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

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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.

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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 study[15] 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 ≥ 50% of recruited patients were receiving MV for ≥ 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:

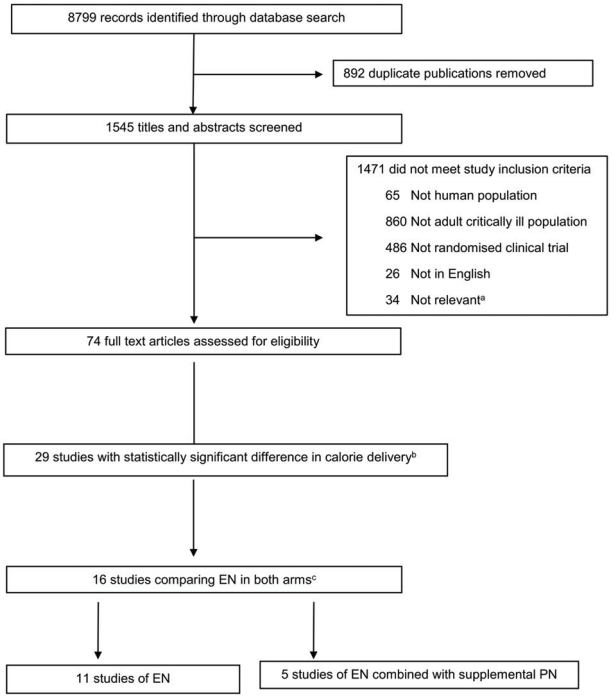
- study characteristics (lead author, publication year, year recruitment commenced)
- participant characteristics (number of patients recruited; edical, surgical or mixed patient cohort; age; sex; body mass index [BMI]); Acute Physiology and Chronic Health Evaluation [APACHE] II score)
- intervention 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

Figure 1. Study selection



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 ($n = 3$).

Table 1. Patient characteristics and mortalities in the included studies

Study first author	Year	Group	*n*	Age, years*	Male, *n* (%)	APACHE II score*	BMI (kg/m²)*	Calories (kcal/day)*	Mortality, *n* (%)
Montecalvo[27]	1992	Lower	19	44.8 (15.9)	13 (68.4)	21.7 (8.2)	na	1182 (603)	5 (26.3)
		Higher	19	50.5 (21.5)	10 (52.6)	24 (6.7)	na	1209 (344)	5 (26.3)
Taylor[28]	1999	Lower	41	28†	na	14†	na	na	6 (14.6)
		Higher	41	34†	na	14†	na	na	5 (12.2)
Kearns[29]	2000	Lower	23	49 (4)	16 (70)	20 (1)	na	812 (122)	6 (26)
		Higher	21	54 (3)	14 (67)	22 (2)	na	1157 (86)	5 (23.8)
Ibrahim[30]	2002	Lower	75	61 (19)	35 (47)	26 (8)	na	126 (115)	20 (27)
		Higher	75	57 (16)	28 (37)	25 (8)	na	474 (400)	15 (20)
Desachy[31]	2008	Lower	50	64 (13)	31 (62)	40 (11)‡	27 (5)	1297 (331)	11 (22)
		Higher	50	58 (19)	38 (76)	42 (17)‡	25 (3)	1715 (331)	14 (28)
Hsu[32]	2009	Lower	62	68 (15.3)	43 (69.4)	20.3 (6.9)	23.1 (4.1)	1426 (110)	24 (30.7)
		Higher	59	70 (13.1)	42 (71.2)	20.5 (6.4)	23.5 (5.8)	1658 (118)	26 (44.1)
Arabi[16]	2011	Lower	120	50 (21)	86 (72)	25 (8)	29 (7)	1067 (306)	36 (30)
		Higher	120	52 (22)	78 (65)	25 (8)	29 (8)	1252 (433)	51 (42.5)
Rice[33]	2011	Lower	98	53 (19)	39 (40)	27 (8)	29 (10)	300 (149)	22 (22.4)
		Higher	102	54 (17)	47 (46)	27 (7)	28 (9)	1418 (686)	20 (19.6)
Singer[24]	2011	Lower	65	62 (17)	41 (63.1)	22.4 (6.8)	27.4 (7.3)	1480 (356)	27 (41.5)
		Higher	65	59 (18)	35 (53.8)	22.1 (7.4)	27.8 (6.3)	2086 (460)	16 (24.6)
Rice[15]	2012	Lower	508	52 (17)	267 (53)	92 (28)§	30 (8)	400†	118 (23.2)
		Higher	492	52 (16)	243 (49)	90 (27)§	30 (8)	1300†	109 (22.1)
Huang[34]	2012	Lower	51	68.3 (6.2)	35 (68.6)	19.6 (6.2)	23.4 (4.1)	na	17 (33.3)
		Higher	50	70.9 (13.2)	37 (74)	21 (6.8)	24 (6.1)	na	20 (40)
Peake[12]	2014	Lower	55	57 (17)	41 (75)	22 (9)	26 (6)	1259 (428)	14 (27)
		Higher	57	56 (17)	42 (74)	23 (9)	28 (8)	1832 (381)	10 (19)
Petros[25]	2014	Lower	46	67.6 (11.5)	32 (69.6)	30.5 (8.5)	28.6 (6.5)	na	17 (36.9)
		Higher	54	64.3 (11.5)	34 (68)	27.7 (8.4)	27.1 (6.8)	na	17 (34)
Charles[26]	2014	Lower	41	50.4 (2.8)	28 (68.3)	16.6 (0.9)	32.9 (2.0)	982 (61)	3 (7.3)
		Higher	42	53.4 (2.7)	31 (73.8)	17.3 (0.8)	28.1 (0.9)	1338 (92)	4 (9.5)
Braunschweig[17]	2015	Lower	38	58.6 (16.2)	21 (55.3)	27.7 (7.9)	30.1 (8.9)	1221 (423)	6 (15.8)
		Higher	40	52.5 (17.1)	19 (47.5)	23.4 (9.3)	29.7 (8.8)	1798 (509)	16 (40)
Arabi[18]	2015	Lower	448	50.2 (19.5)	292 (65.2)	21 (7.9)	29 (8.2)	835 (297)	121 (27)
		Higher	446	50.9 (19.4)	282 (63.2)	21 (8.2)	29.7 (8.8)	1299 (467)	127 (28.5)

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.

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,[21] 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,[22] both packages being implemented in R statistical software (version 3.1.3).[23]

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

Table 2. Protein supplementation in the included studies in which this was reported

Study first author	Group	Protein (g/day)*	Protein (g/kg/day)*	Average protein/day (g)†	Average protein/kg/day (g)†	Calorie:nitrogen ratio§
Kearns[29]	Lower	31 (5)	0.4 (0.1)	37.5	0.55	164.08
	Higher	44 (4)	0.7 (0.1)			
Ibrahim[30]	Lower	5.3 (5.3)	0.06‡	12.0	0.15	136.98
	Higher	18.7 (15.4)	0.23‡			
Hsu[32]	Lower	58.8 (4.9)	0.97 (0.39)	63.35	1.04	152.13
	Higher	67.9 (4.9)	1.11 (0.31)			
Arabi[16]	Lower	47.5 (21.2)	0.62‡	45.55	0.59	159.05
	Higher	43.6 (18.6)	0.59‡			
Rice[33]	Lower	10.9 (6.8)	0.13‡	32.4	0.39	165.7
	Higher	54.4 (33.2)	0.66‡			
Singer[24]	Lower	53 (16)	0.67‡	64.5	0.81	172.7
	Higher	76 (16)	0.95‡			
Peake[12]	Lower	69 (24)	1.05 (0.33)	68.5	1.03	141.0
	Higher	68 (21)	1.02 (0.28)			
Charles[26]	Lower	86 (6)	1.1 (0.1)	84.5	1.1	85.8
	Higher	83 (6)	1.1 (0.1)			
Braunschweig[17]	Lower	60.6 (24)	0.68‡	71.3	0.82	132.3
	Higher	82 (23)	0.95‡			
Arabi[18]	Lower	57 (24)	0.72‡	58	0.725	114.9
	Higher	59 (25)	0.73‡			

* 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.

(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/m^2. The average calorie amount delivered was 126–1480 kcal/day in the lower calorie delivery groups,[24,30] and 474–2086 kcal/day[24,30] 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 T^2 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]

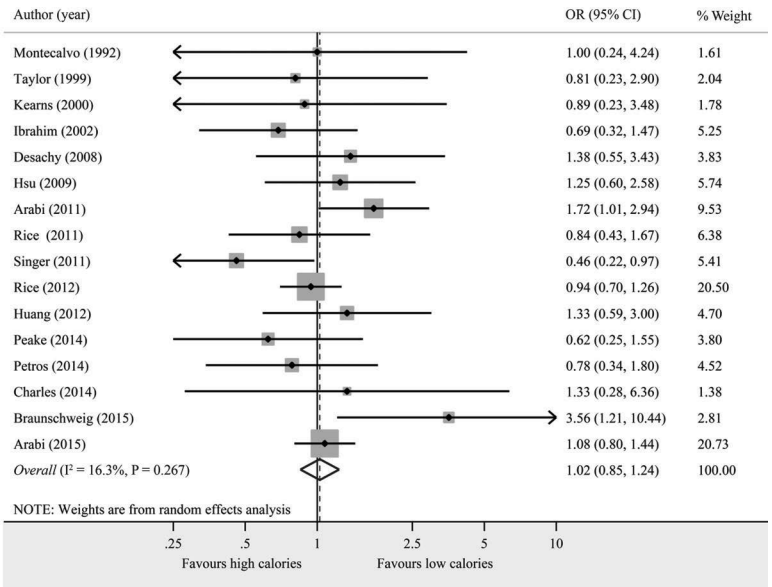
The quality assessment of the included studies is shown in Supplementary Table S2. Only one study was blinded and deemed to be at low risk of bias across all domains.[12] Five other studies had a low risk of bias except for blinding of participants and personnel,[17,18,26,32,33] and 10 were deemed to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

Clinical outcomes

Mortality

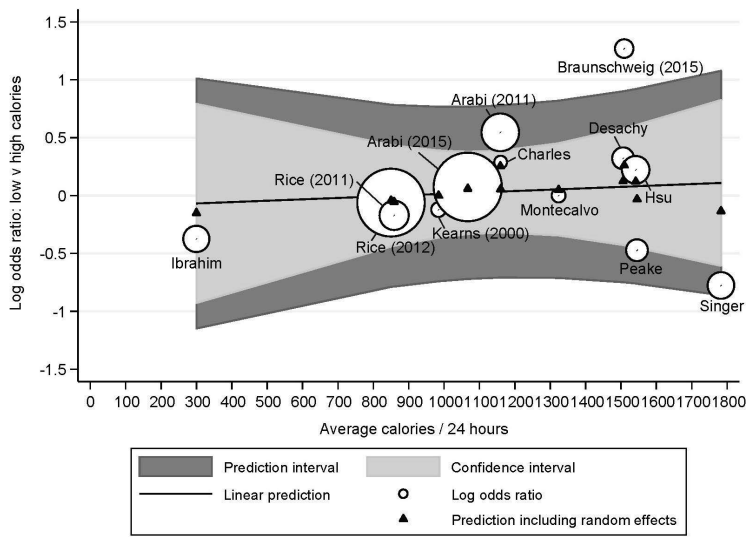
Sixteen trials with a significant difference in calorie delivery between treatment arms reported mortality as an outcome. Thirteen of the 16 trials reported hospital mortality as an endpoint, and three studies reported an undefined mortality endpoint. Overall mortality was 26.0% (453 of 1740 patients) 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

Figure 2. Effect of calorie delivery on mortality for lower and higher calorie delivery groups



OR = odds ratio. Random effects model: individual points denote OR of each study; the lines either side denote 95% confidence intervals; size of square is proportional to study size. Vertical line = null effect. Dashed line = meta-analytic point estimate.

Figure 3. Meta-regression analysis of effect of average calorie delivery on mortality*



* 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 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]

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,[23] 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 = 14.7%; n = 679 patients from five studies) (Supplementary Figure S7). Again, the estimates were robust to differences in random effect distributions, and P for outlier status was 0.99. However, there was no difference in ICU LOS (WMD, –1.052 days; 95% CI, –3.073 to 0.970 days; P = 0.31; I^2 = 86.3%; n = 1085 patients from 10 studies) nor in-hospital LOS (WMD, 0.721 days; 95% CI, –2.954 to 4.396 days; P = 0.70; I^2 = 43.8%; n = 796 patients from seven studies).

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; $P = 0.62$; $I^2 = 44.1\%$; $n = 2782$ 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 ($P = 0.73$; $I^2 = 40.8\%$; 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.[35,36] 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[13] and based on the 1997 American College of Chest Physicians guidelines.[3] The meta-analysis of Choi and colleagues[35] 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[36] 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.[23]

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,[37] conducted using the individual patient data from a previous RCT.[38] In contrast, Elke and colleagues observed that the addition of 1000 kcal/day was associated with more ventilation-free days.[11] 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.[39] Our search strategy was broad and included all studies of EN, with or without supplemental PN, including the recent study by Arabi and colleagues.[18] 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.[12] 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.[10,13,15] 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[12,17] 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; $I^2 = 53.5\%$).

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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Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

CALORIE DELIVERY AND CLINICAL OUTCOMES IN THE CRITICALLY ILL: A SYSTEMATIC REVIEW AND META-ANALYSIS

SUPPLEMENTARY MATERIALS

TABLE OF CONTENTS **PAGE**

1. SEARCH STRATEGY

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to 30 May 2015> Search Strategy:

---

1 Critical Illness/ or Intensive Care Units/ or Critical Care/ or Intensive Care/

2 exp Parenteral Nutrition, Total/

3 exp Parenteral Nutrition/

4 exp Enteral Nutrition/

5 2 or 3 or 4

6 exp Energy Intake/ or calorie.mp. or exp Caloric Restriction/

7 Energy Metabolism/ or energy balance.mp.

8 5 or 6 or 7

9 Nutrition Therapy/

10 8 or 9

11 1 and 10

12 limit 11 to (english language and "all adult (19 plus years)")

13 limit 12 to (controlled clinical trial or randomized controlled trial)

14 mortality.mp. or Hospital Mortality/ or exp Mortality/

15 13 and 14

Database: Embase <1974 to 30 June 2015>

Search Strategy:

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1 exp critical illness/

2 exp intensive care/ or exp intensive care unit/

3 1 or 2

4 exp parenteral nutrition/

5 exp enteric feeding/

6 exp total parenteral nutrition/

7 exp calorie/

8 exp caloric restriction/

9 exp caloric intake/

10 exp energy balance/

11 4 or 5 or 6 or 7 or 8 or 9 or 10

12 3 and 11

13 limit 12 to (english language and (adult <18 to 64 years> or aged <65+ years>))

14 mortality.mp. or exp mortality/

15 13 and 14

16 limit 15 to (randomized controlled trial or controlled clinical trial)

17 limit 16 to yr="1972 -Current"

18 limit 17 to embase

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2013>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 2015>

Search Strategy:

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1 exp critical illness/

2 exp intensive care/ or exp intensive care unit/

3 1 or 2

4 exp parenteral nutrition/

5 exp enteric feeding/

6 exp total parenteral nutrition/

7 exp calorie/

8 exp caloric restriction/

9 exp caloric intake/

10 exp energy balance/

11 4 or 5 or 6 or 7 or 8 or 9 or 10

12 3 and 11

13 limit 12 to (english language and (adult <18 to 64 years> or aged <65+ years>)) (Limit not valid in CCTR,CDSR; records were retained)

14 mortality.mp. or exp mortality/

15 13 and 14

2. Included studies

1. Montecalvo MA, Steger KA, Farber HW, et al (1992) Nutritional outcome and pneumonia in critical care patients randomized to gastic vs. jejunal tube feedings. Crit Care Med 20: 1377-1387

2. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ (1999) Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med 27:2525–2531

3. Kearns P J, Chin D, Mueller L, et al (2000) The incidence of ventilator associated pneumonia and success in nutrient delivery with gastric versus small intestine feedings: A randomized clinical trial. Crit Care Med 28:1742-46

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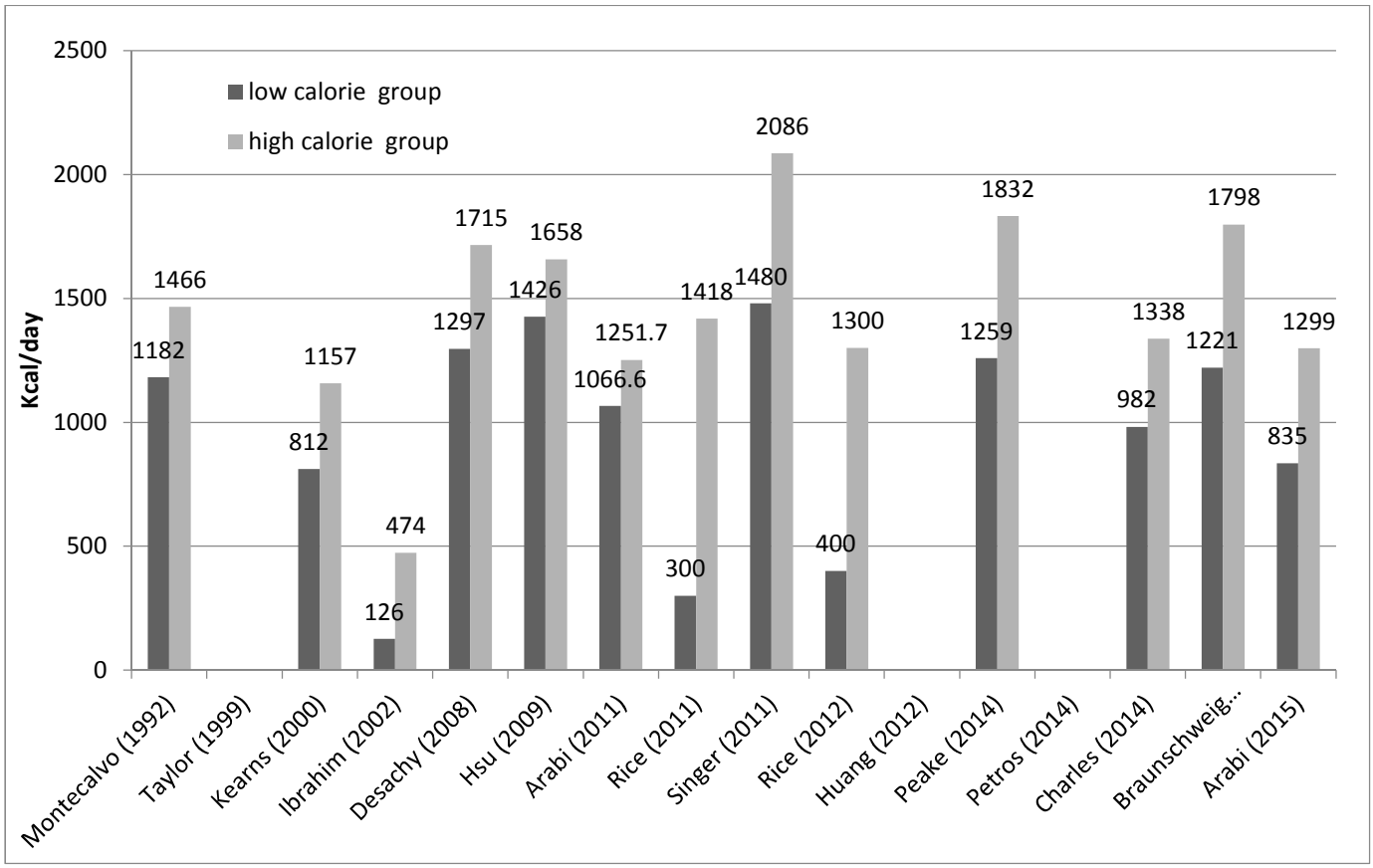
15. Braunschweig CA, Sheean PM, Peterson SJ, et al (2015) Intensive nutrition in acute lung injury: a clinical trial (INTACT). J Parenter Enteral Nutr 39:13–20

16. Arabi YM, Aldawood AS, Haddad SH, et al (2015) Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults- The PermiT Trial. New Engl J Med, DOI: 10.1056/NEJMoa1502826

3. SUPPLEMENTARY FIGURES

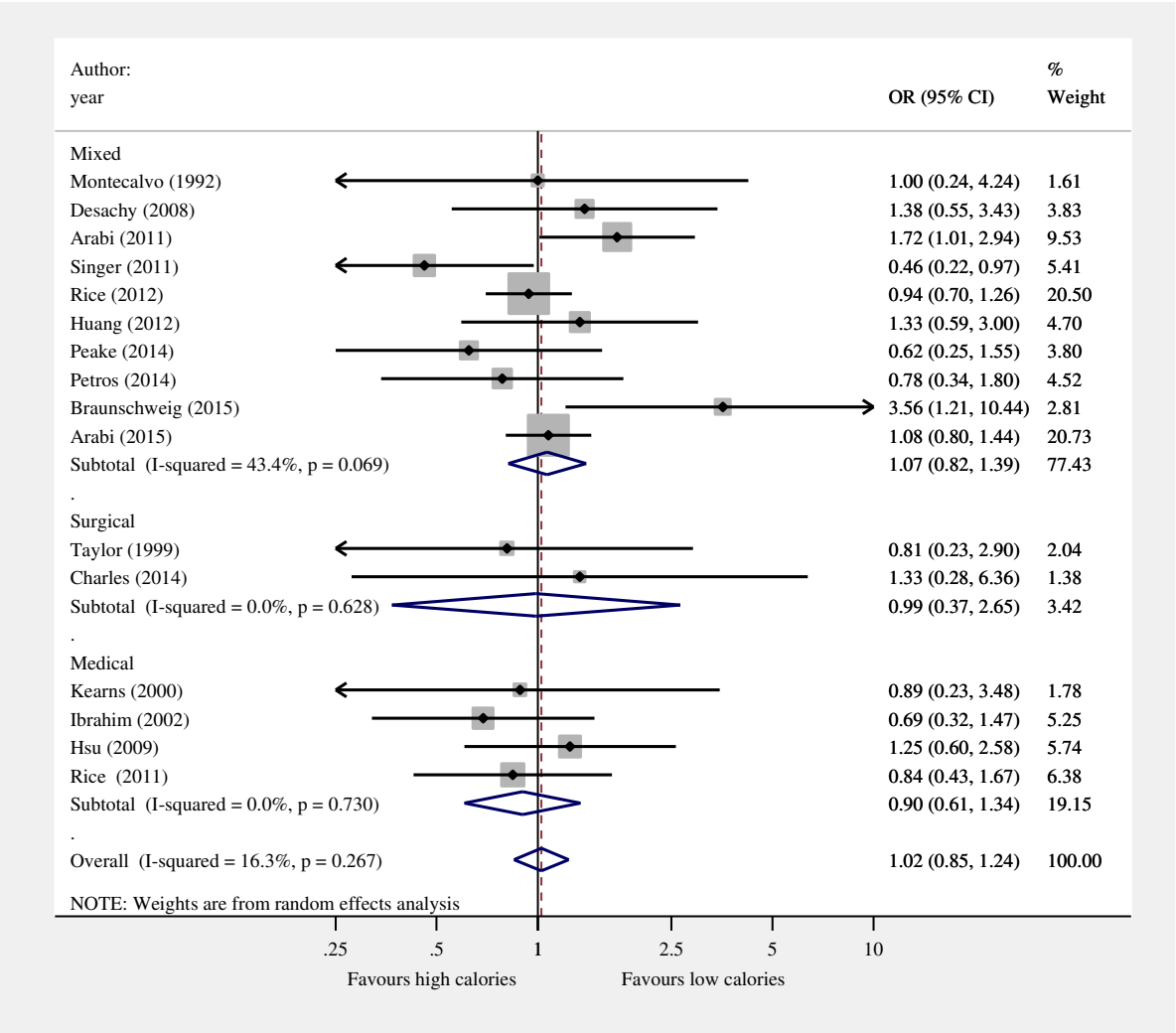
Figure S1. Calorie delivery in both treatment groups



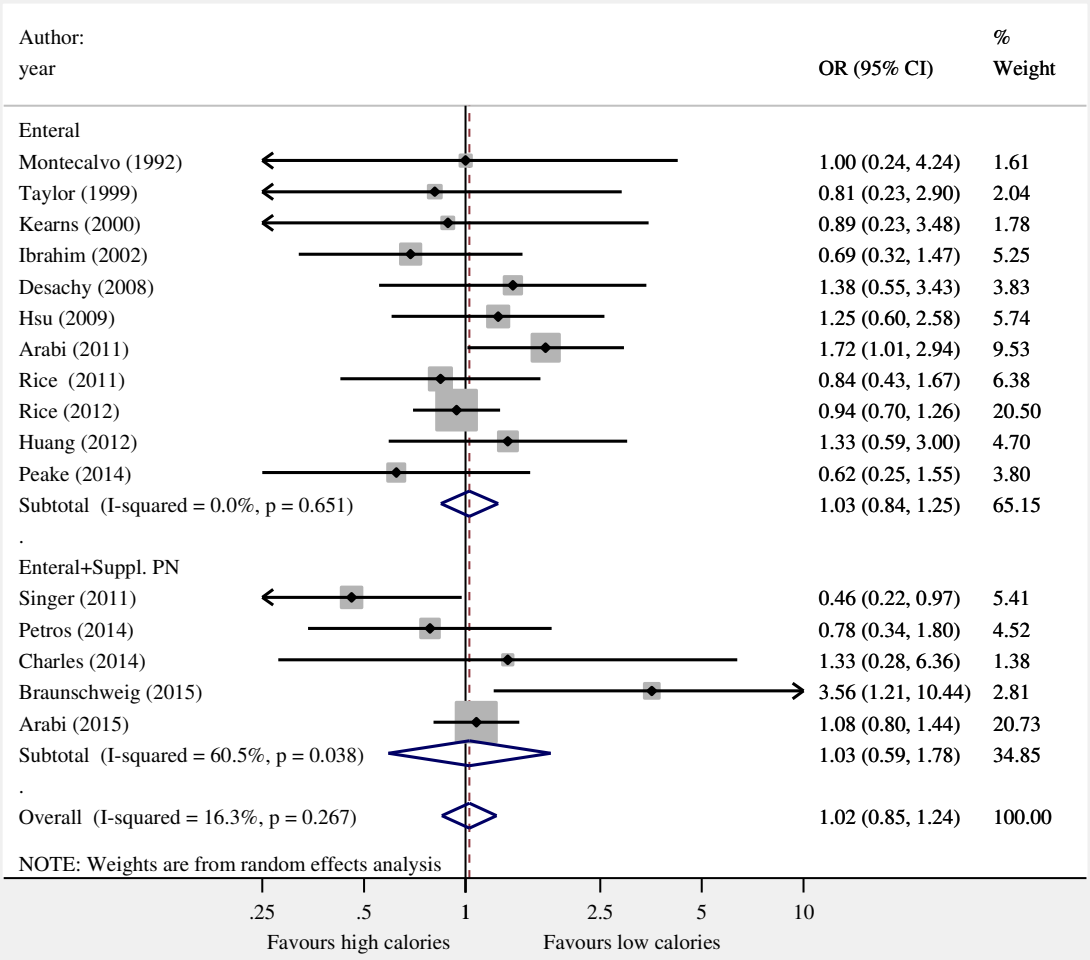
Calorie represented in Kcal/day on Y-Axis. Taylor (1999), Huang(2012) and Petros (2014) trials don't have calorie available in Kcal/day

Figure S2. Effect of calorie delivery on hospital mortality for lower and higher calorie delivery groups

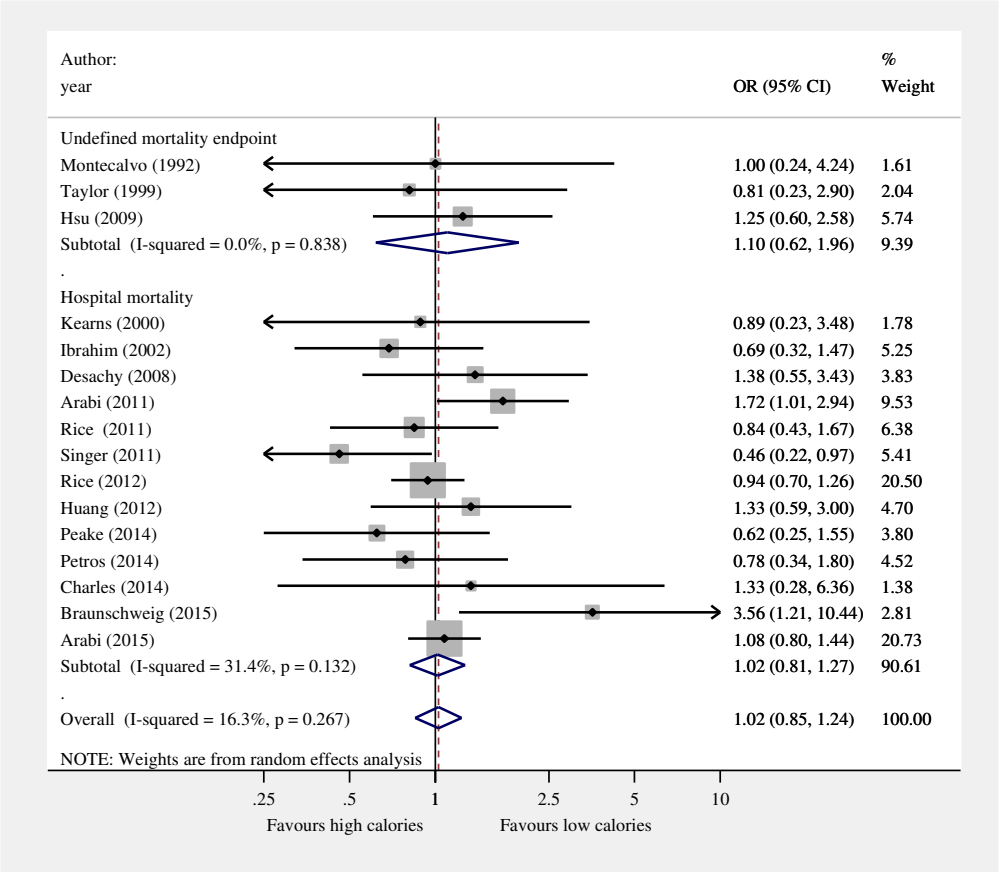
A. By patient type



B. By calorie supplementation



C. By mortality as end point



OR denotes odds ratio; CI, confidence intervals. Random effects model: the individual points denote the OR of each study and the lines either side the 95% CI. The size of the square is proportional to study size. The vertical line represents the null effect

Figure S3 Effect of calorie delivery on hospital mortality stratified on risk of bias

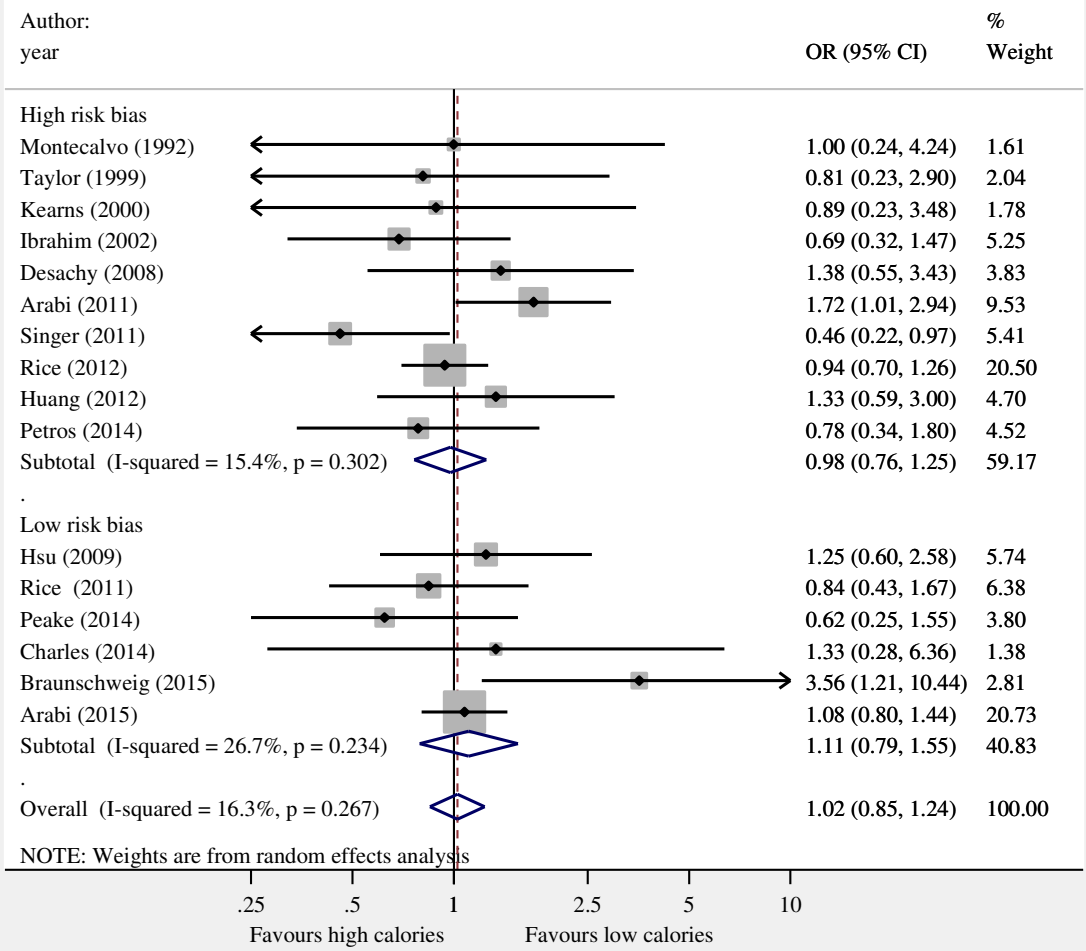
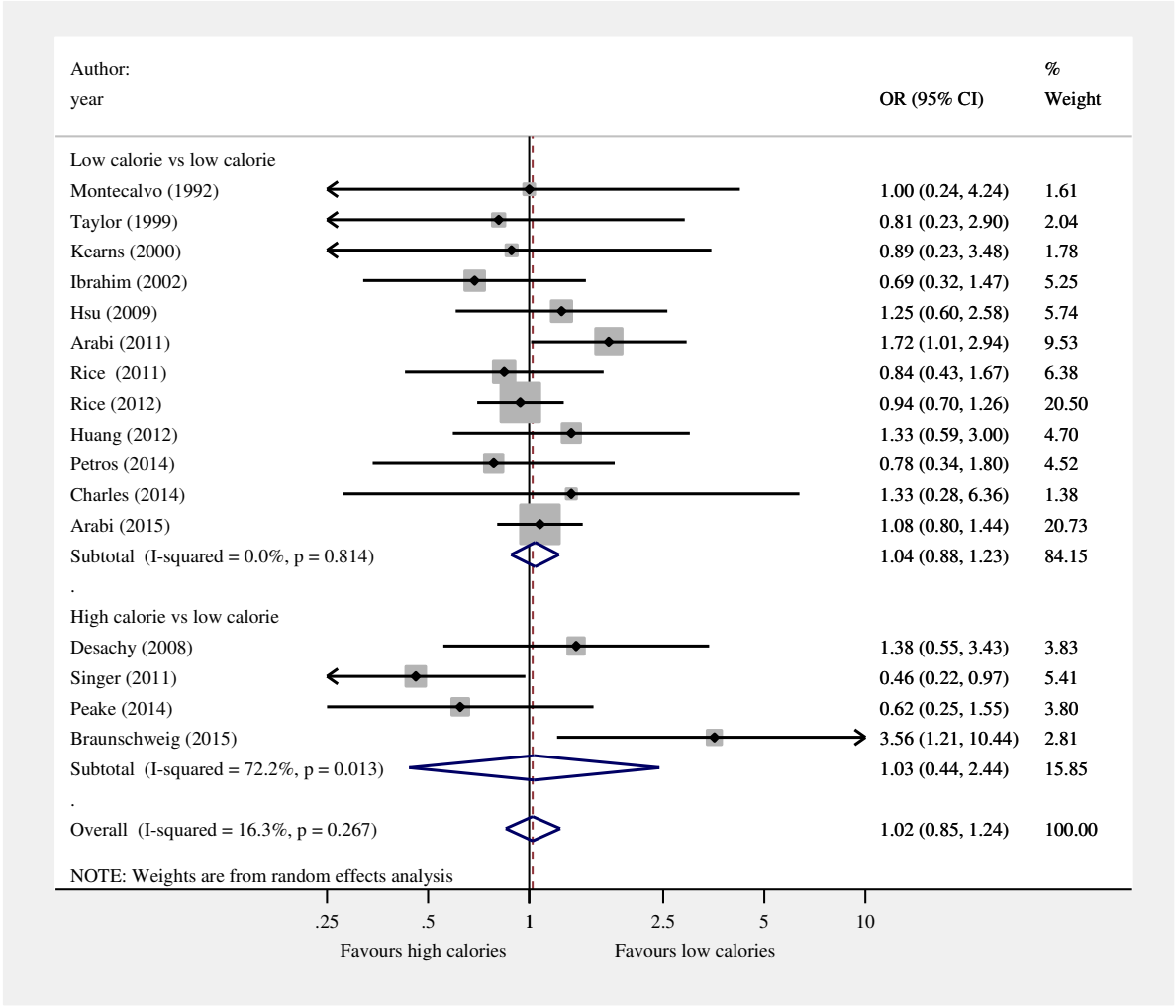


Figure S4. Subgroup analysis "high calorie" vs "low calorie"



OR denotes odds ratio; CI, confidence intervals. Random effects model: the individual points denote the OR of each study and the lines either side the 95% CI. The size of the square is proportional to study size. The vertical line represents the null effect

Figure S5. Outlier probability

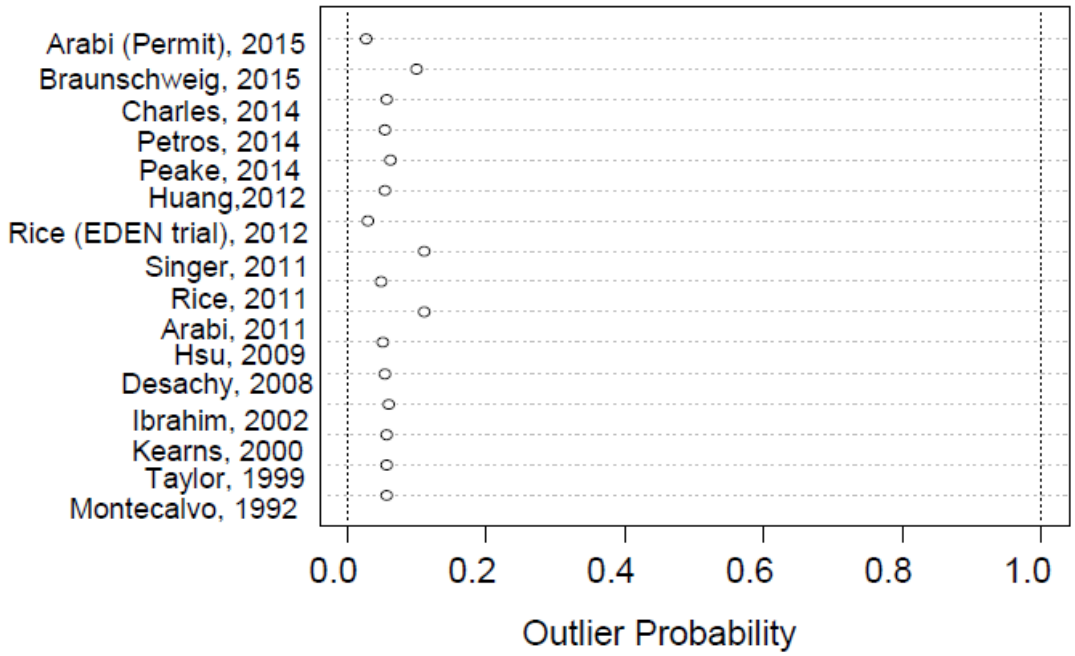


Figure S6. Effect of different RE distributions

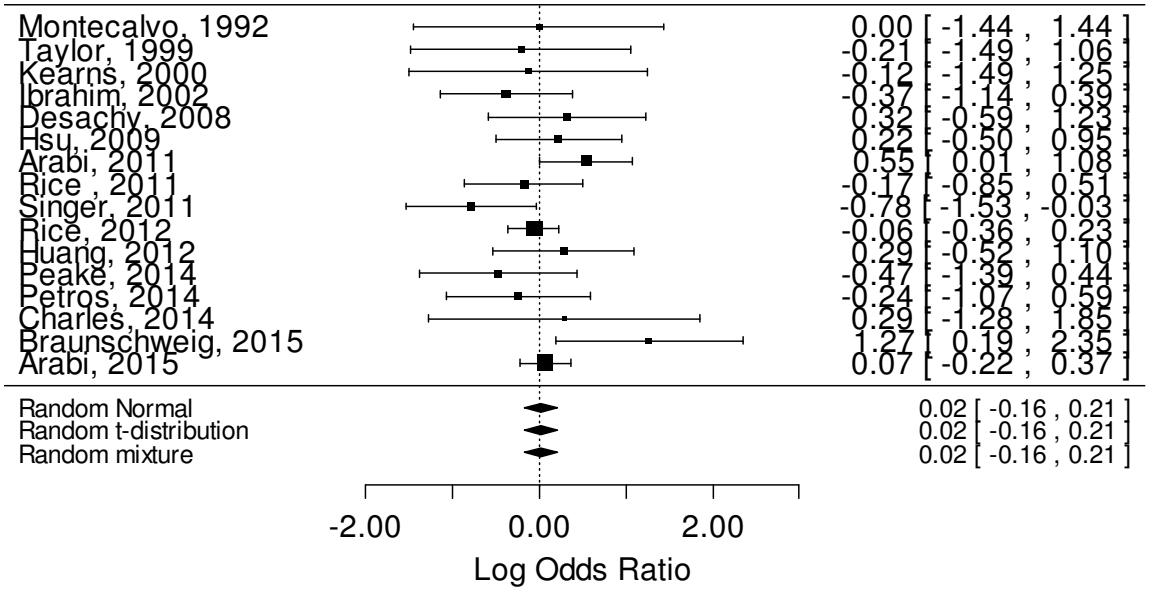
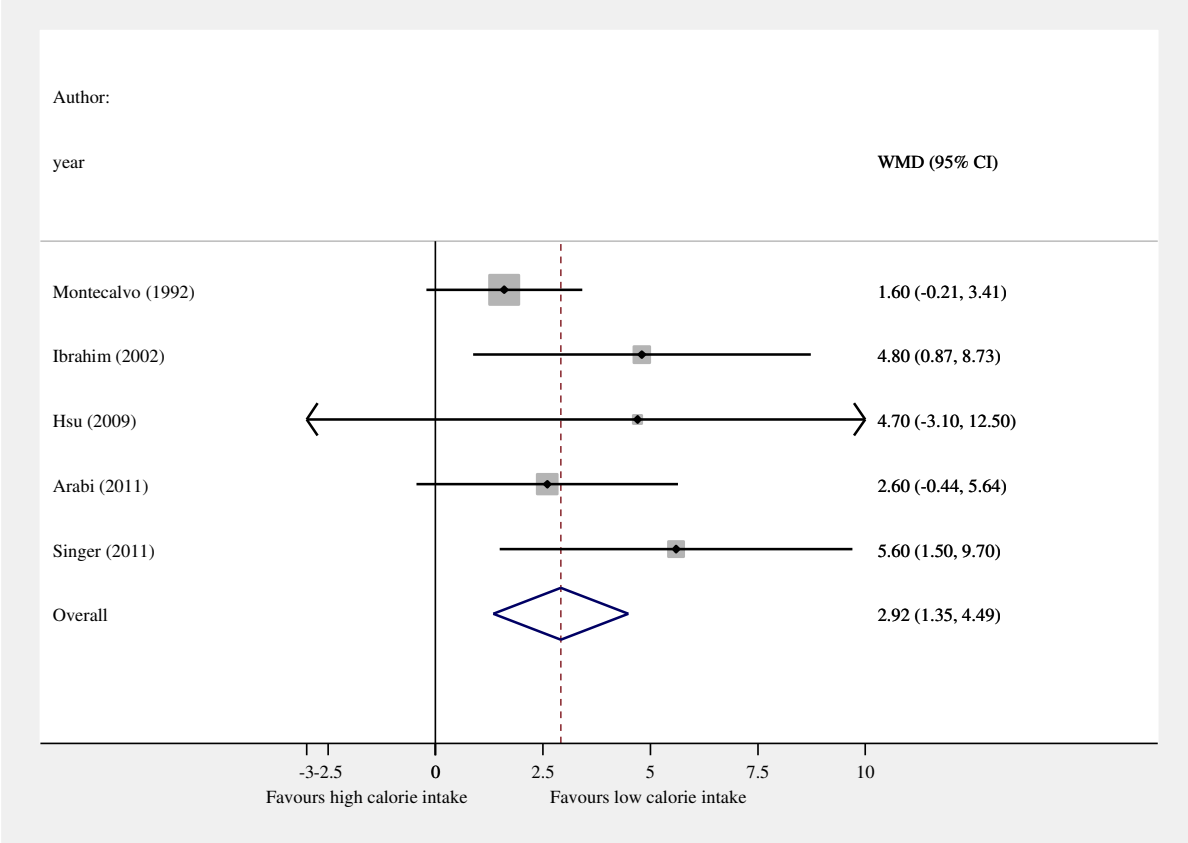


Figure S7. Random effect model of duration of mechanical ventilation



WMD denotes weighted mean difference; CI, confidence intervals. Random effects model: the individual points denote the OR of each study and the lines either side the 95% CI. The size of the square is proportional to study size. The vertical line represents the null effect.

4. SUPPLEMENTARY TABLES

Table S1. Interventions delivered in the included studies

Author	Year	Group	N^0	Intervention
Montecalvo (27)	1992	Lower	19	Enteral feeding via gastric tube
		Higher	19	Enteric feeding via jejunal tube
Taylor (28)	1999	Lower	41	EN gradually increased from 15 mL/hr up to estimated energy and nitrogen requirements
		Higher	41	EN started at a feeding rate that met estimated energy and nitrogen requirements
Kearns (29)	2000	Lower	23	Enteral feeding via nasogastric tube
		Higher	21	Enteral feeding via small intestinal tube
Ibrahim (30)	2002	Lower	75	20% estimated requirements days 1-4 then full requirements from day 5
		Higher	75	Full daily estimated requirements from day 1
Desachy (31)	2008	Lower	50	Early EN at 25 ml/hr and increment of 25 ml/hr per 24 hrs until optimal rate (25 kcal/kg/day)
		Higher	50	Immediate early EN at optimal rate (25 kcal/Kg/day)
Hsu (32)	2009	Lower	62	EN vis nasogastric route
		Higher	59	EN vis naso-duodenal route
Arabi (16)	2011	Lower	120	Permissive underfeeding with caloric goal of 60-70% of calculated requirement
		Higher	120	Target feeding with caloric goal of 90-100% of calculated requirement
Rice (33)	2011	Lower	98	Initial trophic feeding for first 6 days at 10 ml/hr
		Higher	102	EN at 25 ml/hr and increased by 25 ml/hr every 6 hours until target 25-30 kcal/kg/day
Singer (24)	2011	Lower	65	Target calorie calculated by indirect calorimetry *(supplemental PN)*
		Higher	65	Target calorie according to 25 kcal/kg/day *(supplemental PN)*
Rice (15)	2012	Lower	508	Initial trophic feeding at 10-20 ml/hr for 6 days
		Higher	492	Day 1, 25 ml/hr and quickly advanced to target goal rate 25-30 kcal/kg/day
Huang (34)	2012	Lower	51	EN via nasogastric route
		Higher	50	EN via nasoduodenal route
Peake (12)	2014	Lower	55	1 kcal/ml formulation at 1 ml/kg IBW per day for first 10 days
		Higher	57	1.5 kcal/ml formulation at 1ml/kg IBW per day for first 10 days
Petros (25)	2014	Lower	46	50% of daily energy expenditure *(supplemental PN)*
		Higher	54	100%of daily energy expenditure *(supplemental PN)*
Charles (26)	2014	Lower	41	12.5-15 kcal/kg/day via EN (*supplemental PN)*
		Higher	42	25-30 kcal/kg/day via EN (*supplemental PN)*
Braunschweig (17)	2015	Lower	38	Standard nutrition support via EN (*supplemental PN)*
		Higher	40	Greater than 75% of estimated energy and protein via EN (*supplemental PN)*
Arabi (18)	2015	Lower	448	40-70% estimated caloric requirements (*supplemental PN)*
		Higher	446	70-100% estimated caloric requirements (*supplemental PN)*

EN denotes enteral nutrition; PN, parenteral nutrition; IBW, ideal body weight

Table S2. Risk of bias for included studies

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Montecalvo (27)	Low	High	High	High	Low	Low
Taylor (28)	Low	Low	High	Unclear	Unclear	Low
Kearns (29)	High	High	High	High	Low	High
Ibrahim (30)	Low	Low	High	High	Low	Low
Desachy (31)	High	High	High	Unclear	High	Unclear
Hsu (32)	Low	Low	High	Low	Low	Low
Arabi (16)	Low	Low	High	Unclear	High	High
Rice (33)	Low	Low	High	Low	Low	Low
Singer (24)	Low	High	High	High	Low	Low
Rice (15)	Low	Low	High	Low	Low	Unclear
Huang (34)	Low	Low	High	High	Low	Low
Peake (12)	Low	Low	Low	Low	Low	Low
Petros (25)	Low	Low	High	High	Low	Low
Charles (26)	Low	Low	High	Low	Low	Low
Braunschweig (17)	Low	Low	High	Low	Low	Low
Arabi (18)	Low	Low	High	Low	Low	Low

5. ACKNOWLEDGEMENTS

We are grateful to Ms Sue Rockliff (Librarian, The Queen Elizabeth Hospital, Adelaide, South Australia) for assistance with the literature search.