogeneity, we should consider in future studies the role of the enteral nutrition dose between 33.3% and 66.6% of the caloric goal and the amount of protein administered.

It is important to emphasize that, in line with our protocol (Perman 2009), we only included trials comparing any type of 'prescribed' hypocaloric nutrition support with different control groups in critically-ill adults. Although there are several reports in the literature of critically-ill people receiving hypocaloric enteral nutrition due to difficulties, intolerance or complications during the administration (occurring in 59% of the cases, as reported in the international survey done in 158 ICUs by Cahill 2010),

we did not include any study assessing this 'non- prescribed', unintentional hypocaloric nutrition support. Nevertheless, we point out that many trials included in our study could not achieve their prespecified caloric goals.

We included three studies that indirectly assessed our review question by the intentional administration of trophic (hypocaloric) enteral feeding during the first five or six days in ICU versus full enteral (normocaloric) feeding from the beginning of the ICU stay (Ibrahim 2002; NHLBI 2012; Rice 2011). In order to be as inclusive as possible, we also included Battistella 1997 (primary objective to evaluate parenteral nutrition with or without soy-lipid emulsions). It is important to highlight that the results of the latter trial could be associated with the less-caloric parenteral nutrition, with the lack of lipids, or a combination of both factors (ASPEN 2012; Ren 2013). When we did a sensitivity analysis excluding those trials, we found only minor differences in the results.

We did not include studies evaluating enteral nutrition optimized with supplemental parenteral nutrition to reach the 'target energy' (measured by indirect calorimetry or estimated by formulae) to avoid “caloric debts” (Heidegger 2013), or to assess when to initiate supplemental parenteral nutrition (Doig 2013). Both topics are the subject of currently debate.

AUTHORS' CONCLUSIONS

Implications for practice

The inclusion criteria and the data analyses by intention-to-treat defined in the protocol resulted in important clinical and statistical heterogeneity of the included trials. This heterogeneity did not allow us to report pooled estimates of the primary and secondary outcomes, so we have described them in a narrative fashion. We found very low-quality evidence for the effects of prescribed hypocaloric nutrition support on mortality in hospital, in the ICU and at 30 days, as well as in length of hospital and ICU stay, infectious complications and the length of mechanical ventilation. The reasons for downgrading this evidence were unclear or high risk of bias in the included studies, imprecision and inconsistency. For these outcomes there is uncertainty about the effects of prescribed hypocaloric nutrition, since the range of estimates includes both appreciable benefits and harms. Using subgroup and sensitivity analyses, as well as meta-regression, we were not able to explain the causes of the observed heterogeneity.

Implications for research

The evidence available is sparse, heterogeneous, and with limitations in its quality. It is important to have more well-designed, well-powered and well-conducted randomized controlled trials to assess the effects of hypocaloric nutrition support in critical outcomes such as mortality, infectious complications, length of stay and length of mechanical ventilation.

To minimize heterogeneity and to improve external validity, it is important for future studies to better categorize the participants and their nutritional treatments. The adequate report of these categorizations could help us understand the inconsistencies in the findings. Considering that nutrition support is a complex intervention, study authors should consider the following factors:
a) the clinical characteristic of included participants (diagnostic category, severity of disease, metabolic changes, acute or prolonged critical state, nutritional status, comorbidities, and other factors according to the goals of the trials);
b) the methods of nutrition support (early or late initiation, duration, amount of prescribed and administered calories to the intervention and control groups, reported in kcal/kg/day);
c) the detailed amount of prescribed proteins and the amounts effectively administered to participants (reported in grams/kg/day).

Individual-patient data (IPD) meta-analysis could be applied to model the effect of the interventions considering these covariables.

Furthermore, it is important to properly report all research methods (avoiding 'unclear' domains in 'Risk of bias' assessments) and ideally to conduct masked studies, taking into account the difficulties in effectively implementing a prescribed hypocaloric nutrition (performance bias) and in assessing outcomes subject to bias, such as lengths of stay and length of mechanical ventilation (detection bias).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahrens 2005

Methods	**Study design:** prospective, randomized controlled trial. **Study dates**: "study dates not available" **Setting**: level-1 trauma centre. Department of Surgery, Detroit Receiving Hospital, Wayne State University, Detroit, Michigan **Country**: USA
Participants	**Inclusion criteria** 1. Surgical patients, ≥ 18 years old, with requirement for parenteral nutrition by a central catheter due to contraindication or intolerance to enteral nutrition **Exclusion criteria** 1. Baseline blood glucose level > 200 mg/dl 2. Expectation of receiving parenteral nutrition for < 4 days 3. Severily underweight (< 75% of ideal body weight) 4. Morbid obesity (> twice their ideal body weight 5. Currently receiving corticosteroid therapy 6. Admitting diagnosis of burn 7. Receiving parenteral nutrition on admission 8. Not able to provide informed consent **Sample size**: calculated sample size of 26 participants to detect an absolute difference in glucose area under the curve of 50 mg hr/dl with 80% power (P = 0.05). 40 participants were randomized: 20 to each group. Only 18 were ICU participants (8 of the low caloric and 10 of the standard group). At baseline both groups were well matched, with exception of lower creatinine clearance in the standard group. **Age** (years mean ± SD) group 1: 45.3 ± 17.2; group 2: 53.1 ± 17.9 **Sex** (male, %) group 1: 75; group 2: 80 Most frequent admitting diagnosis (groups 1 and 2 respectively): pancreatitis 6 & 6, trauma 7 & 3, bowel obstruction 4 & 5. ICU participants (n). group 1: 8; S group 2: 10 APACHE II score (mean ± SD of participants in ICU). Group 1: 20.1 ± 9.1; Group 2: 18.6 ± 11.1 **Mechanical ventilation** (n). 8 participants in each group Baseline nutrition status No major differences between ideal and actual body weight in both groups Duration of parenteral nutrition (days; median (interquartile range)). group 1 6 (4 to 10); group 2 7 (5 to 10)
Interventions	**Group 1, low caloric parenteral nutrition (n = 20)** 1. 20 non-protein calories/kg ideal body weight/day **Group 2, standard parenteral nutrition (n = 20)** 1. 30 non protein calories/kg ideal body weight/day

Ahrens 2005 *(Continued)*

	In both groups, parenteral nutrition was administered by a multiple-bottle system. Lipids administration was standardized to 1000 kcal 3 times weekly. Proteins administered according the levels of estimated metabolic stress of the disease (mild 1.2 - 1.4; moderate 1.5 - 1.7; or severe 1.8 - 2.2 gr/kg/day)
Outcomes	**Primary outcomes** 1. Incidence and severity of **hyperglycaemia** and daily insulin requirements during parenteral nutrition Incidence of hyperglycaemia was calculated as the number of assessments of glycaemia ≥ 200 mg/dl divided by the total number of assessments Severity of hyperglycaemia was assessed by measuring the area under the curve **Secondary outcomes** 1. **Infectious complications** (new-onset infections according to established criteria) 2. Hospital charges (charges for hospital room, diagnostic services, medication, nursing services, direct expenses)
Funding sources	Not available
Declarations of interest	The authors have no financial interests to disclose
Notes	Total calories administered/kg (median (interquartile range)) were: 26.6 (26.2 to 27.5) and 37.0 (36.6 to 38.4); the amount of protein administered and the duration of PN therapy were similar. The first author sent the data of continuous outcomes expressed as mean and standard deviation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned by means of a computer-generated random-numbers
Allocation concealment (selection bias)	Low risk	Central allocation (pharmacist)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinicians were blinded to which caloric group participants were randomized to, with the exception of the critical care pharmacist who calculated the formula.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinicians were blinded to which caloric group participants were randomized to, with the exception of the critical care pharmacist who calculated the formula.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: outcome data were available for all participants.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No evidence of other bias

Arabi 2011

Methods	**Study design**: prospective, randomized controlled trial **Study dates:** April 2006 to January 2008 **Setting**: 1 tertiary care academic hospital **Country**: Saudi Arabia
Participants	**Inclusion criteria** 1. Participants aged 18 to 80 years, admitted to an ICU, blood glucose concentration of > 110 mg/dl, expected to remain in ICU ≥ 48 hours **Exclusion criteria** 1. Type 1 diabetes 2. Diabetic ketoacidosis 3. Hypoglycaemia 4. Brain death 5. Do-not-resuscitate status 6. Terminal illness 7. Pregnancy 8. Postcardiac arrest 9. Burns 10. Seizures within the past 6 months 11. Liver transplant 12. Readmission to the ICU within the same hospitalization 13. Enrollment in a competing trial 14. Oral feeding 15. Total parenteral nutrition **Sample size:** authors estimated a relative difference of 50% in ICU mortality between participants receiving .90% of caloric requirements and those receiving 60% to70% of caloric requirements (28% compared with 14%). Quote: "on the basis of an estimated 28-d mortality rate of 25%, a power of 0.8, and an α of 0.05, the number of subjects needed to show a reduction in mortality was 120 in each group." **Age (years**): intervention group: 50.3 ± 21.3; Control group: 51.9 ± 22.1 **Sex (male, %):** intervention group: 71.1; Control group: 65 **Primary disease of the participants** Intervention; Control group Admission category (n (%)) Nonoperative 95 (79.2); 103 (85.8) Postoperative 25 (20.8); 17 (14.2) Traumatic brain injury 35 (29.2); 31 (25.8) **Disease severity score**: APACHE II Intervention group: 25.2 ± 7.5; Control group: 25.3 ± 8.2 **Mechanical ventilation** n (%) Intervention group: 119 (99.2); Control group: 119 (99.2) **Comorbidities**: not available **Nutrition status:** intervention group; Control group: Not available **Level of inflammation**: not available
Interventions	**Intervention Group 1 (n = 120)**

Arabi 2011 *(Continued)*

	1. Permissive-underfeeding group: caloric goal 60% to 70% of caloric requirements **Control Group 2 (n = 120)** 1. Target-feeding group: 90% to 100% of caloric requirements Quote: "for both groups, caloric requirement was estimated by the dietitian using the Harris-Benedict equations and adjusting for stress factors. The selection of formula was left to discretion of the attending physician as long as it satisfied the total caloric intake criteria and was not enriched with immunonutrients. Calculation of caloric intake took into account intravenous dextrose and propofol infusions." Quote: "the patients were followed until discharge from the ICU, except if the patient tolerated oral feeding, had a do-not-resuscitate order written (after enrolment), or became brain dead (after enrolment). In the latter situations, the intervention was stopped but the outcome data were collected." **Co-interventions** Quote:"The protein requirement was calculated as 0.8–1.5 g/kg on the basis of patient condition and underlying diseases. To avoid protein malnutrition in the permissive underfeeding group, additional protein (Resource Beneprotein; Nestle Healthcare Nutrition Inc, Minneapolis, MN) was added to maintain the full protein requirement without affecting the assigned caloric intake."
Outcomes	**Primary outcome** 1. **28-day all-cause mortality** **Secondary outcomes** 1. 180-day mortality 2. **ICU mortality** 3. **Hospital mortality** 4. **ICU length of stay** 5. **Hospital length of stay** 6. **Mechanical ventilation duration** 7. **Hypoglycaemic episodes** 8. Packed red blood cell transfusion 9. Renal replacement therapy 10. Hypokalaemic episodes 11. **Health care–associated infections: bacteraemia, catheter-related bloodstream infection, urinary tract infection, ventilator-associated pneumonia, and skin and soft tissue** **How measured or definition and time point measured** 1. 28-day mortality: mortality rate at 28 days of ICU admission 2. 180-day all-cause mortality: mortality rate at 180 days of ICU admission 3. ICU mortality: mortality rate at ICU discharge 4. Hospital mortality: mortality rate at hospital discharge 5. Health care–associated infections:according to the National Nosocomial Infection Surveillance (NNIS) System (Emori 1991) 6. Hypoglycaemia: defined as a blood glucose concentration ≤ 2.2 mmol/L or 40 mg/dL 7. Hypokalaemia: defined as a potassium concentration < 2.8 mmol/L 8. Health care–associated infections: according to Nosocomial Infection Surveillance (NNIS) System **Subgroups** 1. Not available/not performed
Funding sources	Funded by King Abdulaziz City for Science and Technology (LG 10-30).

Arabi 2011 *(Continued)*

Declarations of interest	No potential conflict of interest relevant to this article was reported.
Notes	As it was a 2 x 2 factorial trial, the enrolled participants were randomly assigned by using concealed envelops to 1 of the 4 study groups: 1-permissive underfeeding with intensive insulin therapy (IIT), 2-permissive underfeeding with conventional insulin therapy (CIT), 3-target feeding with IIT, and 4-target feeding with CIT. We grouped 1 and 2; 3 and 4. Blood glucose concentration target was 4.4 – 6.1 mmol/L (80 – 110 mg/dL) in the IIT group and 10 – 11.1 mmol/L (180 – 200 mg/dL) in the CIT group. The frequency of blood glucose monitoring increased to every 20 mins when blood glucose concentrations decreased to > 3.2 mmol/L (58 mg/dL) and reduced to every 2 – 4 hrs when measurements were stable.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On the basis of (quote:) "computer-generated random permuted blocks"
Allocation concealment (selection bias)	Low risk	The enrolled participants were randomly assigned by using concealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded study. Details on healthcare processes to be followed by personnel (e.g. co-interventions) were not described in order to make an appropriate judgement on possible performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded but main and secondary outcomes well-defined. We judge that the outcome measurement was probably not influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: outcome data were available for all participants.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No evidence of other bias

Arabi 2015

Methods	**Study design**: prospective, randomized controlled trial **Study dates**: November 2009 to September 2014 **Setting**: 7 tertiary care centres **Country**: Saudi Arabia and Canada
Participants	**Inclusion criteria** 1. Age 18 to 80 years, admitted to ICU and starting enteral feeding within 48 hours of ICU admission; expected to remain in ICU ≥ 72 hours **Exclusion criteria** 1. Lack of commitment to ongoing life support

Arabi 2015 *(Continued)*

2. Brain death
3. A pre-existing condition with expected 6-month mortality > 50%
4. Post-cardiac arrest
5. Use of total parenteral nutrition
6. Previous enrolment in this study
7. Pregnancy
8. Liver transplantation
9. Burns
10. Receipt of high-dose vasopressors (norepinephrine > 0.4 µg/ kg/min, epinephrine > 0.4 µg/kg/min, dopamine > 20 µg/kg/min, phenylephrine > 300 µg/min, vasopressin > 0.04 unit/min, or 50% of these doses for participants who received 2 or more vasopressors)

Sample size

With 432 participants in each group; with an estimated 3% loss to follow-up, the final calculated sample size was 892 participants. Permissive underfeeding would be associated with an absolute risk reduction in mortality of 8 percentage points. Assuming an estimated 90-day mortality of 25% with standard feeding, they estimated that enrolment of 432 participants in each group would give the study 80% power.

Age (years): intervention group: 50.2 ± 19.5; Control group: 50.9 ± 19.4

Sex (male, %): intervention group: 65.2; Control group: 63.2

Primary disease of the participants Intervention; Control group

Medical no. (%) 336 (75.0); 335 (75.1)

Surgical no. (%) 19 (4.2); 12 (2.7)

Nonoperative trauma no. (%) 93 (20.8); 99 (22.2)

Severe sepsis at admission no. (%) 159 (35.5); 133 (29.8)

Traumatic brain injury no. (%) 55 (12.3); 63 (14.1)

Disease severity score: APACHE II

Intervention group: 21.0 ± 7.9; Control group: 21.0 ± 8.2

Mechanical ventilation no. (%)

Intervention group: 436 (97.3); Control group: 429 (96.2)

Comorbidities: not available

Nutrition status: intervention group; Control group

Albumin g/litre 28 ± 7; 28 ± 6

Prealbumin g/litre 0.15 ± 0.13; 0.14 ± 0.12

Transferrin g/litre 1.36 ± 0.49; 1.38 ± 0.50

24-hour urinary nitrogen excretion mmol 284 ± 176; 303 ± 219

Level of inflammation : not available

Interventions	**Intervention Group (n = 448)** 1. Permissive-underfeeding group: caloric goal 40% to 60% of caloric requirements **Control group (n = 446)**

Arabi 2015 *(Continued)*

1. Standard-feeding group: 70% to 100% of caloric requirements

For both groups, the calculation of caloric requirements was using the Penn State equation for mechanically-ventilated participants who had a BMI < 30 and using the 1992 Ireton-Jones equation for mechanically-ventilated participants who had a BMI of 30 or higher and for spontaneously-breathing participants. Protein requirements were calculated at 1.2 to1.5 g per kilogram of body weight a day, in accordance with clinical practice guidelines.

Co-interventions

Quote. "to ensure that enteral protein and volume delivery in the permissive-underfeeding group would be similar to those in the standard-feeding group, the permissive-underfeeding group received additional protein (Beneprotein, Nestlé Nutrition) and normal saline or water at a dose of 2 ml per kilogram every 4 hours unless otherwise specified by the clinical team. The assigned intervention was continued for up to 14 days or until ICU discharge, initiation of oral feeding, death, or withholding of nutrition as part of palliation."

The study protocol provided suggestions on the selection of enteral formulas on the basis of published guidelines; however, the decision was left to the clinical team. Study centres used their own insulin protocols, with a target blood glucose level of 4.4 to 10 mmol.

Outcomes

Primary outcome

1. 90-day all-cause mortality.

Secondary outcomes

1. **Mortality in the ICU**
2. **28-day mortality**
3. **In-hospital mortality**
4. 180-day mortality
5. Serial SOFA scores.

Tertiary outcomes

1. **Days free from mechanical ventilation**
2. **ICU-free days**
3. **Hospital length of stay**
4. **Hypoglycaemia**
5. Hypokalaemia
6. Hypomagnesaemia
7. Hypophosphataemia
8. Transfusions of packed red cells
9. **Infectious complications** (ICU-associated infections documented by the research co-ordinator according to published definitions)
10. **Non-infectious complications** (feeding intolerance: vomiting, abdominal distention, or a gastric residual volume of more than 200 ml and diarrhoea)

How measured or definition and time point measured

1. 90-day all-cause mortality: mortality rate at 90 days from ICU admission
2. ICU mortality: mortality rate at ICU discharge
3. 28-day mortality: mortality rate at 28 days from ICU admission
4. In-hospital mortality: mortality rate at hospital discharge
5. 180-day mortality: mortality rate at 180 days from ICU admission

Subgroups

1. Non-surgical admission /surgical admission
2. Diabetic/non-diabetic

Arabi 2015 *(Continued)*

3. APACHE II ≤ 18 /APACHE II > 18
4. Admitted with severe sepsis/admitted with no severe sepsis
5. Traumatic brain injury/no traumatic brain injury
6. Vasopressors/no vasopressors
7. Randomization blood glucose ≤ 9.2 mmol/L/ > 9.2 mmol/L

Funding sources	Funded by the King Abdullah International Medical Research Center
Declarations of interest	No potential conflict of interest relevant to this article was reported.
Notes	The total caloric intake included calories from propofol, intravenous dextrose and parenteral nutrition. The author provided additional information about mean and standard deviation values of length of hospital and ICU stay and of mechanical ventilation. In 2017, the researchers published a subgroup analysis using a Nutrition Risk In Critically ill (NUTRIC) score. However these subgroup analyses did not contribute to our review objectives.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomization list was computer-generated"
Allocation concealment (selection bias)	Low risk	Quote: "enrolled patients were randomly assigned to the permissive-underfeeding group or the standard-feeding group with the use of opaque, sealed, sequentially numbered envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	PermiT was a multicentre, pragmatic, open-label international randomized clinical trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was no blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: outcome data were available for 445/448 and 440/446 participants in the intervention and control group respectively.
Selective reporting (reporting bias)	Low risk	Authors reported all protocol outcomes.
Other bias	Low risk	No evidence of other bias

Battistella 1997

Methods	**Study design**: prospective, randomized controlled trial **Study dates**: September 1992 to July 1994 **Setting**: Trauma surgery service. University of California, Davis, Medical Center **Country**: USA

Battistella 1997 *(Continued)*

Participants	**Inclusion criteria** 1. Polytrauma participants,18 to 50 years old, requiring total parenteral nutrition at the 5th post-injury day **Exclusion criteria** 1. If able to tolerate > 10% of their caloric requirement as enteral feeding at the time of randomization 2. If clinical evidence of fatty acid deficiency, hepatic cirrhosis, HIV, malignancy 3. If receiving steroids or nonsteroidal anti-inflammatory agents. **Sample size**: 60 participants randomized, data analysed of 57 participants **Age** (years; mean ± SD). Group 1: 32 ± 9; Group 2: 33 ± 10 **Sex** (male, %). Group 1: 85%; Group 2: 80% Type of injury (blunt trauma %): Group 1: 85%; Group 2: 80% APACHE II score (mean ± SD). Group 1: 22 ± 5; Group 2: 23 ± 6 Injury severity score (mean ± SD). Group 1: 30 ± 9; Group 2: 27 ± 8 Nutrition status. On admission no participants weighted less than ideal body weight
Interventions	Participants randomized at the 5th post-injury day. 10 days study period with parenteral nutrition. **No lipid group (Group 1) (n = 27)** 1. Parenteral nutrition without lipid emulsion. Same formulation but without lipids during 10 days (no added calories to replace the fat calories), so the formulae were isonitrogenous but hypocaloric in relation to the control (lipid) group. **Lipid group (Group 2) (n = 30)** 1. Standard total parenteral nutrition: goal of 30 nonprotein kcal/kg ideal body weight/day (25% provided by lipids) and 1.5 grams amino acids/kg/day, during 10 days
Outcomes	1. **Length of ICU stay** 2. **Length of hospital stay** 3. **Length of mechanical ventilation** 4. **Infectious complications:** total infectious complications (pneumonia, line sepsis, wound infections, acalculous cholecystitis, intra-abdominal abscess, empyaema, bacteraemia) Outcomes evaluated after 10 days of parenteral nutrition **Other outcomes** 1. Clinical signs of fatty acid deficiency; immune function assays (T-cell function: lymphokine activated killer cell activity and natural killer cell activity; T-cell phenotype: CD_4/CD_8)
Funding sources	Study supported in part by National Institutes of Health Grant P30 DK-35747
Declarations of interest	Not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Battistella 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasonable explanation: quote: "Of the 60 patients enrolled, only 57 had data that could be analysed. One patient was ineligible for the study because he had been admitted for management of an entero-cutaneous fistula that had resulted as a complication of a remote trauma and two patients died before being randomized (before the fifth post injury day)".
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No evidence of other bias.

Charles 2014

Methods	**Study design**: prospective, randomized controlled trial **Study dates**: March 2008 to November 2011 **Setting**: Surgical/trauma ICU at a tertiary-care hospital. Department of Surgery, University of Virginia Health System. Charlottesville, Virginia **Country**: USA
Participants	**Inclusion criteria** 1. Age ≥ 18 years; projected need for nutrition support > 48 hrs and for ICU stay > 48 hrs according to the attending intensivist **Exclusion criteria** 1. Participants aged < 18 years, expected to die or ICU discharge within 48 hours, pregnancy and primary diagnosis of burn **Sample size**: From 2892 admissions to the ICU 83 participants were enrolled and randomized: 41 to the hypocaloric group and 42 to the eucaloric group (detailed flow diagram given of the randomization, exclusion and study end) **Age** (years; mean ± SD). Hypocaloric group 50.4 ± 2.8; Eucaloric group 53.4 ± 2.7 **Sex** (male, %). Group 1: 58.3; Group 2: 73.8 **Primary disease. Trauma admission** (%). Group 1: 68.3; Group 2: 59.5. The other participants in the surgical ICU were abdominal, vascular, orthopaedic and liver transplant surgery. **Disease severity, APACHE II score** (mean ± SD) Group 1: 16.6 ± 0.9; Group 2: 17.3 ± 0.8

Charles 2014 *(Continued)*

	Mechanical-ventilation dependence (%). Group 1: 68.3; Group 2: 57.1 **Comorbidities. Diabetes mellitus and coronary artery disease** (%). Group 1. 19.5 and 17.1 respectively; Group 2: 14.3 and 11.9 respectively **Nutrition status** BMI (kg/m^2, mean ± SD). Group 1: 32.9 ± 2.0; Group 2: 28.1 ± 0.9 Risk of refeeding syndrome at admission (due to weigh loss, poor caloric intake or alcohol abuse) (%). Group 1: 31.7; Group 2: 54.8 **Level of inflammation:** not available
Interventions	**Group 1 hypocaloric (n = 41)** 1. The hypocaloric target was 50% of the calculated daily caloric requirement: 12.5 to 15 kcal/kg actual weight/day **Group 2 eucaloric (n = 42)** 1. The goal was 100% of the calculated caloric requirements: 25 to 30 kcal/kg actual weight/day **Co-interventions**: the protein goal of the 2 groups was 1.5 grams protein/kg/day. If the participant's actual weight was > 130% of ideal weight, adjusted weight was used. Participants with severe malnutrition not able to receive enteral nutrition were considered for parenteral nutrition, all others received enteral nutrition. In cases of enteral feeding intolerance, parenteral nutrition was started after 5 to 7 days.
Outcomes	**Primary outcome** 1. Development of hospital-acquired **infectious complications**. The diagnosis of all the infections was done according to the criteria of US Centers for Disease Control and Prevention. **Secondary outcomes** 1. Glucose control during the study period: mean overall glucose values, mean morning glycaemia at 06.00 hours and mean daily insulin requirements 2. **Length of stay in ICU** 3. **Length of stay in hospital** 4. **Hospital mortality: all causes of in-hospital mortality** 5. The study protocol was followed during 10 to 12 days 6. The analysis of participants was done on an intention-to-treat basis **Subgroups** 1. The authors analysed but did not report subgroups of trauma and non-trauma participants, and men versus women
Funding sources	Supported by grant 5-T32-AI-078875-03 from the National Institute of Health, USA
Declarations of interest	The authors stated that "No conflicts of interest were reported"
Notes	Due to slow enrolment, the study was closed before the planned enrolment of 116 participants. Enteral nutrition was given initially. Participants were considered for parenteral nutrition if they were severely malnourished and could not receive enteral feeding, or in case of continuous intolerance of enteral nutrition lasting more than 5 to 7 days. The author provided additional information: mean and standard deviation of the length of mechanical ventilation and to complete the 'Risk of bias' table.
Risk of bias	

Charles 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated 1:1 by using a computer-based random number generator
Allocation concealment (selection bias)	Low risk	Quote: "investigators were blinded to the preparation of the randomization envelopes, and the randomization assignment was determined by opening sequential opaque security envelopes containing the randomization assignment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of participants or personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was blinded (written information provided by the author).
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: outcome data were available for all participants.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified.
Other bias	Low risk	No evidence of other bias

Choban 1997

Methods	**Study design**: prospective, randomized controlled trial **Study dates**: Not stated **Setting**: participants referred to the Nutrition Support Service of the Ohio State University Hospital. Departments of Surgery and Medical Dietetics. College of Medicine. Ohio State University. Columbus, Ohio **Country**: USA
Participants	**Inclusion criteria** 1. Participants weighing > 130% of ideal body weight (formula of Hamwi) and requiring PN. **Exclusion criteria** 1. Pre-existing renal disease 2. Hepatic disease 3. Adrenal disease 4. Receiving exogenous steroids 5. Minors, prisoners, pregnant women, mental or physical retardation **Sample size**: 30 participants, stratified according their hospitalization in ICU (n = 13) or regular floor (n = 17) (randomized with separate randomization tables) **Age** (years; mean ± SD; whole sample): Group 1: 52 ± 19; Group 2: 52 ± 15 **Sex** (male, %: whole sample): Group 1: 31.25; Group 2: 14.29

Choban 1997 *(Continued)*

	Primary disease of the participants, surgical diseases. 70% of the whole-sample diagnosis were cancer with or without enterocutaneous fistulae and pancreatic disease. **Nutrition status. Body weight/BMI** (kg and kg/m^2 respectively; mean ± SD; whole sample). Group 1: 97 ± 19 and 36 ± 5. Group 2: 90 ± 17 and 34 ± 6 **Comorbidities. Diabetes type 1 and 2** (n of ICU participants) Group 1: 2 and 1; Group 2: 2 and 2 **Disease severity score. APACHE II score at the time of enrolment** (mean ± SD of the ICU participants). Group 1: 13 ± 5; Group 2: 15 ± 5 **Level of inflammation** Initial urinary urea nitrogen (grams/24 hours; mean ± SD of the ICU participants). Group 1: 10.1 ± 9.0; Group 2: 10.0 ± 4.2 Duration of PN (days; mean ± SD). Group 1: 10 ± 3; Group 2: 12 ± 2
Interventions	**Group 1 hypocaloric PN** (whole sample n = 16; n of ICU participants = 6) has 50% of the carbohydrate and lipid compared with the standard PN. **Group 2 standard PN** (whole sample n = 14; n of ICU participants = 7) **Co-interventions**: both PN solutions were isonitrogenous, providing 2 grams of protein/kg ideal body weight/day, added with electrolytes, vitamins and trace elements, administered during ≤ 14 days or until they could receive enteral or oral feeding.
Outcomes	1. **Mortality at hospital (events)** 2. **Hospital length of stay (days; mean ± SD)** 3. Carbohydrate metabolic outcomes: glucose control (glycaemia and glycosuria) and insulin requirements (mean daily IU insulin dose ± SD) 4. Protein metabolic outcome:**overall nitrogen balance** (grams/day; mean ± SD) 5. Nutrition status: weigh (kg) and albumin change (gr/L) during hospital stay **Time points reported** 1. Results during the administration of PN **Subgroups** 1. The authors reported most of the results for the whole sample populations. Some results of both intervention groups were reported separately for the ICU and regular-care participants.
Funding sources	Supported by funds from the Bremer Foundation, Department of Surgery Medical Research Development Fund, and Surgical Research, Inc.
Declarations of interest	Not available
Notes	Both groups of participants in ICU had moderate severity of diseases by APACHE II scores, the initial urinary urea nitrogen and the mortality rate (15%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were then randomly assigned to receive either the control parenteral nutrition (PN) formula or the hypoenergetic PN formula by using separate randomization tables by the investigational pharmacist in the research pharmacy of the hospital.

Choban 1997 *(Continued)*

Allocation concealment (selection bias)	Low risk	Participants randomly assigned to receive either the control PN formula or the hypoenergetic PN formula by using separate randomization tables (ICU or regular floor) by the research pharmacist of the hospital (Central allocation)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All care providers as well as participants were blinded to the nutrient composition of the parenteral formulas.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded. All care providers as well as participants were blinded to the nutrient composition of the parenteral formulas.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: outcome data were available for all participants.
Selective reporting (reporting bias)	Low risk	Not clearly described research outcomes, although: (quote:) "this study was designed to determine whether a restricted energy parenteral formulation providing 2 gr protein/kg ideal body weight could be administered to acutely ill obese participants with the same degree of efficacy as a standard parenteral nutrition solution provided to a comparable group of patients". Participants located in the intensive care unit and those with diabetes mellitus were included in the study population to determine the efficacy of this treatment in critically-ill participants and to assess the effect on glycaemic control in obese diabetic participants. Results were reported regarding this description and more detailed measurement methods described in the appropriate section.
Other bias	Unclear risk	Not clear if any bias could have been introduced by some of the funders

Ibrahim 2002

Methods	**Study design**: prospective, randomized controlled trial **Study dates:** May 1999 to December 2000 **Setting**: Medical ICU, Barnes-Jewish Hospital, affiliated to Washington University School of Medicine. St. Louis, Missouri **Country**: USA.
Participants	**Inclusion criteria** 1. ICU participants > 18 years, expected to require mechanical ventilation for > 24 hrs **Exclusion criteria** 1. Transferred to the medical ICU for lack of beds in the other hospital ICUs 2. Expected to die or extubated within 24 hours of ICU admission 3. With prior mechanical ventilation during the same hospitalization 4. With contraindication of enteral feeding (e.g. pancreatitis, short gut, malabsorption) 5. Classified as malnourished at hospital admission 6. With enteral or parenteral nutrition prior to admission to the medical ICU 7. Different strategy of nutrition support according to the prescription of the attending physician 8. Refusal to give informed consent to participate in the study 9. Without tolerance of the placement of oral or naso-gastric tube (e.g. severe coagulopathy, oesophageal varices)

Ibrahim 2002 *(Continued)*

Sample size

189 consecutive participants were evaluated for enrolment, with 39 not included for different reasons, and 150 finally included and analysed. 75 participants were randomized to each study group. The estimated sample size for a significant reduction of the incidence of pneumonia (primary outcome) was 82 participants in each study group.

Age (years, mean ± SD). Group 1: 59.1 ± 19.0; Group 2: 56.5 ± 15.6

Sex (% of male). Group 1: 46.7; Group 2: 37.3

Primary reason for ICU admission. Respiratory diseases (%). Group 1: 58.7; Group 2: 64.0

Disease severity: APACHE II score. Group 1: 25.6 ± 8.3; Group 2: 24.7 ± 8.4

P_aO_2/FiO_2 (mean ± SD). Group 1: 204 ± 108; Group 2: 207 ± 126

Predicted mortality based on APACHE II score (%, mean ± SD). Group 1: 48.7 ± 24.9; Group 2: 49.6 ± 23.9

Process of care variables: with 2 exceptions, all of them had statistically non-significant differences between the study groups: Duration of enteral nutrition and of mechanical ventilation (days, mean ± SD respectively). Group 1: 5.2 ± 5.9 and 8.1 ± 7.4; Group 2: 9.9 ± 12.3 and 12.9 ± 15.7 respectively.

Comorbidities, nutrition status and level of inflammation: not reported

Interventions

Group 1 late feeding-hypocaloric (n = 75)

1. Participants scheduled to receive 20% of their estimated daily requirements for the first 4 days of mechanical ventilation (to prevent atrophy of the intestinal mucosa) and full requirements beginning at day 5 of mechanical ventilation.

Group 2 early feeding-normocaloric (n = 75)

1. Participants scheduled to receive their estimated total daily enteral nutrition requirements starting on day 1 of mechanical ventilation.

Co-interventions

The goal for enteral nutrition daily requirements were defined as 25 kcal/kg ideal body weight/day and 1 to 1.3 grams of protein/kg ideal body weight/day. The enteral nutrition, with a polymeric iso-osmolar formula, was administered in the stomach by bolus feeding, through an orogastric tube inserted on day 1 of mechanical ventilation. In case of 3 consecutive gastric residual volumes > 150 ml, a post-pyloric enteral tube was inserted for continuous drop enteral nutrition.

Outcomes

Primary outcome

1. Occurrence of **ventilator-associated pneumonia**. Diagnosis of pneumonia done by one of the investigators blinded to the group assignment, based on predetermined and well-defined clinical diagnostic criteria of pneumonia; they also registered several described potential risk factors for the development of ventilator-associated pneumonia.

Secondary outcomes

1. **Hospital mortality**
2. **Length of stay in ICU**
3. **Length of stay in hospital**
4. **Length of mechanical ventilation**
5. **Diarrhoea associated with clostridium difficile infection** (rectal swab for culture of the clostridium difficile)
6. 6. Need for a gastrostomy tube
7. Total number of antibiotic days in the ICU

Ibrahim 2002 *(Continued)*

	How measured or defined 1. The authors defined most of the study items. **Time of measurements** 1. During the first 5 days of mechanical ventilation **Subgroups** 1. No subgroups were analysed in the study.
Funding sources	Supported in part by a grant from the Barnes-Jewish-Christian Health Care Innovations Program
Declarations of interest	Information not available
Notes	The total calories and protein received by the participants showed a statistically significant difference between the study groups, but participants in each group only received a percentage of the defined goals during the first 5 days of mechanical ventilation: in the hypocaloric group the participants received 7% of their estimated caloric requirements and 7.7% of the estimated protein requirements, and in the control group they received 27.9% and 26.9% respectively.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The study allocated participants to treatment groups based on the date of their ICU admission using a quasi-randomized design (odd/even-numbered days).
Allocation concealment (selection bias)	High risk	The study allocated participants to treatment groups based on the date of their ICU admission using a quasi-randomized design.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded study. Details on healthcare processes to be followed by personnel (e.g. co-interventions) were not described in order to make an appropriate judgement on possible performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded but main and secondary outcomes well-defined. We judge that the outcome measurement was probably not influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: outcome data were available for all participants.
Selective reporting (reporting bias)	High risk	Some prespecified secondary outcomes (duration of mechanical ventilation, need for gastrostomy tube) not reported
Other bias	Low risk	No evidence of other bias

McCowen 2000

Methods	**Study design**: prospective, randomized, controlled non-blinded trial **Study dates**: Not stated

McCowen 2000 *(Continued)*

	Setting: single-centre, university-affiliated teaching hospital with a dedicated total parenteral nutrition (TPN) service. Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts **Country**: USA
Participants	**Inclusion criteria** 1. Sequential participants requiring TPN according to standard hospital criteria **Exclusion criteria** 1. Severely underweight (< 50 kg) 2. Home TPN 3. Malnutrition requiring specific pre-operative TPN 4. Reinstitution of TPN for a setback of the current illness **Sample size** 48 participants were initially included, but 4 in each group were excluded from the analysis because of PN duration ≤ 4 days, leaving 21 participants in the hypocaloric group and 19 in the control group **Age** (years; mean ± SD). Group 1 hypocaloric: 57.5 ± 14.9; Group 2 control: 56.6 ± 20.4 **Sex (% male)**: Group 1: 57; Group: 53 **Primary disease of the participants**. Mainly surgical participants with different types of complications. Major differences between groups: Group 1 acute pancreatitis and bowel surgery/postoperative ileus: n = 6 and 3 participants respectively; Group 2 n = 1 and 6 respectively. **Mechanically-ventilated participants** (n). Hypocaloric group: 11; Control group: 6 **Comorbidities. Diabetes** (n). Group 1: 5 participants; Group 2: 2 participants. Obesity: 4 participants in each group **Nutrition status.** BMI (mean ± SD). Group 1: 27.6 ± 8.1; Group 2: 25.7 ± 6.2
Interventions	**Group 1 hypocaloric (n = 21)** 1. Administration of 1 litre of fat-free TPN, providing 70 grams protein, 210 grams of dextrose and ˜ 1000 kcal when maximally concentrated **Group 2 control (n = 19)** 1. Standard TPN regimen with a maximum of 25 total kcal/kg actual weight/day (adjusted weight in obese participants). Goal of 20 to 25 kcal/kg/day with 1.5 gr protein/kg/day. Fat could account for up to ⅓ of the calories. **Co-interventions** 1. After 10 days the participants were removed from the experimental protocol and fed in the traditional manner.
Outcomes	1. Reduction of **hyperglycaemia**: frequency rate of glycaemia > 220 mg/d (measured by fingerstick and confirmed in the laboratory), average capillary glycaemia during the TPN administration 2. Incidence of **in-hospital infections**: pneumonia, venous catheter infection, wound infection, abdominal collection/abscess. Infection diagnoses were done by well-defined common clinical objective methods 3. **Nitrogen balance** at day 5 of TPN (difference of measured 24-hr urinary urea nitrogen plus 4 gr/day and TPN nitrogen) **Time points of measurements**

McCowen 2000 *(Continued)*

1. The outcomes were evaluated during the time of TPN.
2. Nitrogen balance was measured in only 12 participants (57%) in the hypocaloric and 10 (53%) of the control group, usually because of an error during collection.

Funding sources	Not available
Declarations of interest	Not available
Notes	Due to a protocol violation, fat was given to 1 participant in the hypocaloric group. Some results associated with hospital rules to avoid iatrogenic hyperglycaemia by gradual increase of nutrients to avoid complications.The hypocaloric group also received less protein than the control group. More participants in the hypocaloric group had acute pancreatitis and mechanical ventilatory support than in the control group. The hypocaloric group received 14 ± 3 kcal/kg/day and the control group 18 ± 4 kcal/kg/day (also hypocaloric). The hypocaloric group not only received significantly fewer calories than the control group (due to fewer dextrose and fat calories), but also less protein (1.1 ± 0.2 versus 1.3 ± 0.2 in the control group). If the infection rate trend observed were to persist, they calculated the study would have required ˜174 participants to see a statistical difference between the 2 groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding: the standard group received parenteral nutrition as 3-in-1 bags, and the hypocaloric group received 1 litre of fat-free parenteral nutrition. Outcomes could have been influenced by different performance of clinical personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding and not clearly-defined and objective outcomes that would warrant a low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants in each group were excluded from the data analysis because of a TPN duration of ≤ 4 days (not prespecified exclusion criteria).
Selective reporting (reporting bias)	High risk	Nitrogen balance was only measured in 12 participants (57%) in the hypocaloric and 10 (53%) of the control group, usually because of an error during collection.
Other bias	Unclear risk	The lack of detail in the description of the Methods section could not warrant a low risk of other sources of bias.

NHLBI 2012

Methods	**Study design**: prospective, randomized controlled trial **Study dates**: January 2008 to April 2011 **Setting**: 44 ICUs of the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network **Country**: USA
Participants	**Inclusion criteria** 1. participants within 48 hours of Acute Lung Injury onset who had received mechanical ventilation < 72 hours and indication for enteral nutrition **Exclusion criteria** 1. Chronic lung disease 2. Unable to provide consent 3. Outside acute lung injury time window 4. Outside mechanical ventilation time window 5. Fatal underlying disease 6. Severe liver disease 7. Moribund 8. Refractory shock 9. Physician refusal 10.Intracranial haemorrhage 11.Total parenteral nutrition 12.Not committed to full support 13.Refused consent 14.Severe neuromuscular disease 15.Severe malnutrition 16.Other **Sample size** 500 participants for each arm, to detect a 2¼-day difference in ventilator-free days (VFDs), assuming a mean of 14 ± 10.5 VFDs. power: 91% α: 0.05 **Age (years)**: intervention group: 52 ± 17; Control group: 52 ± 16 **Sex (male, %)**: intervention group: 53; Control group: 49 **Primary disease of the participants** Diagnosis:% intervention group/% control group Medical ICU: 61; 63 Primary lung injury category % intervention group/control group Pneumonia 67; 63 Sepsis 16; 13 Aspiration 8; 11 Trauma 3; 4 Transfusion 1; 2 **Disease severity score:** APACHE III Intervention group: 92 ± 28; Control group: 90 ± 27

NHLBI 2012 *(Continued)*

	Mechanical ventilation 100% in each group (inclusion criterion) **Comorbidities**: % intervention group; % control group Diabetes: 27; 29 No other data available **Nutrition status**: not available **Level of inflammation**: not available
Interventions	**Intervention (trophic) Group 1 (n = 508)** 1. Initial feeding at 10 ml/hr (10 to 20 kcal/hr for the first 272 participants who also received the omega-3 or control supplement (240 ml volume a day) 2. After the Data and Safety Monitoring Board stopped the OMEGA portion of the factorial design, the initial trophic feeding rate was changed to 20 kcal/hr to approximate the calories that had been delivered in the OMEGA study 3. Enteral nutrition was advanced to full-energy feeding rates following the same protocol used for the full-feeding group if they were still receiving mechanical ventilation at 144 hrs **Control Group 2 (n = 492)** 1. Enteral nutrition was initiated at 25 mL/hr and advanced to goal rates as quickly as possible 2. Full feeding rates were calculated with goals of 25 to 30 kcal/kg a day of nonprotein calories and 1.2 to 1.6 g/kg a day of protein **Co-interventions** 1. Both feeding strategies specified when and for how long to hold enteral nutrition for GRVs greater than 400 mL and for other gastrointestinal intolerances. As in usual ICU practice, participants were maintained in the semirecumbent position whenever possible. 2. Blood glucose control was accomplished using institution-specific insulin protocols targeting ranges of 80 to 150 mg/dL (to convert to mmol/L, multiply by 0.0555), with tighter control allowed.
Outcomes	**Primary outcome** 1. **Ventilator-free days (VFDs) through day 28** **Secondary outcomes** 1. Failure-free days: cardiovascular, renal, hepatic, coagulation 2. **ICU-free days** 3. 60-day mortality 4. **Development of infections:** ventilator-associated pneumonia, clostridium difficile colitis, bacteraemia **How measured or definition** 1. VFDs: defined as the number of days from the time of initiating UAB to day 28 after randomization 2. ICU-free days: calculated similarly to VFDs 3. 60-day mortality: mortality rate at 60 days **Subgroups** 1. Not available
Funding sources	Supported by National Heart, Lung, and Blood Institute (NHLBI) contracts HHSN268200536165C and HHSN268200536179C
Declarations of interest	Authors have not disclosed any potential conflicts of interest.

NHLBI 2012 *(Continued)*

Notes	The initial 272 participants were also simultaneously randomized to a separate trial (the OMEGA study) comparing a nutritional supplement containing omega-3 fatty acids and antioxidants with an isocaloric, isovolemic control in a 2 x 2 factorial design. After the Data and Safety Monitoring Board stopped the OMEGA portion of the factorial design, participants randomized to the initial trophic-feeding group received additional calories to compensate for the calories that had been received in the OMEGA study (240 ml volume a day). We asked the first author for some data not reported in the manuscript or reported differently. He gave us the data we used in the meta-analysis for the following outcomes: 28-day mortality, length of ICU stay (days from randomization to first ICU discharge); length of mechanical ventilation (ventilator days up to day 28); hyperglycaemia (participants with any on-study glucose > 200 mg/dl); incidence of total infectious complications and of diarrhoea, and the amount of calories received by both groups of participants. The author also informed they did not have duplicate participants with the Rice 2011 study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized by a web-based randomization system, stratified by site and presence of shock at enrolment, to receive either trophic or full enteral feeding for the first 6 days of mechanical ventilation.
Allocation concealment (selection bias)	Low risk	Participants were randomized by a web-based randomization system, stratified by site and presence of shock at enrolment, to receive either trophic or full enteral feeding for the first 6 days of mechanical ventilation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded study. Details on healthcare processes to be followed by personnel (e.g. co-interventions) were not described in order to make an appropriate judgement on possible performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was not blinded but most outcomes were objective.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant lost, from the control group. All analyses were by intention-to-treat.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported. All analyses were by intention-to-treat.
Other bias	Low risk	No evidence of other bias

Norouzy 2013

Methods	**Study design**: single-centre double-blind, randomized controlled trial **Study dates**: Not stated **Setting**: Nutrition and neurosurgery departments. Mashad University of Medical Sciences. Mashad **Country**: Islamic Republic of Iran
Participants	**Inclusion criteria** 1. Adults head trauma participants admitted to the ICU

Norouzy 2013 *(Continued)*

	Exclusion criteria 1. Not reported **Sample size** 60 participants randomized **Age**: not reported **Sex**: not reported **Primary disease**: head trauma **Disease severity:** not reported **Mechanical ventilatio**n: number of participants not reported **Comorbidities**: not reported **Nutrition status**: not reported **Level of inflammation**: not reported
Interventions	**Group 1 permissive underfeeding (n = not reported)** 1. Initial caloric goal of 30% to 50% of calculated requirements (not defined) **Group 2 standard full calorie (n = not reported)** 1. Initial caloric goal of 90% to 100% of calculated requirements (not defined) All participants received enteral nutrition
Outcomes	**Primary outcome** 1. **28 day all-cause mortality.** **Secondary outcomes** 1. **Hyperglycaemia** 2. **Length of hospital stay** 3. **Duration of mechanical ventilation** 4. **Gastro intestinal intolerance** 5. **Diarrhoea** 6. Liver enzymes No information about measures or definition of the outcomes The participants in the permissive-underfeeding group received full enteral feeding after the 7th day of the study. No subgroups reported
Funding sources	Not available
Declarations of interest	None declared
Notes	Available only in abstract form. Poster presentation in the 35th ESPEN Congress (Leipzig, Germany, August 2013)
Risk of bias	

Norouzy 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only mentioned in the abstract (quote:) "head trauma randomly assigned to a double-blind randomized controlled clinical trial"
Allocation concealment (selection bias)	Unclear risk	Same as above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mentioned that was double-blind, but did not report the methodology
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mentioned that was double-blind, but did not report the methodology
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned in the abstract
Selective reporting (reporting bias)	Unclear risk	Not mentioned in the abstract
Other bias	Unclear risk	Insuficient information to make judgement (abstract only)

Petros 2016

Methods	**Study design**: prospective, randomized controlled trial **Study dates**: July 2008 to December 2010 **Setting**: 1 tertiary medical ICU **Country:** Germany
Participants	**Inclusion criteria** 1. Participants with presumed need for artificial nutrition support for at least 3 days and informed consent **Exclusion criteria** 1. Pre-existent malnutrition (BMI < 18.5 kg/m^2) 2. Age < 18 years or > 80 years 3. Pregnancy 4. Active malignant disease 5. Current immunosuppressive therapy 6. Readmission to the ICU liver transplantation 7. Do-not-resuscitate decision 8. Refusal of study inclusion by the participant or the guardian, or consent given too late for study inclusion **Sample size:** not available **Age (years):** intervention group: 67.6 ± 11.5; Control group: 64.3 ± 11.5

Petros 2016 *(Continued)*

Sex (male, %): intervention group: 70; Control group: 63

Primary disease of the participants

Diagnosis: % intervention group; % control group

Sepsis: 25; 28

Acute cardiovascular dysfunction: 30; 46

Acute respiratory insufficiency: 22; 33

Other: 9; 11

Disease severity score: APACHE II

Intervention group: 28.6 ± 6.5; Control group: 27.7 ± 8.4

Mechanical ventilation: not available

Comorbidities: % intervention group; % control group

Underlying chronic disease:

None: 26; 43

Diabetes mellitus: 33; 20

Respiratory: 31; 22

Cardiovascular: 19; 20

Neuropsychiatric: 0; 20

Other: 9; 13

Nutrition status: not available

Level of inflammation: not available

Interventions	**Intervention group 1 (n = 54)** 1. Hypocaloric group: 50% of daily energy expenditure during the 1st week of ICU admission **Control group 2 (n = 46)** 1. Normocaloric group: 100% of daily energy expenditure For both groups, energy expenditure was measured with an indirect calorimeter (Deltatrac II, Datex Ohmeda, Helsinki, Finland). If this was not possible, the Ireton-Jones prediction equation was used. **Co-interventions** Quote: "artificial nutrition support was started within 24 hours of ICU admission. Enteral feeding was favoured in every case if there was no sign of gastrointestinal intolerance (defined as gastric aspirate > 300 mL/d) and/or diarrhoea. Diarrhoea was defined as at least 3 watery bowel movements per day or continuous watery stool. In case of enteral feeding, the target energy supply was to be achieved on day 3 at the latest. A commercially available standard solution with a caloric concentration of 1 kcal/mL was used in every case. If at least 70% of the target caloric supply was considered not to be achieved on day 3 via the enteral route based on gastrointestinal tolerance and the consensus of the managing physicians together with members of the trial group, participants received supplementary parenteral nutrition. The expected deficit was calculated everyday during the morning hours by one of the study authors and supplementary PN prescribed as required. If enteral nutrition (EN) was to be interrupted for unforeseen reasons during the course of the day (diagnostic or therapeutic procedures), adjustment of the supply rate was carried out depending on clinical judgment as to whether an increased rate would be tolerated by the participant. In such cases, possible caloric deficits were not compensated

Petros 2016 *(Continued)*

	with PN. Causes of the feeding interruptions were recorded if the interruption lasted at least an hour. The blood glucose level was monitored every 3 hours. The insulin dose was adjusted to a target blood glucose level of 6–8 mmol/L."
Outcomes	**Primary end point** 1. **Rate of nosocomial infections during the ICU stay** **Secondary end points** 1. Insulin demand 2. **ICU mortality rate** 3. **Hospital mortality rate** 4. **28-day mortality rate**
Funding sources	None declared
Declarations of interest	None declared
Notes	Study originally published as a congress abstract with few results. The first author answered several questions, so some of the results originally included in the review came from the information provided by him. During the editorial process the study was published (Petros 2016). All the published data were the same as the first author had originally reported to us.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Electronic randomization list
Allocation concealment (selection bias)	Low risk	Quote: "yes, the allocation was concealed. The electronic randomization was managed by coauthors not directly involved in the management of the patients" (written information provided by the author)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was single-blinded (participants were blinded, the ICU personnel were not). Details on healthcare processes to be followed by personnel (e.g. co-interventions) were not described in order to make an appropriate judgement on possible performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was not blinded but outcomes were objective (written information provided by the author).
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: outcome data were available for all participants (written information provided by the author)
Selective reporting (reporting bias)	Low risk	All outcome assessed were reported (written information provided by the author).
Other bias	Low risk	No evidence of other bias

Rice 2011

Methods	**Study design**: prospective, randomized controlled trial

Rice 2011 *(Continued)*

Study dates: August 2003 to July 2009

Setting: 2 ICUs at a single academic centre

Country: USA

Participants

Inclusion criteria

1. Participants expected to require mechanical ventilation ≥ 72 hrs and indication for enteral nutrition

Exclusion criteria

1. > 48 hours elapsed since inclusion criteria met
2. Participant, legal representative, or physician refuses consent or is unavailable to provide consent
3. Participant, legal representative, or physician not committed to full support
4. Presence of malignant or irreversible condition and estimated 28-day mortality > 50%
5. Severe or refractory shock
6. Chronic respiratory disease that requires home oxygen or results in severe exercise restriction
7. Moribund participants not expected to survive 24 hours from start of enteral nutrition (as decided by primary medical team)
8. Child-Pugh score > 9
9. Presence of partial or complete mechanical bowel obstruction, or ischaemia, or infarction
10. Current parenteral nutrition use or intention to use within 7 days
11. Severe malnutrition with BMI < 18.5 and/or loss of > 30% total body weight in the previous 6 months
12. Neuromuscular disease impairing the ability to ventilate spontaneously
13. Laparotomy expected within 7 days
14. Unable to raise head of bed 45 °
15. > 30% total body surface area burns
16. Absence of GI tract/short-bowel syndrome (defined as entire length of small bowel totaling 4 feet or less)
17. Presence of high-output (> 500 cc/day) enterocutaneous fistula
18. Age < 13 years
19. Allergy to enteral formula

Sample size

94 participants were randomized in each arm. An independent sample *t* test, designed to demonstrate a 15% relative increase of 3.0 VFDs with 80% power and a 2-sided P value of 0.05. The study enrolled 200 to allow for a 5% withdrawal rate and compensate for the single interim analysis.

Age (years): intervention group: 53 ± 19; Control group: 53 ± 19

Sex (male, %): intervention group: 39.8; Control group: 46.1

Primary disease of the participants: 100% medical diagnosis

Acute lung injury: 21; 20

Pneumonia: 15; 19

Altered mental status/neurologic: 14; 15

Sepsis: 10; 12

Overdose: 10; 7

Disease severity score: APACHE II

Intervention group: 26.9 ± 8.1; Control group: 26.9 ± 6.6

Mechanical ventilation 100% in each group (inclusion criteria)

Rice 2011 *(Continued)*

	Comorbidities: % intervention group/ % control group Hypertension 42; 37 Cardiac disease 24; 23 Diabetes 22; 23 Chronic renal insufficiency 18; 12 Chronic obstructive pulmonary disease 16; 18 Immunosuppression 14; 16 Peptic ulcer disease 4; 4 Gastroesophageal reflux 4; 4 **Nutrition status:** not available Albumin concentration (g/dL) 2.8± 0.6; 2.8± 0.7 **Level of inflammation:** not available
Interventions	**Group 1 (n = 98): trophic group** 1. Initial feeding at 10ml/hr; the same feeding rate for 6 days. In participants still ventilated after 6 days, enteral nutrition was advanced to full-energy target feeding rates using the same protocol as for the full-energy feeding group. Most participants received a commercially-available standard formula containing 1 to 1.2 kcal/cm^3. **Group 2 (n = 102): control group** 1. Full feeding rate targeting 25 to 30 kcal/kg ideal body weight/day of non-protein energy and 1.2 to 1.6 g/kg ideal body weight/day of protein. Most participants received a commercially-available standard formula containing 1 to 1.2 kcal/cm^3. Initial feeding at 25 ml/hr; feeding rate increased by 25 ml/hr every 6 hrs until full-energy feeding rate was reached. **Co-interventions** For both groups, in participants who were extubated and then required re-intubation, enteral nutrition was started and managed according to the study protocol through study day 28. Elevated gastric residual volumes (GRV) were defined as > 300 cc of gastric contents withdrawn from the gastric tube at one time. GRVs were checked every 6 hours while feeding rates were being increased to full-energy rates and every 12 hours if the participant was receiving trophic rates or once full-energy rate was achieved. Gastric residuals were only measured in participants with post-pyloric feeding tubes if a separate gastric port on the feeding tube or separate gastric tube was in place. Since a single, isolated elevated GRV has been shown to be a poor predictor of enteral nutrition intolerance, feeding rates were not adjusted after a single elevated GRV. After the first episode of elevated GRV, 300 cc was replaced and the feeding rate was maintained. GRV was rechecked in 2 hours. If this recheck was also above 300 cc, feeds were held until GRV decreased below 300 cc and restarted at a rate of 25 cc/hr < the previous rate in the full-energy group and at 10 cc/hr in the trophic group.
Outcomes	1. **Length of mechanical ventilation** 2. Ventilator-free days (VFDs) **How measured or definition** 1. Defined as the number of days from the time of initiating UAB to day 28 after randomization, assuming survival for at least 48 consecutive hours of UAB **Time points measured and time points reported**

Rice 2011 *(Continued)*

1. If a participant survived for > 48 hours after UAB, but required assisted breathing again (for any reason) before day 28, only the number of days of UAB prior to day 28 were included. Participants who died prior to the earlier of 28 days or hospital discharge were counted as having zero VFDs, regardless of whether or not they ever achieved UAB
2. **Length of stay (ICU):** ICU-free days: calculated similarly to VFDs
3. **Hospital mortality:** hospital mortality: mortality rate at hospital discharge

Subgroups

1. Subgroup: acute lung injury, sepsis, or pneumonia
2. Subgroup: BMI of ≥ 35

Funding sources	Supported, in part, by grants K23HL81431(TWR), P30DK058404 (TWR), and 1 UL1 RR024975 (TWR, GRB) from the National Institutes of Health (Bethesda, MD)
Declarations of interest	Dr Rice, Dr Bernard, and Dr Wheeler received funding from the National Institutes of Health. The remaining authors have not disclosed any potential conflicts of interest.
Notes	Variables were assessed by intention-to-treat analyses. Upon our request, the data for the following outcomes was provided by the first author: hospital and 28-day mortality, length of mechanical ventilation, length of ICU stay and incidence of infectious complications. None of the participants included in this study was included in NHLBI 2012.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block scheme with a random block size of 2, 4 or 6 participants.
Allocation concealment (selection bias)	Low risk	Assignments were placed in consecutively-numbered, opaque envelopes that were sealed before the start of the study by personnel not associated with the trial.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded study. Details on healthcare processes to be followed by personnel (e.g. co-interventions) were not described in order to make an appropriate judgement on possible performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label study but most outcomes were objective. The number of ventilator-free days to study day 28 was the primary efficacy measure. Secondary end points included 28-day and hospital all-cause mortality, organ-failure-free days, ICU-free days, and hospital-free days to study day 28. Only gastrointestinal intolerance and infections are more subjective.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants had complete follow-up to death or hospital discharge.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No evidence of other bias

Rugeles 2013

Methods	**Study design:** prospective, randomized controlled trial

Rugeles 2013 *(Continued)*

	Study dates: August 2011 to July 2012 **Setting**: 30-bed ICU of a tertiary-level university hospital **Country**: Colombia
Participants	**Inclusion criteria** 1. Age ≥18 years 2. Admission to an ICU 3. Expected to require EN through nasoenteric tube for at least 96 hours **Exclusion criteria** 1. Participants with previous nutritional support in the same hospitalization 2. Participants with concomitant parenteral nutrition 3. Participants in transplantation programme 4. Pregnancy 5. Chronic renal failure 6. Uraemic encephalopathy 7. Diabetes 8. Morbid obesity 9. Do-not-resuscitate orders **Sample size** 80 participants: 40 participants in each group to detect an absolute difference in the SOFA score between the 2 measurements of 15% (8.0 expected total score and 1.2 for expected delta SOFA) and a SD between the difference of the means of 3.0. 80% power α error of 0.05 **Age (years):** intervention group: 53.3 (19.5); Control group: 55.7 (19.5) **Sex (male, %)**: intervention group: 55; Control group: 60 **Primary disease of the participants** Reasons for admission- Intervention/Control group n (%) Respiratory disease 16 (40); 14 (35) CNS disorder 13 (33); 12 (30) Cardiac disease 2 (5); 4 (10) Gastrointestinal disease 0 (0); 3 (8) Other 9 (23); 7 (18) **Disease severity score:** APACHE II Intervention group: 13.9 ± 4.8; Control group: 15.1 ± 6.2 **Mechanical ventilation** no. (%) Not available **Comorbidities:** not available **Nutrition status:** not available **Level of inflammation**: not available
Interventions	**Intervention Group 1 (n = 40)** 1. Hypocaloric group: 15 kcal/kg/day, with more than 1.5 g of protein per kg of body weight

Rugeles 2013 *(Continued)*

	Control Group 2 (n = 40) 1. Control group: received standard nutritional regimen with a goal of 25 kcal/kg/day **Co-interventions** "for both groups, it was used an enteral formula in continuous feeding. To reach the protein goal, the study group regimen was enriched with additional protein modules, based on soy protein diluted in water and administered in two daily boluses. Participants in the study group received hyperproteic regimen until day 7, if they needed any further enteral nutrition they were switched to standard nutritional regimen with a goal of 25 kcal/kg/day without protein boluses."
Outcomes	**Primary outcome** 1. Delta SOFA at 48 hours **Secondary outcomes** 1. SOFA score at baseline 2. SOFA score at 48 hours 3. SOFA score at 96 hours 4. Participants achieving a delta SOFA of 2 or more 5. Insulin requirements 6. **Hyperglycaemic events per day** 7. **ICU length of stay, days** 8. **Ventilator requirement (days)** **Subgroups** Not available
Funding sources	This research was supported by an unrestricted grant from Lafrancol Colombia.
Declarations of interest	No potential conflict of interest relevant to this article was reported.
Notes	The first author sent us the final manuscript of the study before publication, and answered our questions about the average time of the participants on enteral nutrition, the standard deviation of the calories and proteins received by both groups, why they did not report mortality and the way they gave the protein supplements to achieve the double blinding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using dark sealed envelopes with computer-generated random allocations.
Allocation concealment (selection bias)	Low risk	Randomization was performed using dark sealed envelopes with computer-generated random allocations.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind clinical trial. Although one of the investigators was not blind: (quote:) "only one of the members of the team (JDR) knew patient allocation, prescribed the formulations, and supervised the administration of the regimens; but ICU staff, who decided on daily care patient, was blind to patient allocation". The authors, upon request, gave further explanations about how there was low risk of blinding being broken.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind clinical trial. Although one of the investigators was not blind (quote:) "only one of the members of the team (JDR) knew patient allocation, prescribed the formulations, and supervised the administration of the regi-

Rugeles 2013 *(Continued)*

		mens; but ICU staff, who decided on daily care patient, was blind to patient allocation". The authors, upon request, gave further explanations about how there was low risk of blinding being broken.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "only patients who completed 96 hours of follow-up were considered for the analysis; patients who did not fulfil the follow-up period were excluded, and the envelope was returned to the sequence for patient replacement, until completion of the sample size (40 in each group)". Although the inclusion criteria stated that "Study population consisted of adult patients (18 years or older) admitted in the ICU, who were expected to require enteral nutrition through nasoenteric tube for at least 96 hours.", having participants randomized, intervened, and then excluded if they did not have 96 hours of enteral feeding could lead to a high risk of selection bias. Especially if the primary endpoint was "change in SOFA score at 48 hours". The number of excluded participants was significant: "In total, 115 potential patients met the initial inclusion criteria for enrolment, but only 80 completed the follow-up and were included in the per protocol analysis".
Selective reporting (reporting bias)	High risk	Mortality, a secondary outcome, was not reported. Nevertheless, upon request, the authors responded that given that they excluded participants that did not fulfil the 96 hours of enteral nutrition requirement, they did not report mortality because this result would have been biased (they only measured mortality in participants who completed the 96 hours). This is why they did not report it. This is correct, although the best thing would have been to perform an intention-to-treat analysis and also report premature deaths.
Other bias	Low risk	No evidence of other bias

Rugeles 2016

Methods	**Study design**: prospective, randomized controlled trial **Study dates**: December 2013 to July 2015 **Setting**: 30-bed ICU of a tertiary-level university hospital **Country**: Colombia
Participants	**Inclusion criteria** 1. age ≥18 years 2. admission to an ICU 3. expected to require EN through nasoenteric tube for at least 96 hours **Exclusion criteria** 1. participants with previous nutritional support in the same hospitalization 2. participants with concomitant parenteral nutrition 3. participants in transplantation programme 4. pregnancy 5. chronic renal failure 6. uraemic encephalopathy 7. diabetes 8. morbid obesity 9. do-not-resuscitate orders **Sample size**

Rugeles 2016 *(Continued)*

	60 participants in each group to detect a 15% (1.7 points) difference in SOFA at 48 hours between the 2 groups with an SD of 1.9 with a 2-tailed t test. 80% power α error of 0.05 **Age (years)**: intervention group: 53.8 ± 19.0; Control group: 51.8 ± 20.3 **Sex (male, %)**: intervention group: 45; Control group: 55 **Primary disease of the participants** Reasons for admission- Intervention/Control group n (%) Cardiovascular 7 (12%); 7 (12%) Gastrointestinal 4 (7%); 6 (10%) Hematology 4 (7%); 1 (2%) Orthopaedics 0 (0%); 1 (2%) Respiratory 31 (52%); 22 (37%) Central nervous system 8 (13%); 18 (30%) Trauma 1 (2%); 1 (2%) Urology 1 (2%); 0 (0%) Other 4 (7%); 4 (7%) **Disease severity score:** APACHE II Intervention group: 13.5 ± 6.4; Control group: 13.7 ± 6.8 **Mechanical ventilation** no. (%) Not available **Comorbidities**: not available **Nutrition status**: intervention group; Control group Subjective global assessment nutritional status, n (%) b A 4 (7%); 4 (7%) B 36 (60%); 43 (72%) C 20 (33%); 13 (22%) **Level of inflammation**: not available
Interventions	**Intervention Group 1 (n = 60)** 1. Hypocaloric group: 15 kcal/kg per day of total calories and high protein intake (1.7 g of protein/kg a day) 1. **Control Group 2 (n = 60)** 1. Normocaloric group: 25 kcal/kg per day with high protein intake (1.7 g of protein/kg a day). For both groups, ideal body weight was used to calculate caloric and protein requirements. A commercial enteral formula was adjusted to achieve caloric goals and was enriched with additional modules of whey and soy protein diluted in water, given in 3 or 4 daily boluses. All participants received allocated nutritional regimen until day 7. If further EN was necessary, all participants received normocaloric nutrition. **Co-interventions** 1. Not available
Outcomes	**Primary outcome**

Rugeles 2016 *(Continued)*

1. Change in SOFA score from baseline at 48 hours.

Secondary outcomes

1. SOFA at 96 hours
2. Insulin requirements (mean daily units of insulin)
3. Frequency of **hyperglycaemia episodes** (glycaemic measurements > 180 mg/dL) or **hypoglycaemia episodes** (glycaemic measurements < 45 mg/dL)
4. **Length of ICU stay**
5. **Days on ventilator**
6. **Days to start nutrition**
7. **Mortality within 28 days of randomization**

Subgroups

1. Not available

Funding sources	This research was supported by an unrestricted grant from Lafrancol Colombia and Hospital Universitario San Ignacio.
Declarations of interest	No potential conflict of interest relevant to this article was reported.
Notes	The study sponsor (Lafrancol S.A) provided an unrestricted grant and was not involved in any of the stages of the study. The authors sent us the full paper of this clinical trial before it was indexed in MEDLINE (registered in clinicaltrials.gov with the Identifier: NCT02577211). They gave us the mean and SD values for length of ICU stay and of mechanical ventilation, and also some additional information to complete the 'Risk of bias' table.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using dark sealed envelopes with computer-generated random allocations.
Allocation concealment (selection bias)	Low risk	Randomization was performed using dark sealed envelopes with computer-generated random allocations
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors considered 1 limitation of the study could be lack of proper blinding of ICU staff. One investigator knew participant allocation and prescribed and supervised the administration of nutritional regimens after randomization. Participants and ICU staff deciding on the rest of medical care were blinded to participant allocation. Nutritional information and regimen formulation were not registered in clinical records, except for general information such as total liquids administered.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear if outcome assessors were blinded to participant allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data were reported for non-excluded participants.
Selective reporting (reporting bias)	Low risk	All the outcomes were registered and reported (written information provided by the author)

Rugeles 2016 *(Continued)*

Other bias	Low risk	No other bias (written information provided by the author)

Theodorakopoulou 2016

Methods	**Study design**: prospective, randomized controlled trial **Study dates**: period of one year, but study dates not available **Setting**: single centre. ICU at Attikon University Hospital. Athens. Greece
Participants	**Inclusion criteria** 1. Mechanically-ventilated septic participants **Exclusion criteria** 1. Obese patients **Sample size** Total number of participants enrolled: 74 **Age (years):** whole group age of 68.4 ± 18.4 years **Sex (male, %):** 38 men included (100%) **Primary disease of the participants:** all participants met the consensus criteria for sepsis. **Disease severity score**: at entry overall APACHE II score 22 ± 4. etc. and SOFA score 8 ± 4 **Mechanical ventilation:** 100% of the participants were mechanically ventilated **Comorbidities:** not reported **Nutrition status:** non-obese participants. Overall BMI ≈ 21.5 ± 3.4 kg/m^2
Interventions	**Permisive underfeeding group (n = not available)** 1. Caloric goal 50% to 70% of calculated caloric requirements. During the study period the participants received 962 ± 314 kcal/day or 51 ± 14% of the caloric requirements, and 57 ± 24 grams protein day. **Standar protocol feeding group (n = not available)** 1. 80% to 100% of calculated caloric requirement. During the study period the participants received 1308 ± 513 kcal/day or 82 ± 14% of the caloric requirements, and 59 ± 25 grams of protein day. Same protein intake for both groups: 1.5 gr protein/kg/day **Each participant monitored for 14 days**
Outcomes	**Primary outcome** 1. **28-day mortality**
Funding sources	Not available.
Declarations of interest	Not available
Notes	This information was extracted from an abstract. We contacted Dr. Maria Theodorakoupoulou to request the missing data (including outcome data).

Theodorakopoulou 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information for judgement (abstract only)
Allocation concealment (selection bias)	Unclear risk	Insufficient information for judgement (abstract only)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information for judgement (abstract only)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information for judgement (abstract only)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information for judgement (abstract only)
Selective reporting (reporting bias)	Unclear risk	Insufficient information for judgement (abstract only)
Other bias	Unclear risk	Insufficient information for judgement (abstract only)

Abbreviations:
APACHE = acute physiology and chronic health evaluation; BMI = Body Mass Index ; CD = cluster of differentiation; CIT = conventional insulin therapy; dl = decilitre; EN = enteral nutrition; gr = gram; GRV = gastric residual volumes; hr = hour; ICU = intensive care unit; IIT = intensive insulin therapy; IVFE = Intravenous fat emulsion; kcal = kilocalories; kg = kilograms; mg = milligrams; NHLBI = National Heart, Lung, and Blood Institute; NNIS = National Nosocomial Infection Surveillance; OMEGA = OMEGA study (Rauch 2010); PN = parenteral nutrition; SD = standard deviation; SOFA = sequential organ failure assessment; TPN = total parenteral nutrition; UAB = unassisted breathing; VFD = ventilator-free days

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alberda 2009	Non-randomized or quasi-randomized controlled trial. Observational cohort study to examine the relationship between the amount of energy and protein administered and clinical outcomes.
Arabi 2010	Non-randomized or quasi-randomized controlled trial assessing hypocaloric nutrition versus control. It is a nested cohort study of participants enrolled in a randomized controlled clinical trial that compared intensive to conventional insulin therapy. The clinical outcomes were analysed according to tertiles of caloric administration.
Berg 2013	Study of whole-body protein turnover with d5-phenylalanine and 13C.leucine tracers. The only clinical parameter evaluated was nitrogen balance.
Casadei 2006	Non-randomized nor quasi-randomized controlled trial. Retrospective study
Desachy 2008	Not primarily hypocaloric nutrition support study; the goal was to evaluate caloric intake and tolerability of 2 early enteral nutrition protocols in which the optimal flow rate was introduced either immediately or gradually.

Study	Reason for exclusion
Dickerson 2002	Non-randomized or quasi-randomized controlled trial. Retrospective study
Dissanaike 2007	Not hypocaloric nutrition support study. Not randomized clinical trial (cohort study)
Doig 2013	Multicentre, randomized, single-blind clinical trial in critically-ill adults with relative contraindications to early enteral nutrition. Random allocation to pragmatic standard care or early parenteral nutrition. The objective was different from prescribed hypocaloric nutrition (determine if early parenteral nutrition alters outcomes). No numerical data of calories administered to the groups (only in 1 figure).
Esterle 2010	Hypocaloric nutrition support was not evaluated. Their goal was to evaluate if volume-based enteral nutrition causes less caloric deficit than rate-base feeding in critically-ill ventilated participants.
Fiaccadori 2005	Not hypocaloric nutrition support trial. Open-label, cross-over trial in critically-ill people with acute renal failure and renal replacement therapy, comparing iso-nitrogenous parenteral nutrition providing 30 and 40 kcal/kg/day (normocaloric versus hypercaloric parenteral nutrition)
Garrel 1995	Not hypocaloric nutrition support trial. They compared isocaloric enteral nutrition with less fat (but more carbohydrates) in people with burns.
Iapichino 1990	Non-randomized or quasi-randomized controlled trial assessing hypocaloric nutrition versus control. During 3 days, the participants received randomly 4 different types of parenteral nutrition (2 types of amino acids and 2 different doses of glucose). The authors only assessed metabolic outcomes (no clinical outcomes).
Lau 2010	Retrospective study to evaluate 3 different caloric regimes on the incidence of hyperglycaemia and hypoglycaemia in critically-ill participants on intensive insulin treatment
Mackenzie 2005	Not a prospective controlled trial of hypocaloric nutrition support. Prospective study to evaluate the proportion of participants meeting their caloric goals with the implementation of an evidence-based enteral nutrition protocol.
Moses 2009	Hypocaloric nutrition support was not evaluated against normo- or hypercaloric feeding. Prospective controlled randomized trial realized exclusively in ventilated participants with acute organophosphate poisoning, to evaluate if enteral nutrition could be possible (due to the treatment with high dose of atropine) and had different clinical outcomes than the participants on intravenous fluids
Müller 1995	Not randomized trial to study the metabolic effects of different caloric regimens in medical participants with multiple organ failures. The participants received 7 parenteral nutrition regimens with different amounts of calories, carbohydrates, amino-acids and lipids, for 12 hours each regimen.
Owais 2014	Single-blinded randomized clinical trial of 50 consecutive participants requiring parenteral nutritional support; permissive underfeeding in participants requiring parenteral nutrition. Participants were randomized to receive either normocaloric or hypocaloric feeding (respectively 100% vs 60% of estimated requirements). The primary end point was septic complication and the secondary end points included the metabolic, physiological and clinical outcomes to the 2 feeding protocols. Only 26% (12 out of 46) of included participants were ICU participants and the results did not distinguish between ICU and non-ICU participants.
Rodríguez 2005	Hypocaloric nutrition support was not evaluated. They assess clinical results with 2 different calories/protein relationships.
Schricker 2005	Not critically-ill participants . Surgical participants (hemicolectomy, sigmoid colectomy) to assess if hypocaloric nutrition could induce anabolism in participants with perioperative epidural analgesia.

Study	Reason for exclusion
Wewalka 2010	Hypocaloric nutrition support was not evaluated. The aim of the study was the evaluation of 2 nutrition support programmes: isocalorically right from the beginning compared with a hypocaloric beginning (50% of the dose in the first day, 75% the second day and 100% from the third day): abstract with no results of the clinical outcomes.

Abbreviations:
kcal = kilocalories; kg = kilograms

Characteristics of ongoing studies *[ordered by study ID]*

NCT01665664

Trial name or title	Hypocaloric vs full-energy enteral feeding in critically ill patients guided by indirect calorimetry, a prospective, blinded, randomized controlled trial
Methods	**Study design**: randomized controlled double-blind trial with measurement of REE by indirect calorimetry to establish the exact amount of calories to be delivered to the intervention and control groups
Participants	**Inclusion criteria** 1. Participants ≥ 18 years with mechanical ventilation ≥ 72 hrs **Exclusion criteria** 1. Abdominal surgery with inability to feed enterally 2. FiO_2 > 80% 3. Bronchopleural fistula 4. Haemodynamic instability in spite of the use of vasopressors
Interventions	**Group 1 hypocaloric feeding group** 1. Only 20% of REE will be provided but not less than 300 kcal/day **Full energy feeding group** 1. 100% of REE will be provided
Outcomes	**Primary outcomes** 1. All-cause mortality 2. ICU mortality 3. Hospital mortality **Secondary outcomes** 1. ICU and hospital length of stay 2. Length of mechanical ventilation 3. Rate of infections
Starting date	September 2012
Contact information	Arie Soroksky: soroksky@gmail.com (Israel)
Notes	Unknown state of the trial up to the end of June 2016. The principal investigator did not answer a question about the state of the trial. Clinical trial record states: (quote:) "the recruitment status of this study is unknown. The completion date has passed and the status has not been verified in

NCT01665664 *(Continued)*	more than two years." "Verified August 2012 by Soroksky Arie, Wolfson Medical Center. Recruitment status was: not yet recruiting"

Ochoa 2017

Trial name or title	Hypocaloric high-protein enteral nutrition improves glucose management in critically ill patients
Methods	**Study design**: prospective, randomized, multicenter clinical trial **Settings and countries**: ICU of 7 academic centres at USA and Canada. In USA: Wake Forest University, Winston-Salem, North Carolina; University of Kentucky, Lexington, Kentucky; Emory University, Atlanta, Georgia; Medicine, University of Chicago, Hinsdale, Illinois; Pulmonary Medicine, Regions Hospital, St Paul, Minnesota; Vanderbilt University, Nashville, Tennessee. In Canada: Kingston Hospital, Kingston, Ontario. **Funding**: Nestlé Health Science
Participants	**Inclusion criteria** 1. Mechanically-ventilated critically-ill, obese and overweight participants requiring enteral nutrition. **Exclusion criteria** 1. Not reported. **Sample size**: calculated sample size of 100 participants per group, based in a reduction of "out-of-range" glycaemic events and their standard deviation (glucose variability). Sample size of each arm of the study not reported. "Ninety-eight subjects were randomized into the study at the time of interim analysis. Of these subjects, 40 had at least 5 days of data collected. The remaining subjects withdrew primarily due to removal of the feeding tube" **Age** (years, mean ± SD): Group 1: hypocaloric: 60.7 ± 15.07; Group 2: 62.6 ± 12.09 **Sex** (% of women): Group 1: 42.9; Group 2: 55.1 Primary disease of the participants. Not reported Disease severity: APACHE II score (mean ± SD). Group 1: 25.1 ± 9.0; Group 2: 26.3 ± 9.24 Nutrition status: BMI (kg/m^2; mean ± SD). Group 1: 33.7 ± 4.57; Group 2: 32.5 ± 5.65 Mechanical ventilation: not available Comorbidities: not available Level of inflammation: not available
Interventions	**Group 1 hypocaloric (n = not available)** 1. Enteral nutrition with a hypocaloric, high-protein formulation **Group 2 (n = not available)** 1. Enteral nutrition with a normocaloric, high-protein formulation **Co-interventions** In both study groups the quantity of the assigned formula was enough to provide 1.5 grams of protein/kg ideal body weight/day
Outcomes	**Primary endpoint**

Ochoa 2017 *(Continued)*	1. Number of glycaemic events in the first 7 days in ICU > 150 mg/dL or < 110 mg/dL **Other endpoints** 1. Not defined, but reported results of mean daily glycaemia, blood glucose variability, hypoglycaemia (< 81 mg/dl) and insulin administered **Outcomes and time points**: not clearly defined **Subgroups:** not available
Starting date	Not available
Contact information	Juan.Ochoa@US.nestle.com. We contacted the study author and he replied that he would send us the study results.
Notes	An interim analysis was scheduled when 40 participants completed at least 5 days of data collection. All the current information comes from the abstract of a congress presentation (ASPEN, CNW, Orlando, Florida, 18 to 21 February, 2017) regarding the preliminary analysis of the intention-to-treat data.

Abbreviations:
APACHE = Acute Physiology And Chronic Health Evaluation II; BMI = Body Mass Index; ICU = Intensive Care Unit; REE = resting energy expenditure; SD = standard deviation; µg/kg/min = micrograms/kilograms/minute

DATA AND ANALYSES

Comparison 1. Hypocaloric nutrition (intervention) vs. Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality in hospital	9		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Mortality in ICU	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mortality at 30 days	7		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Length of Hospital stay (days)	10		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Length of ICU stay (days)	11		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Infectious complications	10		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Length of mechanical ventilation (days)	12		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Non-infectious complications (diarrhoea)	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Hyperglycaemia	6		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Hypoglicaemia	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Nitrogen balance (g/day)	3		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 1 Mortality in hospital.

Study or subgroup	Hypocaloric nutrition n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Arabi 2011	36/120	51/120		0.71[0.5,1]
Arabi 2015	108/447	123/445		0.87[0.7,1.09]
Battistella 1997	2/27	0/30		5.54[0.28,110.42]
Charles 2014	3/41	4/42		0.77[0.18,3.22]
Choban 1997	0/6	2/7		0.23[0.01,4]
Ibrahim 2002	20/75	15/75		1.33[0.74,2.4]
McCowen 2000	2/21	3/19		0.6[0.11,3.23]
Petros 2016	17/46	17/54		1.17[0.68,2.03]
Rice 2011	22/98	20/102		1.14[0.67,1.96]
		Favours Hypocaloric	0.005 0.1 1 10 200	Favours Control

Analysis 1.2. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 2 Mortality in ICU.

Study or subgroup	Hypocaloric nutrition n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Arabi 2011	21/120	26/120		0.81[0.48,1.35]
Arabi 2015	72/448	85/446		0.84[0.63,1.12]
Battistella 1997	2/27	0/30		5.54[0.28,110.42]
Petros 2016	10/46	12/54		0.98[0.47,2.05]
		Favours Hypocaloric	0.005 0.1 1 10 200	Favours Control

Analysis 1.3. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 3 Mortality at 30 days.

Study or subgroup	Hypocaloric n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Arabi 2011	22/120	28/120		0.79[0.48,1.29]
Arabi 2015	93/447	97/444		0.95[0.74,1.23]
NHLBI 2012	99/508	95/492		1.01[0.78,1.3]
Norouzy 2013	3/30	1/30		3[0.33,27.23]
Petros 2016	18/46	18/54		1.17[0.7,1.98]
Rice 2011	22/98	20/102		1.14[0.67,1.96]
Rugeles 2016	18/60	16/60		1.13[0.64,1.99]
		Favours Hypocaloric	0.05 0.2 1 5 20	Favours control

Analysis 1.4. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 4 Length of Hospital stay (days).

Study or subgroup	Hypocaloric Nutrition		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Norouzy 2013	30	19.9 (11)	30	35.6 (25)		-15.7[-25.47,-5.93]
Battistella 1997	27	27 (16)	30	39 (24)		-12[-22.5,-1.5]
Ibrahim 2002	75	16.7 (12.5)	75	22.9 (19.7)		-6.2[-11.48,-0.92]
Arabi 2015	448	48.3 (67.5)	446	54.4 (73.9)		-6.1[-15.38,3.18]
Ahrens 2005	20	23.4 (23.9)	20	27.8 (17.4)		-4.4[-17.36,8.56]
McCowen 2000	21	19 (14)	19	17 (15)		2[-7.02,11.02]
Choban 1997	6	48 (30)	7	45 (38)		3[-34,40]
Arabi 2011	120	70.2 (106.9)	120	67.2 (93.6)		3[-22.42,28.42]
Charles 2014	41	35.2 (4.9)	42	31 (2.5)		4.2[2.52,5.88]
Petros 2016	46	38.1 (33.4)	54	27.4 (21.9)		10.7[-0.58,21.98]

Favours Hypocaloric — Favours Control

Analysis 1.5. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 5 Length of ICU stay (days).

Study or subgroup	Hypocaloric Nutrition		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Battistella 1997	27	18 (12)	30	29 (22)		-11[-20.08,-1.92]
Ahrens 2005	8	16.8 (10.4)	10	23 (15.2)		-6.25[-18.09,5.59]
Ibrahim 2002	75	9.8 (7.4)	75	13.6 (14.2)		-3.8[-7.42,-0.18]
Arabi 2011	120	11.7 (8.1)	120	14.5 (15.5)		-2.8[-5.93,0.33]
Rugeles 2013	40	9.5 (5.5)	40	10.4 (5)		-0.9[-3.2,1.4]
Arabi 2015	448	15.8 (11.6)	446	16.4 (12.1)		-0.6[-2.15,0.95]
Rugeles 2016	60	13.2 (6)	60	13.5 (8.3)		-0.22[-2.82,2.38]
NHLBI 2012	508	11.5 (11)	492	11 (9.8)		0.5[-0.79,1.79]
Rice 2011	98	8.1 (6.1)	102	7.6 (5.9)		0.5[-1.16,2.16]
Charles 2014	41	16.7 (2.7)	42	13.5 (1.1)		3.2[2.31,4.09]
Petros 2016	46	22.4 (25.5)	54	17 (16.1)		5.4[-3.13,13.93]

Favours Hypocaloric — Favours Control

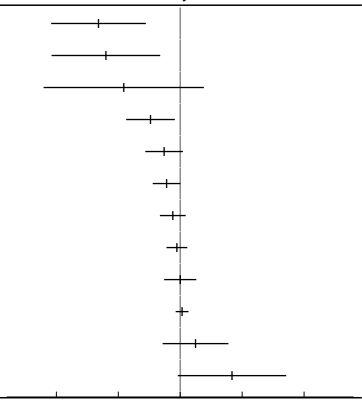
Analysis 1.6. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 6 Infectious complications.

Study or subgroup	Hypocaloric nutrition	Control	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Ahrens 2005	5/20	2/20		2.5[0.55,11.41]
Arabi 2011	53/120	56/120		0.95[0.72,1.25]
Arabi 2015	161/448	169/446		0.95[0.8,1.13]
Battistella 1997	13/27	22/30		0.66[0.42,1.03]
Charles 2014	23/41	24/42		0.98[0.67,1.43]
Ibrahim 2002	23/75	37/75		0.62[0.41,0.94]
McCowen 2000	6/21	10/19		0.54[0.24,1.21]
NHLBI 2012	96/508	79/492		1.18[0.9,1.54]
Petros 2016	13/46	6/54		2.54[1.05,6.16]
Rice 2011	30/98	33/102		0.95[0.63,1.42]

Favours Hypocaloric — Favours control

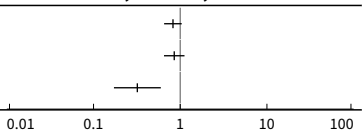
Analysis 1.7. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 7 Length of mechanical ventilation (days).

Study or subgroup	Hypocaloric nutrition		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Norouzy 2013	30	4.7 (4)	30	17.9 (21)		-13.2[-20.85,-5.55]
Battistella 1997	27	15 (12)	30	27 (21)		-12[-20.77,-3.23]
Ahrens 2005	8	11.1 (9.4)	8	20.3 (16.1)		-9.12[-22.06,3.82]
Ibrahim 2002	75	8.1 (7.4)	75	12.9 (15.7)		-4.8[-8.73,-0.87]
Arabi 2011	120	10.6 (7.6)	120	13.2 (15.2)		-2.6[-5.64,0.44]
Arabi 2015	448	11.3 (9.2)	446	13.5 (22.3)		-2.2[-4.44,0.04]
Rugeles 2013	40	8.5 (4.6)	40	9.7 (4.9)		-1.2[-3.28,0.88]
Rice 2011	98	5.7 (5.5)	102	6.2 (6.6)		-0.54[-2.22,1.14]
Rugeles 2016	60	10.8 (6.6)	60	10.8 (7.8)		0[-2.59,2.59]
NHLBI 2012	508	10.5 (8.7)	492	10.2 (8)		0.3[-0.74,1.34]
Charles 2014	41	10.8 (16.2)	42	8.3 (6.2)		2.47[-2.84,7.78]
Petros 2016	46	20.7 (26.6)	54	12.4 (15.7)		8.36[-0.39,17.11]



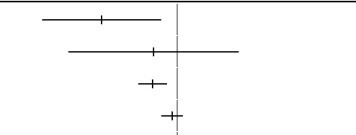
Analysis 1.8. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 8 Non-infectious complications (diarrhoea).

Study or subgroup	Hypocaloric nutrition	Control	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Arabi 2015	97/448	117/446		0.83[0.65,1.04]
NHLBI 2012	81/508	92/492		0.85[0.65,1.12]
Petros 2016	9/46	33/54		0.32[0.17,0.6]



Analysis 1.9. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 9 Hyperglycaemia.

Study or subgroup	Hypocaloric Nutrition	Control	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Ahrens 2005	5/20	14/20		0.36[0.16,0.8]
McCowen 2000	4/21	5/19		0.72[0.23,2.31]
NHLBI 2012	124/508	168/492		0.71[0.59,0.87]
Petros 2016	39/46	49/54		0.93[0.8,1.08]
Rugeles 2013	6/40	10/40		0.6[0.24,1.49]
Rugeles 2016	27/60	33/60		0.82[0.57,1.17]



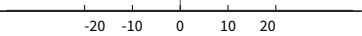
Analysis 1.10. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 10 Hypoglicaemia.

Study or subgroup	Hypocaloric Nutrition n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Ahrens 2005	3/20	2/20		1.5[0.28,8.04]
Arabi 2011	25/120	21/120		1.19[0.71,2.01]
Arabi 2015	6/448	7/446		0.85[0.29,2.52]
Petros 2016	12/46	8/54		1.76[0.79,3.93]
Rugeles 2016	0/60	0/60		Not estimable

Favours Hypocaloric | Favours control

Analysis 1.11. Comparison 1 Hypocaloric nutrition (intervention) vs. Control, Outcome 11 Nitrogen balance (g/day).

Study or subgroup	Hypocaloric nutrition N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
McCowen 2000	12	-8.3 (9.2)	10	-0.6 (4.8)		-7.7[-13.7,-1.7]
Battistella 1997	27	-9 (5)	30	-9 (7)		0[-3.14,3.14]
Choban 1997	6	4 (4)	7	2 (3)		2[-1.9,5.9]



Favours Hypocaloric | Favours control

ADDITIONAL TABLES

Table 1. Differences in participants, interventions and outcomes across included studies

Study ID	Type of participants Primary outcomes	Arm	Number of ICU participants	APACHE II score mean ± SD	Route (enteral or parenteral)	Duration of PN or EN (days)	Mechanical ventilation (% of participants)	ICU mortality %	Hospital mortality %
Ahrens 2005	Surgical participants with PN requirement Incidence/severity hyperglycaemia and insulin received by the participants	Hypoc.	8 (other 12 non-ICU)	20 ± 9	Parenteral	6 (4 to 10)	100	Not reported	Not reported
		Control	10 (other 10 non-ICU)	19 ± 11		7 (5 to 10)	80		
Arabi 2011	Medical (mainly) and surgical participants with EN. 2 x 2 factorial trial with Intensive Insuline therapy 28 days all-cause mortality	Hypoc.	120	25 ± 8	Enteral	Not reported	99	18	30
		Control	120	25 ± 8			99	22	43
Arabi 2015	Critically-ill participants (75% medical) 90-day all-cause mortality	Hypoc.	448	21 ± 7.9	Enteral	9.1 ± 4.6	97.3	16.1	24.2
		Control	446	21 ± 8.2		9.4 ± 4.4	96.2	19.1	27.6
Battistella 1997	Trauma participants with PN requirement Length of hospital stay, length of stay in the ICU, number of days on mechanical ventilation and infectious complications.	Hypoc.	27	22 ± 5	Parenteral	10	Not reported	7.4	Not reported
		Control	30	23 ± 6		10		0	
Charles 2014	Critically-ill surgical participants Hospital-acquired infection	Hypoc.	41	16.6 ± 0.9	Enteral & parenteral	12.6 ± 2.8	68	N/A	7.3
		Control	42	17.3 ± 0.8		10.4 ± 1.1	57	N/A	9.5
Choban 1997	Obese participants with PN requirement. Predominantly surgical diseases Achievement of nitrogen balance	Hypoc.	6 (other 10 non-ICU)	13 ± 5	Parenteral	10 ± 3	Not reported	Not reported	0
		Control	7 (other 7 non-ICU)	15 ± 5		11 ± 2			28.6
Ibrahim 2002	Medical ICU participants with EN	Hypoc.	75	26 ± 8	Enteral	5 ± 6	100	Not reported	27
		Control	75	25 ± 8		10 ± 12	100		20

Table 1. Differences in participants, interventions and outcomes across included studies *(Continued)*

	Incidence of ventilator-associated pneumonia								
McCowen 2000	Participants with predominantly surgical diseases requiring PN Glycaemic control and Infections	Hypoc.	21	not reported	Parenteral	≥ 5	50	10	Not reported
		Control	19	not reported		≥ 5	33	16	
NHLBI 2012	Acute lung injury predominantly due to medical diseases (61% and 63% of participants) with EN Ventilator-free days at study day 28	Hypoc.	508	APACHE III 92 ± 28	Enteral	6	100	Not reported	22.4
		Control	492	APACHE III 90 ± 27	Enteral	6	100		19.6
Norouzy 2013	Critically-ill head trauma participants 28 days of all-cause mortality	Hypoc.	30	Not reported	Enteral	7	Not reported	Not reported	10.7[a]
		Control	30			7			3.8[a]
Petros 2016	Medical ICU with EN and/or PN requirement Glycaemic control and mortality	Hypoc.	46	31 ± 9	Enteral & parenteral	7	not reported	22	37
		Control	54	28 ± 8		7		22	31
Rice 2011	Acute lung injury, predominantly due to medical diseases with EN Ventilator-free days at study day 28	Hypoc.	98	27 ± 8	Enteral	6 ± 4	100	Not reported	22
		Control	102	27 ± 7		5 ± 3	100		20
Rugeles 2013	Medical ICU participants with EN requirement Change in SOFA score at 48 hours	Hypoc.	40	14 ± 5	Enteral	7	Not reported	Not reported	Not reported
		Control	40	15 ± 6					
Rugeles 2016	Medical ICU participants with EN requirement Change in SOFA score at 48 hours	Hypoc.	60	13.5 ± 6.4	Enteral	7	Not reported	Not reported	30[a]
		Control	60	13.7 ± 6.8					27[a]
Theodorakopoulou 2016	Septic, mechanically ventilated critically-ill participants 28-day mortality	Hypocal.	Total sample of 74 participants	Total sample 22 ± 4	Enteral	Not reported	Not reported	Not reported	Not reported
		Control							

[a]28-day mortality.
EN = Enteral nutrition; ICU = Intensive Care Unit; N/A: not available; PN = Parenteral nutrition; SOFA = Sequential Organ Failure Assessment

Table 2. Calories and protein received in both study groups

Studies	How data was reported	Hypocaloric (intervention) group	Control group	Calories received by the "hypocaloric" intervention group (kcal/kg/day)	Calories received by the "normocaloric" control group (kcal/kg/day)	Categories denominated by the calories really received in the intervention and the control groups [a]
Ahrens 2005	Total calories/kg/day (median (IQ))[b]	26.6 (26.2 to 27.5)	37 (36.0 to 38.4)	26.60 (median)	37.00 (median)	Normocaloric vs hypercaloric
	Protein g/kg/day (mean± SD)	1.61 ± 0.13	1.53 ± 0.26			
Arabi 2011	Calories/day (mean ± SD)	1066.6 ± 306.1	1251.7 ± 432.5	13.85	16.40	Hypocaloric vs hypocaloric
	Protein g/day (mean ± SD)	47.5 ± 21.2	43.6 ± 18.9			
Arabi 2015	Calories/day (mean ± SD)	835 ± 297	1299 ± 2470	10.56	16.04	Hypocaloric vs hypocaloric
	Protein g/day (mean ± SD)	57 ± 24	59 ± 25			
Battistella 1997	Calories/kg ideal body weight/day (mean ± SD)	27.4 ± 2	34.4 ± 2	27.4 (of ideal body weight)	34.4 (of ideal body weight)	Normocaloric vs. normocaloric
	Protein g/kg ideal body weight/day (mean± SD)	1.6 ± 0.1	1.6 ± 0.2			
Charles 2014	Calories/kg/day (mean ± SD)	12.3 ± 0.7	17.1 ± 1.1	12	17	Hypocaloric vs hypocaloric
	Protein g/kg/day (mean ± SD)	1.1 ± 0.1	1.1 ± 0.1			
Choban 1997	Kcal/kg actual body weight/day (mean ± SD) Kcal/kg ideal body weight/day (mean ± SD)	8.6 ± 2.39 13.88 ± 2.87	17.45 ± 4.06 27.99 ± 3.83	14.00 (of ideal body weight)	28.00 (of ideal body weight)	Hypocaloric vs normocaloric
	Protein g/kg actual body weight/day (mean ± SD) Protein g/kg ideal body weight/day (mean ± SD)	1.2 ± 0.2 2.0 ± 0.1	1.2 ± 1.2 2.0 ± 0.1			
Ibrahim 2002	Calories/day (mean ± SD)	126 ± 115	474 ± 400	1.53	5.81	Very hypocaloric vs very hypocaloric
	Proteins g/day (mean) (mean ± SD)	5.3 ± 5.3	18.7 ± 15.4			
McCowen 2000	Calories/kg/day (mean ± SD)	14 ± 3	18 ± 4	14.30	18.40	Hypocaloric vs hypocaloric
	Proteins g/kg/day (mean ± SD)	1.1 ± 0.2	1.3 ± 0.2			
NHLBI 2012	Calories/day (mean ± SD)	399 ± 225	1365 ± 596	4.64 (estimated by	15.69 (estimated by	Very hypocaloric vs hypocaloric

Table 2. Calories and protein received in both study groups *(Continued)*

	Proteins: information not collected	-	-	kcal/day divided by weight from the baseline table)	kcal/day divided by weight from the baseline table)	
Norouzy 2013	Calories/kg/day (mean ± SD)	Not reported	Not reported	N/A	N/A	N/A
	Protein g/kg/day (mean ± SD)	Not reported	Not reported			
Petros 2016	Calories/kg/day (mean ± SD)	11.3 ± 3.1	19.7 ± 5.7	11.30	19.70	Hypocaloric vs hypocaloric
	Protein	Data not reported	Data not reported			
Rice 2011	Calories/day (mean ± SD of study days 1 to 5)	300 ± 149	1418 ± 686	3.60	17.31	Very hypocaloric vs hypocaloric
	Proteins g/day (mean ± SD of study days 1 to 5)	10.9 ± 6.8	54.4 ± 33.2			
Rugeles 2013	Calories/kg/day (mean ± SD)	12 ± 3.9	14 ± 6.2	12.00	14.00	Hypocaloric vs hypocaloric
	Protein g/kg/day (mean ± SD)	1.4 ± 0.44	0.76 ± 0.32			
Rugeles 2016	Total calories/kg ideal body weight/day (mean ± SD)	12.6 ± 3.4	20.5 ± 5.1	13	21	Hypocaloric vs hypocaloric
	Protein g/kgIBW/day (mean ± SD)	1.4 ± 0.4	1.4 ± 0.3			
Theodorakopoulou 2016	Calories/day (mean ± SD)	962 ± 314	1308 ± 513	Not reported Estimated[c] 16.63 kcal/kg/day	Not reported Estimated[c] 22.62 kcal/kg/day	Estimated[c] Hypocaloric vs normocaloric
	Protein g/day (mean ± SD)	57 ± 24	59 ± 25	Not reported Estimated[c] 0.99 g/kg/day	Not reported Estimated[c] 1.02 g/kg/day	

[a]Categories denominated by the amount of calories really received by both study groups, according to the following: very hypocaloric = < 10 kcal/kg/day; hypocaloric = ≥ 10 to < 25 kcal/kg/day; normocaloric = ≥ 25 to < 35 kcal/kg/day; hypercaloric = ≥ 35 kcal/kg/day.
[b]IQ: interquartile range - Median total calories received by all 20 participants (ICU and non-ICU participants) in each group (the total calories received by the 8 and 10 ICU participants in each group were not reported).
[c]Not reported in the abstract. The numbers are a crude estimation of kcal and grams of protein/kg/day from the whole sample data of height and BMI.
BMI = Body Mass Index; g = gram; ICU = Intensive Care Unit; kcal = kilocalories; N/A: not available; SD = standard deviation; vs = versus

Table 3. Main outcomes in individual studies ordered by the magnitude of the differences in calories received between the control and hypocaloric groups

Study	Difference in calories between groups (kcal/kg/day)	Hospital mortality (%) IG vs CG	ICU mortality (%) IG vs CG	Mortality at 30 days (%) IG vs CG	Infectious complications (%) IG vs CG	Length of hospital stay (days)[a] IG vs CG	ICU length of stay (days)[a] IG vs CG	Length of mechanical ventilation (days)[a] IG vs CG	Categories denominated by the calories really received in the intervention and the control groups[b]
Rugeles 2013	2.00	N/A	N/A	N/A	N/A	N/A	9.5 vs 10.4	8.5 vs 9.7	Hypocaloric vs hypocaloric
Arabi 2011	2.55	30% vs 42.5%	17.5% vs 21.7%	18.3% vs 23.3%	44.2% vs 46.7%	70.2 vs 67.2	11.7 vs 14.5	10.6 vs 13.2	Hypocaloric vs hypocaloric
McCowen 2000	4.10	9.5% vs 15.8%	N/A	N/A	28.6% vs 52.6%	19 vs 17	N/A	N/A	Hypocaloric vs hypocaloric
Ibrahim 2002	4.28	26.7% vs 20%	N/A	N/A	30.7% vs 49.3%	16.7 vs 22.9	9.8 vs 13.6	8.1 vs 12.9	Very hypocaloric vs very hypocaloric
Charles 2014	5.00	7.3% vs 9.5%	N/A	N/A	56.1% vs 57.1%	35.2 vs 31	16.7 vs 13.6	10.8 vs 8.3	Hypocaloric vs hypocaloric
Arabi 2015	5.48	24.2% vs 27.6%	16.1% vs 19.1%	20.8% vs 21.8%	35.9% vs 37.9%	48.3 vs 54.4	15.8 vs 16.4	11.3 vs 13.5	Hypocaloric vs hypocaloric
Battistella 1997	7.00	7.4% vs 0%	7.4% vs 0%	N/A	48.2% vs 73.3%	27 vs 39	18 vs 29	15 vs 27	Normocaloric vs normocaloric
Rugeles 2016	7.90	N/A	N/A	30% vs 26.7%	N/A	N/A	13.2 vs 13.5	10.8 vs 10.8	Hypocaloric vs hypocaloric
Petros 2016	8.40	37% vs 31.5%	21.7% vs 22.2%	39.1% vs 33.3%	28.3% vs 11.1%	38.1 vs 27.4	22.4 vs 17	20.7 vs 12.4	Hypocaloric vs hypocaloric
Ahrens 2005	10.40	N/A	N/A	N/A	25% vs 10%	23.4 vs 27.8	16.8 vs 23	11.1 vs 20.3	Normocaloric vs hypercaloric
NHLBI 2012	11.05	N/A	N/A	19.5% vs 19.3%	18.9% vs 16.1%	N/A	11.5 vs 11	10.5 vs 10.2	Very hypocaloric vs hypocaloric

Table 3. Main outcomes in individual studies ordered by the magnitude of the differences in calories received between the control and hypocaloric groups *(Continued)*

Rice 2011	13.71	22.4% vs 19.6%	N/A	22.4% vs 19.6%	30.6% vs 32.4%	N/A	8.1 vs 7.6	5.7 vs 6.2	Very hypocaloric vs hypocaloric
Choban 1997	14.00	0% vs 29%	N/A	N/A	N/A	48 vs 45	N/A	N/A	Hypocaloric vs normocaloric
Norouzy 2013	N/A	N/A	N/A	10% vs 3.3%	N/A	19.9 vs 35.6	N/A	4.7 vs 17.9	N/A
Theodor-akopoulou 2016	N/A	N/A	N/A	18.4% vs 28.9%	N/A	N/A	N/A	N/A	Hypocaloric vs normocaloric

[a]Lengths of hospital, ICU stays and of mechanical ventilation presented in mean days.
[b]Categories denominated by the amount of calories really received by both study groups, according to the following: very hypocaloric = < 10 kcal/kg/day; hypocaloric = ≥ 10 to < 25 kcal/kg/day; normocaloric = ≥ 25 to < 35 kcal/kg/day; hypercaloric = ≥ 35 kcal/kg/day.
IG = Intervention Group; CG = Control Group; N/A = Not available; vs = versus

Table 4. Subgroup analyses

Subgroup	N participants (n studies)	Subgroup testing
1. Nutrition status		
1.1. Length of hospital stay		
Obese	13 (1 RCT)	I^2 = 0%, P = 0.76
General	1664 (9 RCTs)	
2. Route of nutrition support		
2.1. Length of hospital stay		
Parenteral	150 (4 RCTs)	I^2 = 0%, P = 0.72
Enteral	1725 (6 RCTs)	
2.2. Length of ICU stay		
Parenteral	75 (2 RCTs)	I^2 = 83.3%, P < 0.01
Enteral	2867 (9 RCTs)	
2.3. Infectious complications		
Parenteral	137 (3 RCTs)	I^2 = 0%, P = 0.35
Enteral	2667 (7 RCTs)	
2.4. Length of mechanical ventilation		
Parenteral	73 (2 RCTs)	I^2 = 85.4%, P < 0.01
Enteral	2927 (10 RCTs)	
3. Type of participant		
3.1. Length of hospital stay		
Surgical participants	223 (5 RCTs)	I^2 = 0%, P = 0.55
Medical participants	1354 (5 RCTs)	
3.2. Length of ICU stay		
Surgical participants	158 (3 RCTs)	I^2 = 0%, P = 0.52
Medical participants	2784 (8 RCTs)	
3.3. Infectious complications		
Surgical participants	220 (4 RCTs)	I^2 = 0%, P = 0.45
Medical participants	2584 (6 RCTs)	

Table 4. Subgroup analyses *(Continued)*

3.4. Length of mechanical ventilation		
Surgical participants	156 (3 RCTs)	I^2 = 0%, P = 0.45
Medical participants	2854 (9 RCTs)	
4. Amount of calories received by each study group		
4.1. Length of hospital stay		
Normo-hypercaloric	97 (2 RCTs)	I^2 = 84.1%, P < 0.01
Hypocaloric	1370 (6 RCT)	
Very hypocaloric	150 (RCT)	
4.2. Length of ICU stay		
Normo-hypercaloric	75 (2 RCTs)	I^2 = 0%, P = 0.42
Hypocaloric	1517 (6 RCTs)	
Very hypocaloric	1350 (3 RCTs)	
4.3. Infectious complications		
Normo-hypercaloric	97 (2 RCTs)	I^2 = 0%, P = 0.94
Hypocaloric	1357 (5 RCTs)	
Very hypocaloric	1350 (3 RCTs)	
4.4. Length of mechanical ventilation		
Normo-hypercaloric	73 (2 RCTs)	I^2 = 73.1%, P = 0.02
Hypocaloric	1517 (6 RCTs)	
Very hypocaloric	1350 (3 RCTs)	

RCT = randomized controlled trial; ICU = Intensive care unit

APPENDICES

Appendix 1. Search strategy for CENTRAL, The Cochrane Library

#1 MeSH descriptor: [Critical Illness] explode all trees
#2 stressed:ti,ab,kw
#3 critical* next ill*:ti,ab,kw
#4 MeSH descriptor: [Critical Care] explode all trees
#5 MeSH descriptor: [Intensive Care Units] explode all trees
#6 #1 or #2 or #3 or #4 or #5
#7 (feeding or food or nutrition* or diet* or intake*) .ti
#8 (eucalor* or hypoenerg* or underfeed* or (low calor*) or hypocalor*):ti,ab,kw
#9 MeSH descriptor: [Diet] explode all trees

#10 MeSH descriptor: [Parenteral Nutrition] explode all trees
#11 MeSH descriptor: [Enteral Nutrition] explode all trees
#12 #7 or #8 or #9 or #10 or #11

Appendix 2. Search strategy for MEDLINE (Ovid SP)

1 exp Critical Illness/
2 stressed.ti,ab.
3 (critical adj3 ill*).mp.
4 Critical Care/
5 Intensive Care/
6 Intensive Care Units/
7 1 or 2 or 3 or 4 or 5 or 6
8 (feeding or food or nutrition* or diet* or intake*).ti.
9 (eucalor* or hypoenerg* or underfeed* or (low adj3 calor*) or h?pocalor*).mp.
10 Diet/ or Parenteral-Nutrition/ or Enteral-Nutrition/
11 8 or 9 or 10
12 7 and 11
13 "Randomized Controlled Trial".pt.
14 "Controlled Clinical Trial".pt.
15 randomi?ed.ti,ab.
16 placebo*.ti,ab.
17 "drug therapy".sh.
18 randomly.ti,ab.
19 trial.ti,ab.
20 groups.ti,ab.
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 Animals/ not (Humans/ and Animals/)
23 21 not 22
24 12 and 23

Appendix 3. Search strategy for Embase (Ovid SP)

1 eucalor*.ti,ab.
2 hypoenerg*.ti,ab.
3 underfeed*.ti,ab.
4 (low adj3 calor*).ti,ab.
5 h?pocalor*.ti,ab.
6 1 or 2 or 3 or 4 or 5
7 (feeding or food or nutrition* or diet* or intake*).ti.
8 *diet/
9 *parenteral nutrition/
10 6 or 7 or 8 or 9
11 critical*.ti,ab.
12 stressed.ti,ab.
13 *intensive care unit/
14 *intensive care/
15 *critical illness/
16 11 or 12 or 13 or 14 or 15
17 10 and 16
18 random.tw. or placebo.mp. or double-blind.tw.
19 17 and 18

Appendix 4. Search strategy for LILACS, (BIREME)

(tw:(("ENFERMEDAD CRITICA" OR "UNIDADES DE TERAPIA intensiva" OR "CUIDADOS INTENSIVOS" OR trauma* OR "TRAUMA multiple" OR "SEPSIS" OR septicemia* OR "ENFERMEDAD AGUDA" OR "cuidados criticos" OR "cuidado critico" OR "cuidado intensivo" OR "cuidados intensivos" OR icu* OR uti*)))
AND

(tw:((desnutricion* OR hypocalor* OR hipocalor* OR hypoenerg* OR hipoenerg* OR underfeed* OR subaliment* OR "bajas calorias" OR "bajo valor" OR hiponutr* OR malnutr* OR calorimetr*)))

AND

(instance:"regional") AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

Appendix 5. Meta-regression

STATA 14.1 outputs exploring the effect of several explanatory variables on the primary outcomes with the highest number of included studies: mortality in hospital, infectious complications, length of hospital stay and length of ICU stay. The covariates included in the models were: type of participants [**typepatient**]; calories received by the intervention group in three categories categorized [**catcal**]; difference in the amount of calories received by the control groups minus the intervention group [**difcal**].

The explanatory variables were defined as follow:

1. **typepatient**: surgical participant vs medical participant (all surgical participants received parenteral nutrition and medical received enteral nutrition) (See Table 1).
2. **catcal:** categories denominated by the amount of calories really received by the intervention groups, according to the following: very hypocaloric ≤ 10 kcal/kg/day (**icatcal 2**); hypocaloric ≥ 10 to < 25 kcal/kg/day (**icatcal 1**); normocalcaloric or hypercaloric ≥ 25 kcal/kg/day (**icatcal 0**) (see Table 2).
3. **difcal:** absolute difference in kcal/kg/day received by the control minus the intervention groups (see Table 3).

We analysed several different models for each outcome. We only presented the model with the three covariates of each outcome, including the full output of the STATA 14.1 statistics.

In each model the covariates were typed in bold (see above definitions). The other codes in tables were:

1. **logrr**: Relative risk of dichotomic outcomes.
2. **ES**: Mean difference of continuous outcomes.
3. **Coef.:** Value of the relative risk or the mean difference in their units
4. **P > t**: Probability that the Logrr difference adjusted by other covariates could be related to chance if P is higher than 0.05
5. **Std. Err**: Standard error of the coefficient.
6. **t:** test.
7. **P > t**: Probability that the Logrr difference adjusted by other covariates could be related to chance if P is higher than 0.05 (not significant).
8. **95% conf. interval**: 95% confidence interval of the Logrr or ES values.

It is important to state the limitations of this meta-regression because of the limited number of studies for the number of covariates in the model. Meta-regression should generally not be considered when there are fewer than 10 studies in a meta-analysis.

1. Mortality in hospital

xi: metareg logrr**difcal i.catcal typepatient**, wsse(selogrr) bsest(reml)

i.catcal _Icatcal_0-2 (naturally coded; _Icatcal_0 omitted)

note: _Icatcal_1 dropped because of collinearity

numerical derivatives are approximate

nearby values are missing

Meta-regression Number of observations = 7

REML estimate of between-study variance tau2 = 0

% residual variation due to heterogeneity I-squared_res = 0.00%

Proportion of between-study variance explained Adj R-squared = 100.00%

Joint test for all covariates Model F(3,3) = 1.16

With Knapp-Hartung modification Prob > F = 0.4542

logrr[a]	Coef.	Std. Err.	t	P > t	(95% Conf.	Interval)

(Continued)

difcal	.0237277	.0333315	0.71	0.528	−.0823481	.1298035
_Icatcal_2	.2621164	.2656104	0.99	0.396	−.5831745	1.107407
typepatient	−.3222415	.8614032	−0.37	0.733	−3.063611	2.419128
_cons	−.2805905	.1894936	−1.48	0.235	−.8836437	.3224628

[a]Relative Risk

Interpretationof hospital mortality. None of the covariates had a statistically significant influence on the size of the intervention effect on hospital mortality (P > 0.05).

2. Infectious complications

xi: metareg logrr **difcal i.catcal typepatient,** wsse(selogrr) bsest(reml)

i.catcal _Icatcal_0-2 (naturally coded; _Icatcal_0 omitted)

Meta-regression Number of obs = 10

REML estimate of between-study variance tau2 = .0115

% residual variation due to heterogeneity I-squared_res = 40.22%

Proportion of between-study variance explained Adj R-squared = 24.55%

Joint test for all covariates Model F(4,5) = 1.48

With Knapp-Hartung modification Prob > F = 0.3346

logrr[a]	**Coef.**	**Std. Err.**	**t**	**P > t**	**(95% Conf. Interval)**	
difcal	.0660771	.0343893	1.92	0.113	−.0223233	.1544776
_Icatcal_1	−.1032021	.5736509	−0.18	0.864	−1.577819	1.371415
_Icatcal_2	−.511068	.5948386	−0.86	0.430	−2.040149	1.018013
typepatient	−.5686713	.502095	−1.13	0.309	−1.859348	.7220049
_cons	−.209952	.6345331	−0.33	0.754	−1.841071	1.421167

[a]Relative Risk

Interpretation of infectious complications. None of the covariates had a statistically significant influence on the size of the intervention effect on infectious complications (P > 0.05).

3. Hospital length of stay

xi: metareg _ES **difcal i.catcal typepat**, wsse(_seES) bsest(reml)

i.catcal _Icatcal_0-2 (naturally coded; _Icatcal_0 omitted)

Meta-regression Number of obs = 9

REML estimate of between-study variance tau2 = .1866

% residual variation due to heterogeneity I-squared_res = 84.83%

Proportion of between-study variance explained Adj R-squared = -0.95%

Joint test for all covariates Model F(4,4) = 0.95

With Knapp-Hartung modification Prob > F = 0.5178

_ES[a]	Coef.	Std. Err.	t	P > t	(95% Conf.	Interval)
difcal	.0227448	.0664972	0.34	0.750	−.1618811	.2073708
_Icatcal_1	.5450151	.5673605	0.96	0.391	−1.03023	2.12026
_Icatcal_2	−.1219102	.7756573	−0.16	0.883	−2.27548	2.03166
typepat	−.2502513	.5116285	−0.49	0.650	−1.67076	1.170257
_cons	−.3512504	.7353122	−0.48	0.658	−2.392804	1.690304

[a]Mean difference

Interpretation of length of hospital stay. None of the covariates had a statistically significant influence on the size of the intervention effect on hospital length of stay (P > 0.05).

4. ICU length of stay

xi: metareg _ES **difcal i.catcal typepat**, wsse(_seES) bsest(reml)

i.catcal _Icatcal_0-2 (naturally coded; _Icatcal_0 omitted)

note: typepat dropped because of collinearity

Meta-regression Number of obs = 11

REML estimate of between-study variance tau2 = .2453

% residual variation due to heterogeneity I-squared_res = 83.29%

Proportion of between-study variance explained Adj R-squared = -3.80%

Joint test for all covariates Model F(3,7) = 0.99

With Knapp-Hartung modification Prob > F = 0.4503

_ES[a]	Coef.	Std. Err.	t	P > t	(95% Conf.	Interval)
difcal	.0459442	.0578779	0.79	0.453	−.0909154	.1828038
_Icatcal_1	.8943999	.5321506	1.68	0.137	−.3639364	2.152736
_Icatcal_2	.4275402	.5473569	0.78	0.460	−.8667533	1.721834
_cons	−.9390958	.6599035	−1.42	0.198	−2.49952	.621328

[a]Mean difference

Interpretation of length of ICU stay. None of the covariates had a statistically significant influence on the size of the intervention effect on length of ICU stay (P > 0.05).

Appendix 6. Database for meta-regression

We conducted the meta-regressions of each of the outcomes according to the following databases. The codes used to identify each column of the databases were:

1. **trialnam**: study ID.
2. **cases1**: number of events in the intervention group.
3. **cases0**: number of events in the control group.
4. **tot1**: number of participants in the intervention group.
5. **tot0**: number of participants in the control group.
6. **mean 1**: mean value in the intervention group.
7. **SD 1**: standard deviation in the intervention group.
8. **total 1**: total number of participants in the intervention group.
9. **mean 2**: mean value in the control group.
10. **SD 2**: standard deviation in the control group.
11. **total 2**: total number of participants in the control group.
12. **difcal**: absolute difference in kcal/kg/day between the control minus the study group.
13. **catcal**: categories according the amount of calories received by the intervention groups. 0 ≥ 25 kcal/kg/day; 1 ≥ 10 to < 25 kcal/kg/day; 2 < 10 kcal/kg/day.
14. **typepatient**: medical participants 0; surgical participants 1 (also equivalent to enteral nutrition and parenteral nutrition respectively)
15. n/a: not available.

Database of mortality in hospital

Mortality in hospital							
trial name	**cases1**	**tot1**	**cases0**	**tot0**	**difcal**	**catcal**	**typepatient**
Arabi 2011	36	120	51	120	2.55	1	0
Arabi 2015	108	447	123	445	5.48	1	0
Battistella 1997	2	27	0	30	7	0	1
Charles 2014	3	41	4	42	5	1	0
Choban 1997	0	6	2	7	14	1	1
Ibrahim 2002	20	75	15	75	4.28	2	0
McCowen 2000	2	21	3	19	4.1	1	1
Petros 2016	17	46	17	54	8.4	1	0
Rice 2011	22	98	20	102	13.71	2	0

Database of infectious complications

Infectious complications							
trial name	**cases1**	**tot1**	**cases0**	**tot0**	**difcal**	**catcal**	**typepatient**
Ahrens 2005	5	20	2	20	10.4	0	1
Arabi 2011	53	120	56	120	2.55	1	0
Arabi 2015	161	448	169	446	5.48	1	0
Battistella 1997	13	27	22	30	7	0	1
Charles 2014	23	41	24	42	5	1	0
Ibrahim 2002	23	75	37	75	4.28	2	0
McCowen 2000	6	21	10	19	4,1	1	1
NHLBI 2012	96	508	79	492	11.05	2	0
Petros 2016	13	46	6	54	8.4	1	0
Rice 2011	30	98	33	102	13.71	2	0

Database of length of hospital stay

Length of hospital stay									
trial name	Mean 1	SD 1	total 1	mean 2	SD 2	total 2	difcal	catcal	typepa-tient
Ahrens 2005	23.4	23.92	20	27.8	17.4	20	10.4	0	1
Arabi 2011	70.2	106.9	120	67.2	93.6	120	2.55	1	0
Arabi 2015	48.3	67.7	448	54.4	73.9	446	5.48	1	0
Battistella 1997	27	16	27	39	24	30	7	0	1
Charles 2014	35.2	4.9	41	31	2.5	42	5	1	0
Choban 1997	48	30	6	45	38	7	14	1	1
Ibrahim 2002	16.7	12.5	75	22.9	19.7	75	4.28	2	0
McCowen 2000	19	14	21	17	15	19	4.1	1	1
Norouzy 2013	19.9	11	30	35.6	25	30	n/a	n/a	0
Petros 2016	38.1	33.4	46	27.4	21.9	54	8.4	1	0

Database of length of ICU stay

Length of ICU stay									
trial name	**mean 1**	**SD 1**	**total 1**	**mean 2**	**SD 2**	**total 2**	**difcal**	**catcal**	**typepatient**
Ahrens 2005	16.75	10.35	8	23	15.2	10	10.4	0	1
Arabi 2011	11.7	8.1	120	14.5	15.5	120	2.55	1	0
Arabi 2015	15.8	11.6	448	16.4	12.1	446	5.48	1	0
Battistella 1997	18	12	27	29	22	30	7	0	1
Charles 2014	16.7	2.7	41	13.5	1.1	42	5	1	0
Ibrahim 2002	9.8	7.4	75	13.6	14.2	75	4.28	2	0
NHLBI 2012	11.5	11	508	11	9.8	492	11.05	2	0
Petros 2016	22.4	25.5	46	17	16.1	54	8.4	1	0
Rice 2011	8.1	6.1	98	7,6	5.9	102	13.71	2	0
Rugeles 2013	9.5	5.5	40	10.4	5	40	2	1	0
Rugeles 2016	13.23	6.03	60	13.45	8.33	60	7.9	1	0

WHAT'S NEW

Date	Event	Description
13 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 3, 2009
Review first published: Issue 6, 2018

Date	Event	Description
4 October 2018	Amended	Acknowledgement section amended to include Co-ordinating Editor

CONTRIBUTIONS OF AUTHORS

Conception, design and coordination of the review: Mario I Perman (MP)
Design of search strategies: Virginia Garrote (VG), MP, Agustín Ciapponi (ACi)
Searching: VG, MP
Manual searches: Cecilia Loudet (CL), Adriana Crivelli (ACr), VG and MP.
Screening search results: MP, CL, ACr.
Organizing retrieval of papers: VG, MP.
Obtaining copies of trials: MP, ACr, CL, GP, VG
Screening retrieved paper against inclusion criteria: MP, CL, ACr, GP.
Selection of trials to include: MP, CL, ACr, GP.
Appraising quality of papers: GP, CL, AC, Juan Franco (JF).
Extracting data from trials: MP, CL, ACr.

Meta-regression in STATA 14.1 AC
Writing to authors of papers for additional information: MP.

Data management for the review

Entering data into RevMan: MP, GP, ACi.
Analysis of data: MP, ACi, GP, CL, ACr, JF.
Interpretation of data: MP, GP, ACi, CL, JF.
Providing a methodological perspective: ACi, JF.
Providing a clinical perspective: MP, GP, ACi, CL.
Writing the review: MP, ACi, GP, CL, JF.
Update of the review: MP.

DECLARATIONS OF INTEREST

Mario I Perman received honoraria from laboratory Fresenius-Kabi S.A (Buenos Aires-Argentina) for doing educational activities in the field of parenteral nutrition in different clinical settings. He has not received any type of financial support from Fresenius-Kabi S.A. for doing or writing this Cochrane review.

Agustín Ciapponi: none declared.

Cecilia Loudet: none declared.

Adriana Crivelli: none declared.

Virginia Garrote: none declared.

Gastón Perman: none declared.

Juan VA Franco: none declared.

SOURCES OF SUPPORT

Internal sources

- None, Argentina.

External sources

- None, Argentina.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Background section

1. The original Background section contained a single description without subheadings. We updated the references and divided them into level two subheadings according to the *Cochrane Handbook for Systematic Reviews of Interventions* recommendations (Higgins 2011).

Objectives and outcomes

1. Modifications in order to comply with the latest MECIR standards (Higgins 2016): we modified the wording of the objectives in order to comply with Standard R5 and R22; we provided additional detail for the definition of outcomes in order to comply with Standard R32; we provided detail on the GRADE methods in order to comply with Standard C23 and R98; we provided detail on subgroup analysis (Standard R52)
2. In order to have only three primary outcomes (according to Higgins 2011), we changed the order of the primary and secondary outcomes stated in the protocol (Perman 2009), while maintaining all the predefined ones. The primary outcomes for this review were: mortality (in hospital, in ICU and at 30 days); length of stay (in hospital and in ICU) and infectious complications. The secondary outcomes we were able to evaluate were: length of mechanical ventilation, non-infectious complications, carbohydrate metabolic outcomes (hyperglycaemia, hypoglycaemia), protein metabolic outcomes (nitrogen balance). However, we include seven outcomes in the 'Summary of findings' table. These main outcomes were considered for the subgroup analysis.

Criteria for inclusion of studies

1. We provided further detail on the inclusion criteria for the Types of interventions that initially was broadly defined as " 1) normo- or hypercaloric NS: equal or more than the measured REE or 25 kcal/kg/day (with the same characteristics as above); or 2) no nutrition support at all: fasting or dextrose solutions". We added "We evaluated results of trials designed to compare prescribed hypocaloric enteral or parenteral nutrition support (or permissive underfeeding) with standard nutrition support, or with no nutrition, even if those trials did not reach their caloric goals in the intervention or control groups (intention-to treat analysis). We did not include trials that planned to provide full nutrition support but resulted in unintended hypocaloric provision (for any reason)."

Search methods

In Electronic searches we made some changes: we applied the trial filter for therapy, maximizing sensitivity developed by HIRU (Health Information Research Unit at McMaster University: hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx. We consulted the following trial registries: ClinicalTrials.Gov: clinicaltrials.gov/ct2/home; International Clinical Trials Registry Platform (WHO): apps.who.int/trialsearch/); and ISRCTN Registry: www.isrctn.com/. The LILACS strategy was improved (Appendix 4). We did not perform ISI SciSearch due to lack of access to the database. We did not contact relevant societies to identify abstracts, since we checked the conference proceedings of those societies directly.

Data collection and analysis

1. We updated the sections Selection of studies, Data extraction and management, Assessment of risk of bias in included studies according to the latest MECIR standards (2016) and *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They were initially in different subheadings and now use the current recommended subheadings.
2. We added the sections Measures of treatment effect, Unit of analysis issues, Dealing with missing data and Assessment of reporting biases that were not present in the original protocol.
3. We constructed the section Assessment of heterogeneity and Data synthesis with the information present in "Analysis" in the original protocol.
4. We modified the sections Assessment of heterogeneity and Data synthesis, to adjust the cut-off points to classify and report heterogeneity according to Higgins 2011 (Section 9.5.2).
5. We added a section for the methods used to develop the 'Summary of findings' table using the GRADE approach (see Sensitivity analysis).

Methods not implemented

1. Several outcomes stated in the protocol were not reported in the trials; for this reason we were not able to conduct some predefined subgroup analyses. We did a subgroup analysis not prespecified in the protocol to assess the effect of the route of nutrition support (enteral or parenteral). We considered this to be relevant after the search strategy was performed, but before we had conducted any analysis.

Post hoc analysis

1. After collecting the data about the calories received by both groups of participants in the included studies, and before the analysis of results, we decided to perform the subgroup analysis of the amount of calories received according to the following categories: very hypocaloric, hypocaloric, normocaloric and hypercaloric.
2. We performed two sensitivity analyses not previously stated in the protocol. In one of them we excluded three studies (Ibrahim 2002; NHLBI 2012; Rice 2011) with a different primary goal: they evaluated early initiation of low-dose enteral nutrition (hypocaloric trophic feeding) against full enteral dose from the beginning (normocaloric standard feeding). In the other sensitivity analysis, we excluded a study (Battistella 1997), primarily designed to compare parenteral nutrition without the administration of intravenous lipid emulsion (hypocaloric) and with lipids (normocaloric).
3. When we found high levels of clinical and statistical heterogeneity, we performed a non-prespecified meta-regression using STATA 13.1 to explore the effect of several covariates on the main outcomes (Appendix 5).

Change in authorship

1. Juan VA Franco has joined the review team.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness [mortality]; Caloric Restriction [*methods]; Cause of Death; Critical Care; Enteral Nutrition [methods]; Hospital Mortality; Length of Stay; Nutritional Support [*methods]; Parenteral Nutrition [methods]

MeSH check words

Adult; Humans