Calorie delivery and clinical outcomes in the critically ill: a systematic review and meta-analysis

Harshel G Parikh, Asaf Miller, Marianne Chapman, John L Moran, Sandra L Peake

ABSTRACT

Objectives: To determine the effect of calorie delivery on hospital mortality among critically ill adults receiving enteral nutrition (EN). Secondary outcomes included the effect of calorie delivery on intensive care unit and hospital length of stay (LOS), duration of mechanical ventilation (MV) and incidence of new-onset pneumonia.

Methods: We identified randomised clinical trials of EN, with or without supplemental parenteral nutrition (PN), involving adult ICU patients for whom mortality data were available, and when there was a significant difference in calorie supplementation between intervention arms (P < 0.05). We searched English language electronic databases (1946–2014), bibliographies of nutrition society guidelines and high-impact nutrition and critical care journals. We calculated summary odds ratio (OR) estimates and 95% confidence intervals using a random effects estimator, and used meta-regression to assess the effect on mortality of average calories delivered.

Results: Of 1545 articles identified, 16 eligible studies involving 3473 patients were included. Five studies involved supplemental PN. Mean calorie delivery ranged from 126 kcal/day (SD, 115 kcal/day) to 2086 kcal/day (SD, 460 kcal/day). Mortality was 26.0% in the lower calorie delivery group and 26.5% in the higher calorie delivery group. There was no effect of increased calorie delivery on mortality (OR, 1.02; 95% CI, 0.85–1.24; P = 0.27; I² = 16.3%). ICU and hospital LOS and incidence of new-onset pneumonia did not differ between groups. Duration of MV was decreased with lower calorie delivery (weighted mean difference, 2.92 days; 95% CI, −4.49 to −1.35 days; P < 0.001; I² = 14.7%). Meta-regression analysis did not show an overall effect on mortality of average calories delivered (P = 0.73; I² = 40.8%).

Conclusion: Delivery of increased calories via the enteral route, with or without supplemental PN, was not associated with a survival benefit.

The generally accepted goals of artificial nutrition support in the critically ill are to prevent nutrient deficiencies by providing adequate macronutrients and micronutrients, preferably via the enteral route, and to avoid metabolic disturbances and delivery-associated complications such as vomiting and aspiration.1–8

Studies examining the relationship between calorie delivery and outcome have yielded conflicting results. Observational studies have suggested that a cumulative calorie deficit is associated with adverse clinical outcomes, including increased infectious complications and a prolonged length of stay (LOS) in the intensive care unit.9,10 In critically ill patients with sepsis, the delivery of an additional 1000 kcal/day has also been associated with decreased hospital mortality (censored at 60 days; odds ratio [OR], 0.61; 95% CI, 0.48–0.77).11 Similarly, in a double-blind, randomised feasibility trial conducted in 112 patients on mechanical ventilation (MV), Peake and colleagues reported that enteral delivery of 100% of estimated calorie requirements was associated with a trend towards improved 90-day survival, compared with delivery of 70% of requirements (OR, 0.62; 95% CI, 0.25–1.55).12

Conversely, a lower calorie intake has also been associated with improved clinical outcomes in critically ill patients. In 2003, a small observational study of 187 patients suggested a negative relationship between full-feeding and mortality.13 Receipt of 33%–66% of estimated calorie requirements was associated with increased survival. Subsequent randomised controlled trials (RCTs) have reported that increased calorie delivery was not associated with decreased mortality, morbidity or duration of MV,14–18 but, importantly, none of these trials was blinded, and the Eden study15 was not powered to detect a mortality difference. Braunschweig and colleagues, in a single-centre RCT, recently reported that receiving more than 75% of estimated energy and protein requirements was associated with significantly higher in-hospital mortality in critically ill patients with acute lung injury.17

The question of how many calories should be given to critically ill patients to optimise survival and functional outcomes therefore remains unanswered. The primary aim of our systematic review and meta-analysis was to examine the relationship between calories delivered and mortality in critically ill adult patients. Secondary aims were to determine the effect of calorie delivery on the other clinically important outcomes of ICU and hospital LOS, and incidence of new-onset pneumonia.
Methods

The methods for article selection, analysis and reporting of results were based on a protocol developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.\(^{19}\)

Selection of trials

We included only RCTs of enteral nutrition (EN), with or without supplemental parenteral nutrition (PN), involving critically ill adult patients, in which mortality was reported as an outcome, and which had a significant difference in calorie delivery between two or more intervention arms \((P < 0.05)\). To ensure that included studies were representative of critically ill patients, we included only studies conducted in ICUs and in which \(\geq 50\%\) of recruited patients were receiving MV for \(\geq 24\) hours.

Search strategy

We performed a computerised literature search using the PubMed, Ovid, Embase, Cumulative Index to Nursing and Allied Health (CINAHL) and Cochrane databases for the period 1 January 1946 to 30 May 2015. We restricted our search to adult human studies and used the following search terms: critical illness, intensive care, critical care, enteral nutrition, parenteral nutrition, caloric supplementation, burn units, pneumonia, trauma, trophic, permissive underfeeding, full enteral feeding, nutritional support, enteral nutrition, hypocaloric feeding, PEG tube, gastrostomy tube, post-pyloric feeding, nasogastric tube, gastric tube, NG tube, Levin tube, J tube, G tube, NJ tube, PEJ, energy intake, and hospital mortality. Our search strategy is reported in detail in the Appendix (online at cicm.org.au/Resources/Publications/Journal). We also performed a manual search of high-impact nutrition and critical care journals, including the American Journal of Nutrition, Journal of Enteral and Parenteral Nutrition, Critical Care Medicine and Intensive Care Medicine, for 1 January 2000 to 30 May 2015. We reviewed references of all identified articles and nutrition guidelines\(^3-7\) to identify other relevant articles. We also searched an international clinical trials registry (http://www.clinicaltrials.gov) to identify relevant ongoing or recently completed clinical trials.

Data extraction and quality assessment

Two investigators (HP and AM) independently identified all relevant studies using the pre-specified selection criteria. Differences of opinion were resolved with discussion, and consensus with the other study investigators was reached. Data extracted included:

- study characteristics (lead author, publication year, year recruitment commenced)
- participant characteristics (number of patients recruited; edical, surgical or mixed patient cohort; age; sex; body mass index [BMI]); Acute Physiology and Chronic Health Evaluation [APACHE] II score
- intervention studied (type of nutritional support, calories and protein delivered)
- outcomes (hospital mortality, ICU and hospital LOS, incidence of new-onset pneumonia).

The same investigators independently performed a quality assessment of the selected studies, as recommended in the Cochrane handbook for systematic reviews of interventions,\(^{20}\) and included evaluation of the risk of bias in sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias.

Statistical analysis

Regardless of the actual calorie amount delivered in the individual trials, the intervention arms were coded “higher calorie delivery” and “lower calorie delivery” relative to the comparator group for the respective trials. Summary estimates for hospital mortality and other binary outcomes were calculated using the generic inverse variance method, with random-effects models for all outcomes. We used the fixed-effect model to estimate the effect of higher calorie delivery on hospital mortality. We expressed results as risk ratios (RR) with 95% confidence intervals (CIs). We assessed the publication bias using funnel plots, which included all studies identified (up to a point on the plot). We performed sensitivity analyses for the secondary outcomes. We planned to include a subgroup analysis for patients with burns. We calculated the number of patients recruited in these trials and the minimum number that would be required if the RR was 0.8 for hospital mortality (objective #1), 0.9 for ICU mortality (objective #2) and 0.9 for hospital LOS (objective #3). We used the generic inverse variance method with fixed-effect models for mortality outcomes and random-effects models for hospital LOS outcomes.

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**Figure 1. Study selection**

- 8759 records identified through database search
- 602 duplicate publications removed
- 1545 titles and abstracts screened
- 1471 did not meet study inclusion criteria
  - 65 Not human population
  - 880 Not adult critically ill population
  - 456 Not randomised clinical trial
  - 26 Not in English
  - 34 Not relevant
- 74 full text articles assessed for eligibility
- 29 studies with statistically significant difference in calorie delivery
- 10 studies comparing EN in both arms
- 11 studies of EN
- 5 studies of EN combined with supplemental PN

EN = enteral nutrition. PN = parenteral nutrition. a. Not related to nutrition support or related to micronutrients, trace elements or immune nutrition, etc. b. Defined as when the reported difference in calorie delivery was \(P < 0.05\). c. 13 studies excluded: EN v PN (\(n = 6\)); PN v PN (\(n = 2\)); EN v intravenous fluids (\(n = 2\)); total daily calories delivered not reported (\(n = 3\)).
were analysed using the DerSimonian–Laird random effects estimator and are reported as ORs with 95% confidence intervals.

Continuous outcomes, such as ICU and hospital LOS and duration of MV, are reported as a weighted mean difference (WMD) in days, with 95% confidence intervals. Effect estimates are shown as forest plots. Statistical heterogeneity across trials was analysed using the $I^2$ statistic, with values of 35%–50% and ≥50% indicating moderate and substantial evidence of heterogeneity, respectively. Meta-regression (restricted maximum likelihood estimate of between-study variance) was used to assess the effect on mortality of average calories delivered. Small-study effects were assessed using the Harbord modification of the Egger test, and funnel plot asymmetry was assessed and tested using the regtest function of the metafor R module (Vide Infra).

As a sensitivity analysis, we explored the effect of different random effect distributions (normal, $t$ and normal–mixture) and outlier status using the metaplus module (http://cran.rproject.org/web/packages/metaplus/metaplus.pdf). We also used a suite of diagnostic tools for the identification of influential studies in the metafor module, both packages being implemented in R statistical software (version 3.1.3).

Results

Our preliminary search identified 1545 clinical trials of artificial nutrition support (Figure 1). Of these, 1471 studies were initially excluded for the following reasons: non-critically ill adult population ($n = 860$); not an RCT ($n = 486$); non-human studies ($n = 65$); non-English language

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Table 1. Patient characteristics and mortalities in the included studies

<table>
<thead>
<tr>
<th>Study first author</th>
<th>Year</th>
<th>Group</th>
<th>$n$</th>
<th>Age, years*</th>
<th>Male, n (%)</th>
<th>APACHE II score*</th>
<th>BMI (kg/m²)*</th>
<th>Calories (kcal/day)*</th>
<th>Mortality, n (%)</th>
</tr>
</thead>
<tbody>
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<td>Montecalvo²⁷</td>
<td>1992</td>
<td>Lower</td>
<td>19</td>
<td>44.8 (15.9)</td>
<td>13 (68.4)</td>
<td>21.7 (8.2)</td>
<td>na</td>
<td>1182 (603)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher</td>
<td>19</td>
<td>50.5 (21.5)</td>
<td>10 (52.6)</td>
<td>24 (6.7)</td>
<td>na</td>
<td>1209 (344)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Taylor²⁸</td>
<td>1999</td>
<td>Lower</td>
<td>41</td>
<td>28¹</td>
<td>na</td>
<td>14¹</td>
<td>na</td>
<td>na</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher</td>
<td>41</td>
<td>34¹</td>
<td>na</td>
<td>14¹</td>
<td>na</td>
<td>na</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Kearns²⁹</td>
<td>2000</td>
<td>Lower</td>
<td>23</td>
<td>49 (4)</td>
<td>16 (70)</td>
<td>20 (1)</td>
<td>na</td>
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<td>22 (2)</td>
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<tr>
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<td>Lower</td>
<td>75</td>
<td>61 (19)</td>
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<td>26 (8)</td>
<td>na</td>
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<td></td>
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<td>75</td>
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<td>25 (8)</td>
<td>na</td>
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<td>15 (20)</td>
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<td>2008</td>
<td>Lower</td>
<td>50</td>
<td>64 (13)</td>
<td>31 (62)</td>
<td>40 (11)¹</td>
<td>27 (5)</td>
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<td>11 (22)</td>
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<td>58 (19)</td>
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<td>42 (17)¹</td>
<td>25 (3)</td>
<td>1715 (331)</td>
<td>14 (28)</td>
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<td>Hsu³²</td>
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<td>Lower</td>
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<td>68 (15.3)</td>
<td>43 (69.4)</td>
<td>20.3 (6.9)</td>
<td>23.1 (4.1)</td>
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<td>Lower</td>
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<td>29 (8)</td>
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<tr>
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<td>Lower</td>
<td>98</td>
<td>53 (19)</td>
<td>39 (40)</td>
<td>27 (8)</td>
<td>29 (10)</td>
<td>300 (149)</td>
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<td>28 (9)</td>
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<td>Lower</td>
<td>65</td>
<td>62 (17)</td>
<td>41 (63.1)</td>
<td>22.4 (6.8)</td>
<td>27.4 (7.3)</td>
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<td>35 (53.8)</td>
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<tr>
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<td>2012</td>
<td>Lower</td>
<td>508</td>
<td>52 (17)</td>
<td>267 (53)</td>
<td>92 (28)³</td>
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<td></td>
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<td>52 (16)</td>
<td>243 (49)</td>
<td>90 (27)³</td>
<td>30 (8)</td>
<td>1300³ (221)</td>
<td>109 (22.1)</td>
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<tr>
<td>Huang³⁴</td>
<td>2012</td>
<td>Lower</td>
<td>51</td>
<td>68.3 (6.2)</td>
<td>35 (68.6)</td>
<td>19.6 (6.2)</td>
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<td>2014</td>
<td>Lower</td>
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<td>26 (6)</td>
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<td>28 (8)</td>
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<td>21 (55.3)</td>
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<td>30.1 (8.9)</td>
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<td>6 (15.8)</td>
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<tr>
<td></td>
<td></td>
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<td>40</td>
<td>52.5 (17.1)</td>
<td>19 (47.5)</td>
<td>23.4 (9.3)</td>
<td>29.7 (8.8)</td>
<td>1798 (509)</td>
<td>16 (40)</td>
</tr>
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<td>Arabi¹⁸</td>
<td>2015</td>
<td>Lower</td>
<td>448</td>
<td>50.9 (19.5)</td>
<td>292 (65.2)</td>
<td>21 (7.9)</td>
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<td>835 (297)</td>
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<td></td>
<td>Higher</td>
<td>446</td>
<td>50.9 (19.4)</td>
<td>282 (63.2)</td>
<td>21 (8.2)</td>
<td>29.7 (8.8)</td>
<td>1299 (467)</td>
<td>127 (28.5)</td>
</tr>
</tbody>
</table>

APACHE = Acute Physiology and Chronic Health Evaluation. BMI = body mass index. Lower = lower calorie delivery group. Higher = higher calorie delivery group. na = not applicable. * Mean (SD). † Standard deviation not available. ‡ Simplified Acute Physiology score. § APACHE III score.
n (n = 26); and not relevant (studies not related to nutrition support at all or studies on micronutrients, trace elements, immune nutrition, etc) (n = 34). A total of 74 articles on EN support were short-listed for detailed review, of which 29 reported a significant difference in calorie delivery between treatment groups. Sixteen of the 29 studies compared EN in both arms; 11 used EN alone and five used EN combined with supplemental PN in both arms. In the five studies that used supplemental PN, the predominant mode of calorie supplementation was EN, and when the target calorie requirements were not met, PN was used to achieve the end target caloric requirement.17,18,24–26

Study characteristics

Table 1 and Supplementary Table S1 (see Appendix online at cicm.org.au/Resources/Publications/Journal) summarise the patient characteristics of the 16 included studies and the interventions delivered. The total number of patients enrolled was 3473, comprising 1740 in the lower calorie delivery group and 1733 in the higher calorie delivery group. Patient demographics were similar between the calorie delivery groups. BMI was reported in 12 of the 16 trials and ranged from 23.1 to 32.0 kg/m². The average calorie amount delivered was 126–1480 kcal/day in the lower calorie delivery groups, 24,30 and 474–2086 kcal/day24,30 in the higher calorie delivery groups (Table 1 and Supplementary Figure S1). The within-trial calorie difference ranged from 185 to 1118 kcal/day,16,33 and this set of values was significantly different from zero (Hotelling T² test, P = 0.0001). Ten of the 16 studies reported the amount of protein delivered (Table 2). The average protein delivery was 0.72 g/kg/day (range, 0.15–1.1 g/kg/day).26,30

The quality assessment of the included studies is shown in Supplementary Table S2. Only one study was blinded and deemed to be at low risk of bias across all domains.12 Five other studies had a low risk of bias except for blinding of participants and personnel, 17,18,26,32,33 and 10 were deemed to have additional high or unclear risk of bias in one or more domains.

Clinical outcomes

Mortality

Sixteen trials with a significant difference in calorie delivery between treatment arms reported mortality as an outcome. Thirteen of the 16 trials reported hospital mortality as an endpoint, and three studies reported an undefined mortality endpoint. Overall mortality was 26.0% (453 of 1740 patients) in the lower calorie delivery group and 26.5% (460 of 1733 patients) in the higher calorie delivery group (Table 1). Higher calorie delivery did not confer a mortality benefit (pooled OR, 1.02; 95% CI, 0.85–1.24; P = 0.80) (Figure 2). There was no effect of calorie delivery

<table>
<thead>
<tr>
<th>Study first author</th>
<th>Group</th>
<th>Protein (g/day)*</th>
<th>Protein (g/kg/day)*</th>
<th>Average protein/day (g)†</th>
<th>Average protein/kg/day (g)†</th>
<th>Calorie:nitrogen ratio§</th>
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</thead>
<tbody>
<tr>
<td>Kearns²⁹</td>
<td>Lower</td>
<td>31 (5)</td>
<td>0.4 (0.1)</td>
<td>37.5</td>
<td>0.55</td>
<td>164.08</td>
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<td>0.7 (0.1)</td>
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<td>Lower</td>
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<td>0.06†</td>
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<td>0.15</td>
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<td>0.23†</td>
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<td>Lower</td>
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<td>0.97 (0.39)</td>
<td>63.35</td>
<td>1.04</td>
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<td>1.11 (0.31)</td>
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<td>Lower</td>
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<td>0.62†</td>
<td>45.55</td>
<td>0.59</td>
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<td>43.6 (18.6)</td>
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<td>10.9 (6.8)</td>
<td>0.13†</td>
<td>32.4</td>
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<td>53 (16)</td>
<td>0.67†</td>
<td>64.5</td>
<td>0.81</td>
<td>172.7</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>76 (16)</td>
<td>0.95†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peake¹²</td>
<td>Lower</td>
<td>69 (24)</td>
<td>1.05 (0.33)</td>
<td>68.5</td>
<td>1.03</td>
<td>141.0</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>68 (21)</td>
<td>1.02 (0.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charles²⁶</td>
<td>Lower</td>
<td>86 (6)</td>
<td>1.1 (0.1)</td>
<td>84.5</td>
<td>1.1</td>
<td>85.8</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>83 (6)</td>
<td>1.1 (0.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Braunschweig¹⁷</td>
<td>Lower</td>
<td>60.6 (24)</td>
<td>0.68†</td>
<td>71.3</td>
<td>0.82</td>
<td>132.3</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>82 (23)</td>
<td>0.95†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arabi¹⁸</td>
<td>Lower</td>
<td>57 (24)</td>
<td>0.72†</td>
<td>58</td>
<td>0.725</td>
<td>114.9</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>59 (25)</td>
<td>0.73†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean (SD). † Calculated average per study. § Standard deviation not available. § Calorie:nitrogen ratio calculated by average calorie x 6.25/average protein. Lower = lower calorie delivery group. Higher = higher calorie delivery group.
according to mortality endpoint (hospital, undefined), patient type (mixed, surgical, medical) or mode of calorie delivery (EN with or without supplemental PN) (Supplementary Figure 2). There was no overall evidence of heterogeneity ($I^2 = 16.3\%$; $P = 0.267$), although there was significant heterogeneity in the EN plus supplemental PN subgroup ($I^2 = 60.5\%$; $P = 0.038$ [Supplementary Figure S2B]). There was, again, no effect of calorie delivery on mortality when trials were stratified by low or high risk of bias (Supplementary Figure S3).

Four studies delivered more than 1700 kcal/day$^{12,17,24,31}$ in a high calorie group, and the remaining 12 studies delivered a low calorie amount in both treatment arms. In subgroup analysis of high calorie v low calorie (OR, 1.03; 95% CI, 0.44–2.44; $I^2 = 72.2\%$) and low calorie v low calorie (OR, 1.04; 95% CI, 0.88–1.23; $I^2 = 0\%$), no effect of calorie delivery on mortality was shown (Supplementary Figure S4).

The estimates were robust to differences in random effect distributions, and the posterior probability of any individual study being an outlier was non-significant ($P = 0.169$) (Supplementary Figures S5 and S6). The estimates were also robust to potential influential studies, and two studies$^{15,18}$ were consistently identified across a suite of influence diagnostics. Deletion of these two studies resulted in no change in the overall treatment estimate (OR, 1.03; 95% CI, 0.79–1.35; $I^2 = 25.5\%$). The Harbord modified test for small-study effects was non-significant ($P = 0.90$) and there was no convincing funnel plot asymmetry ($P = 0.89$).

**MV duration and ICU and hospital LOS**

The duration of MV was significantly shorter with lower calorie delivery (WMD, $-2.92$ days; 95% CI, $-4.49$ to $-1.35$ days; $P < 0.001$; $I^2 = 40.8\%$) (W is % residual variation due to heterogeneity). A prediction interval is shown in the dark grey zone and may be interpreted as the region within which one may realistically hope to find the next large study.$^{23}$

* Using log-odds scale with linear prediction effect-line, 95% confidence intervals and point estimate with circles that reflect study size. Triangles represent best linear unbiased predictions (BLUPS, inclusive of random effects), assuming the fitted model is correct. These estimates are shrunk towards the population average effect, consistent with random effects estimation. $I^2 = 40.8\%$ ($I^2$ is % residual variance due to heterogeneity). A prediction interval is shown in the dark grey zone and may be interpreted as the region within which one may realistically hope to find the next large study.$^{23}$
feeding (which aims to deliver > 90%–100% of standard calorie prescription and delivery. Our meta-regression of calories delivered in the context of imbalance between the lower and higher calorie groups can be due to different calculated target calorie intakes. All studies except two had low average calorie intakes.

Infectious complications
There was no difference in the incidence of new-onset pneumonia between the lower and higher calorie delivery groups (OR, 0.92; 95% CI, 0.64–1.30; P = 0.62; I² = 44.1%; n = 2782 patients from 10 studies).

Meta-regression
Random effects meta-regression analysis of the effect of average calories did not show an overall effect of calories delivered on hospital mortality. There was modest heterogeneity across the studies (P = 0.73; I² = 40.8%; Figure 3). The effect of calorie delivery on mortality was not affected by variation in the protein load (P = 0.52) or BMI (P = 0.96).

Discussion
In our meta-analysis of nearly 3500 critically ill adult patients enrolled in 16 RCTs of EN support, with or without supplemental PN, we found no mortality difference between lower and higher calorie delivery groups. We also found no regression effect on mortality for the calorie amount delivered.

Two recent meta-analyses have addressed calorie delivery and clinical outcomes after critical illness. Both studies employed subgroup analysis based on tertiles of standard caloric requirement that was achieved. This strategy was referenced to a medical cohort study of Krishnan and colleagues and based on the 1997 American College of Chest Physicians guidelines. The meta-analysis of Choi and colleagues reported data from only four studies (1540 patients) and found no overall mortality benefit, with an OR of 0.94 (95% CI, 0.74–1.19; P = 0.61) for underfeeding (< 60%–70% of standard calorie requirement) versus full-feeding (which aims to deliver > 90%–100% of standard calorie requirement). In the pre-defined subgroups, there were two studies in the lower tertile and two studies in the middle tertile of standard calorie requirement achieved. The underfeeding group in the lower tertile had significantly lower mortality compared with full feeding (P = 0.05), compared with a non-significant result in the middle tertile subgroup.

A second meta-analysis by Tian and colleagues reported that mortality was significantly lower in the middle tertile of calorie provision compared with the high calorie group. These subgroup analyses should be interpreted with considerable caution because they are based on small study numbers (two to four) and an empirical tertile categorisation of calories delivered in the context of imbalance between study calorie prescription and delivery. Our meta-regression of average calories with hospital mortality suggested no difference in mortality between the two groups with modest heterogeneity. The prediction intervals (Figure 3) imply that a future large RCT may not find a mortality difference between lower and higher calorie delivery groups.

Duration of MV in the lower calorie delivery group was significantly less than in the higher calorie delivery group, which is in accordance with a nested cohort study by Arabi and colleagues conducted using the individual patient data from a previous RCT. In contrast, Elke and colleagues observed that the addition of 1000 kcal/day was associated with more ventilation-free days. Therefore, our MV results should be interpreted with caution because they are based on only five studies and 679 patients.

Strengths and limitations
Our meta-analysis, with a sample size of 3473 and 913 mortality events, may be considered to be adequately powered to evaluate a moderate calorie-treatment effect, as suggested by the work of Flather and colleagues. Our search strategy was broad and included all studies of EN, with or without supplemental PN, including the recent study by Arabi and colleagues. We used a structured and accepted assessment approach, the Cochrane Collaboration tool, to assess the risk of bias. However, our study has certain limitations. First, although the meta-analysis involved 16 studies and 3473 patients, most of the studies were small, underpowered to show an effect of calories on mortality, and had methodological flaws. Only one study was blinded. This being said, the possibility of non-normal distribution of the random effects implied by the standard (DerSimonian–Laird) approach and/or the presence of outliers was excluded in our sensitivity analysis. Our study protocol was completed before we started the meta-analysis, but it was not registered or pre-published, and non-English studies were not included, introducing potential bias in the results.

Second, there were marked differences in the target calories and the calorie amounts actually delivered to patients in lower and higher calorie groups in individual trials; differences that have frequently been observed. The differences in target and delivered calories in the lower calorie groups can be due to different feeding regimens of the individual trials and different feed formulations. The differences in target and delivered calories in the higher calorie groups can be due to different calculated target calorie intakes. All studies except two had low average calorie intakes.

Third, it is also important to consider the impact of protein dose when determining the effect of calorie delivery on outcomes. Calorie and protein delivery are interrelated, so there are potential problems in conducting separate analyses. It has also been suggested that calorie delivery may only have an outcome effect when the protein dose exceeds...
a certain threshold (postulated to be about 1.2–1.5 g/kg/day).⁴⁰ Ten of the 16 trials we examined documented the amount of protein delivered, but the protein dose varied substantially among the trials and was less than recommended in guidelines (1.2–1.5 g/kg/day).⁴,⁵ Although variation in protein supplementation may be considered a potential confounding factor of the calorie effect, meta-regression of the mortality effect of protein load (P = 0.52) suggested that the primary outcome results of our meta-analysis were robust. Not surprisingly a multivariate meta-regression analysis of the effect of calorie provision and protein load on mortality showed non-significant effects for both predictors (P = 0.46 for calorie provision, and P = 0.34 for protein load; interaction, P = 0.47; joint test of both covariates, P = 0.61 in 10 studies; I² = 53.5%).

Fourth, there was also marked variability in the BMI although, again, the effect of BMI was not significant (P = 0.96). Finally, there was variability in the reporting of secondary outcomes and in the definitions of pneumonia.

Conclusion
Our meta-analysis of all published trials reporting a significant difference in calorie delivery and hospital mortality did not show an effect of calorie delivery on mortality outcome. A large multicentre RCT is needed, as the current set of trials was beset by lack of allocation concealment, and the sample size of our meta-analysis could be insufficient to identify a small treatment effect.

Competing interests
None declared.

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