

Appendix

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

SUPPLEMENTARY MATERIALS

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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:

-
- 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:

- 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

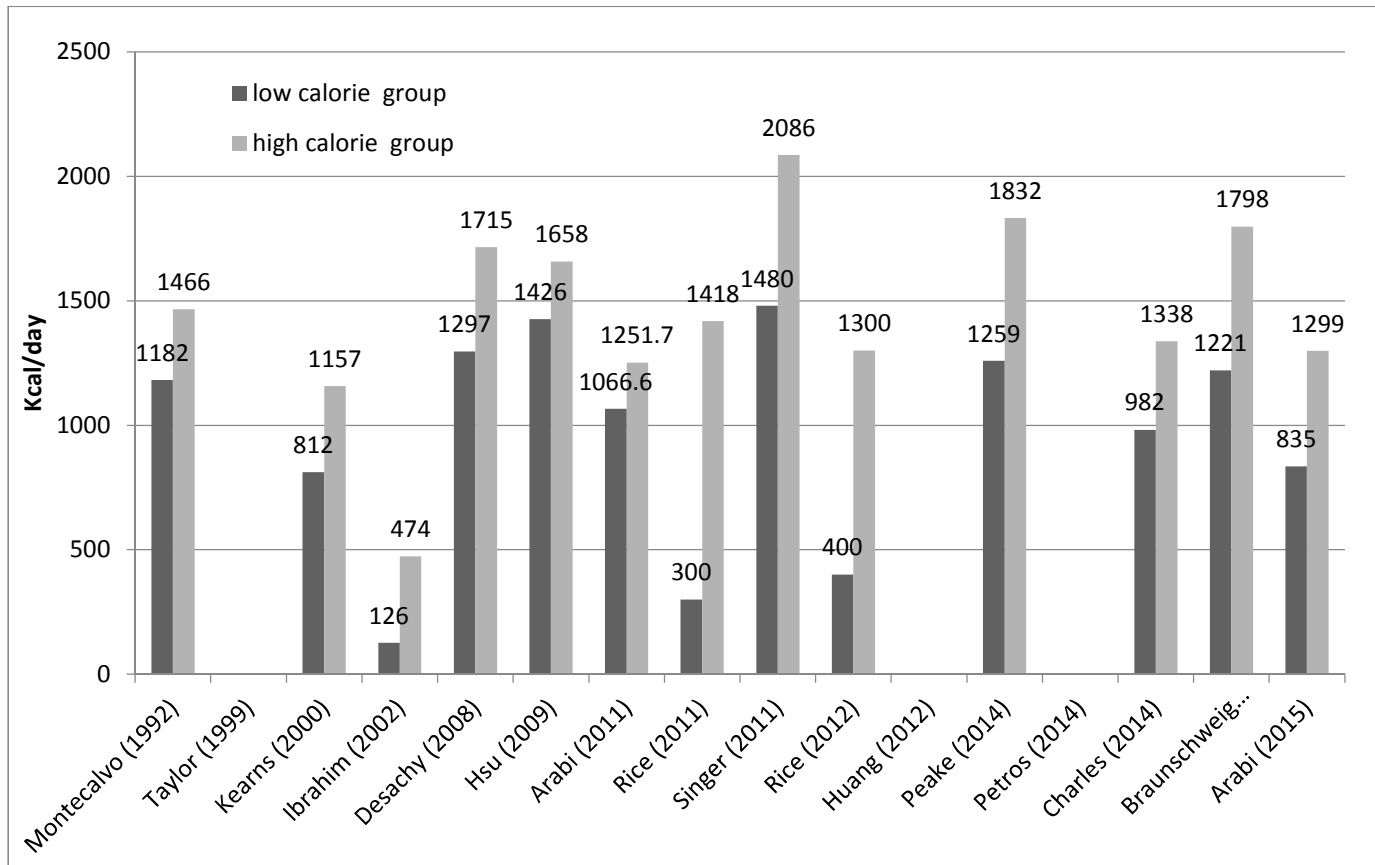
2. Included studies

1. Montecalvo MA, Steger KA, Farber HW, et al (1992) Nutritional outcome and pneumonia in critical care patients randomized to gastric 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
4. Ibrahim E H, Mehringer L, Prentice D, et al (2002) Early vs late enteral feeding of mechanically ventilated patients: Results of a clinical trial. *JPEN J Parenter Enteral Nutr* 26:174-181
5. Desachy A, Clavel M, Vuagnat A et al (2008) Initial efficacy and tolerability of early enteral nutrition with immediate or gradual introduction in intubated patients. *Intensive Care Med* 34:1054-1059
6. Hsu CW, Sun SF, Lin SL et al (2009) Duodenal versus gastric feeding in medical intensive care unit patients: a prospective, randomized, clinical study. *Crit Care Med* 37:1866-72
7. Arabi YM, Tamin HM, Dhar GS, et al (2011) Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *Am J Clin Nutr* 93:569-577
8. Rice TW, Mogan S, Hays MA, et al (2011) Randomized trial of initial trophic vs full energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Crit Care Med* 39:967-973
9. Singer P, Anbar R, Cohen J, et al (2011) The tight calorie control study (TICACOS): A prospective, randomized, controlled pilot study of nutritional support in critically ill patients; *Intensive Care Med* 37: 601-609
10. Rice TW, Wheeler AP, Thompson BT, et al (2012) Initial trophic vs full enteral feeding in patients with acute lung injury: The EDEN randomized trial. *JAMA* 307:795-803
11. Huang HH, Chang SJ, Hsu CW et al (2012) Severity of illness influences the efficacy of enteral feeding route on clinical outcomes in patients with critical illness. *J Acad Nutr Diet* 2012: 1138-1146

12. Peake SL, Davies AR, Deane AM, et al (2014): Use of a concentrated enteral nutrition solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical trial; *Am J Clin Nutr* 100:616-625
13. Petros S, Horbach M, Seidel F, Weidhase L (2014) Hypocaloric vs normocaloric nutrition in critically ill patients: a prospective randomized pilot trial. *JPEN J Parenter Enteral Nutr* April 3, 2014;doi:10.1177/0148607114528980
14. Charles EJ, Petroze RT, Metzger R, et al (2014) Hypocaloric compared with eucaloric nutritional support and its effect on infection rates in a surgical intensive care unit: a randomized controlled trial. *Am J Clin Nutr* 100:1337–1343
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

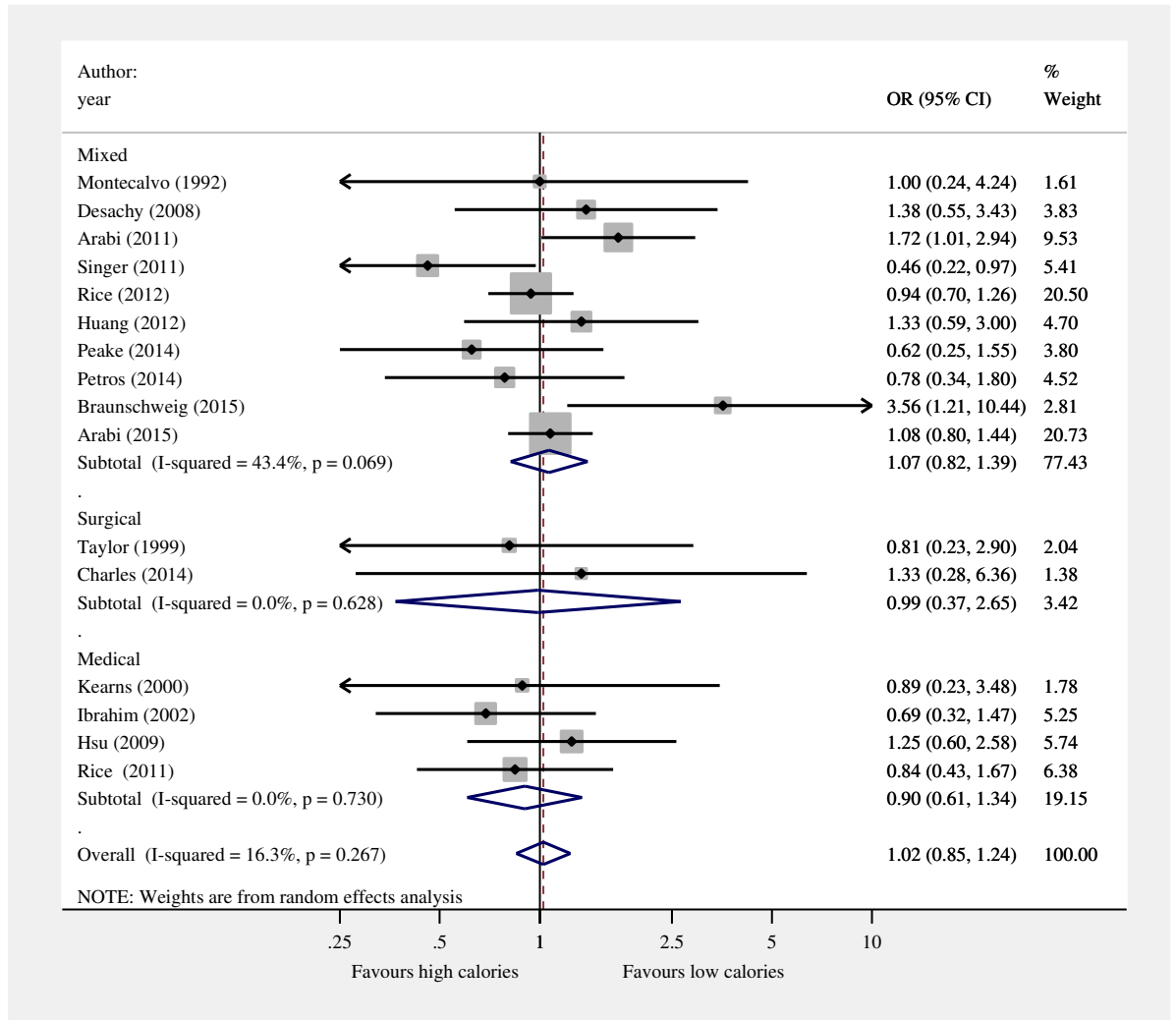
Figure S1. Calorie delivery in both treatment groups



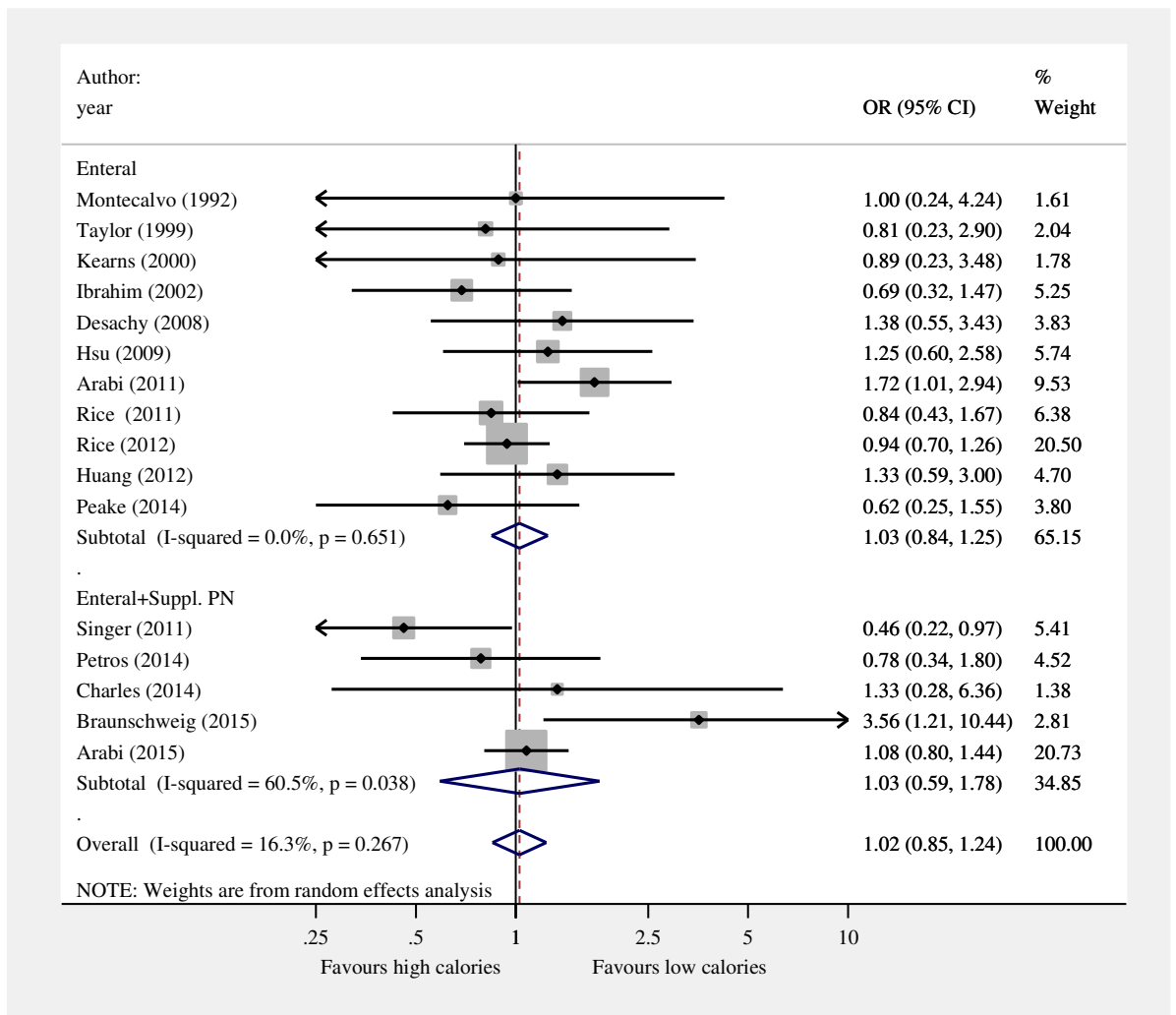
Calorie represented in Kcal/day on Y-Axis. Taylor (1999), Huang(2012) and Petros (2014) trials don't have calorie available in Kcal/day

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

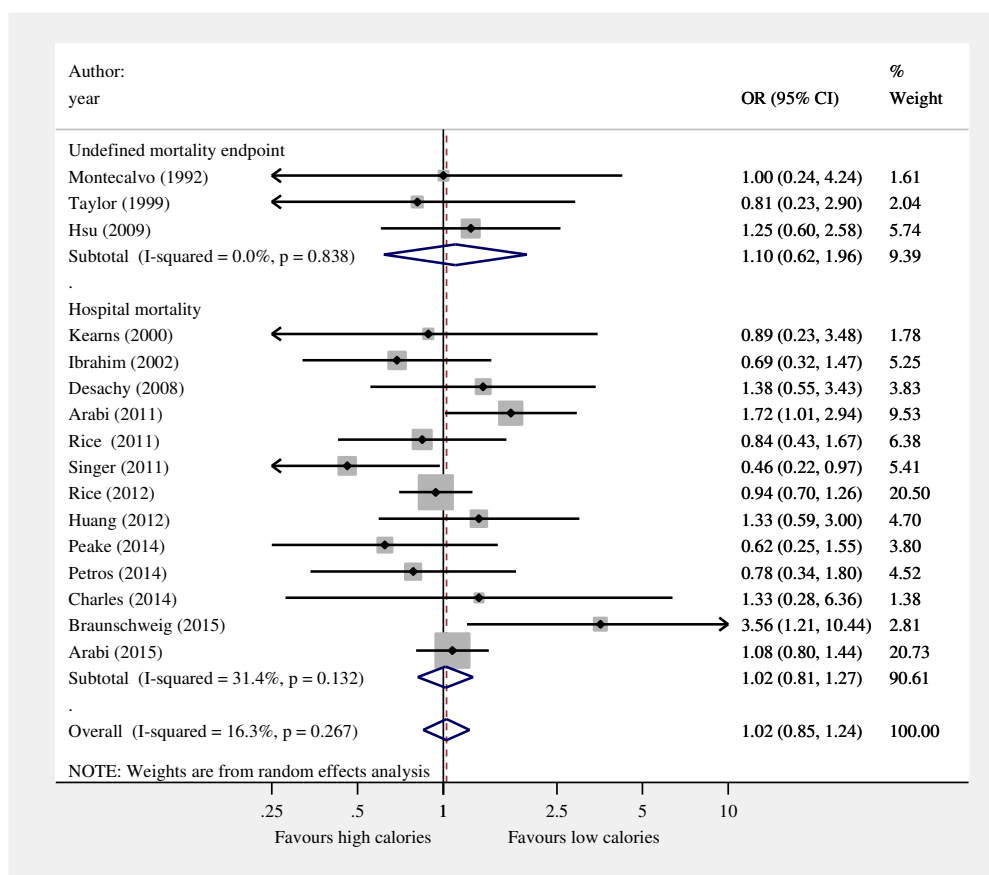
A. By patient type



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

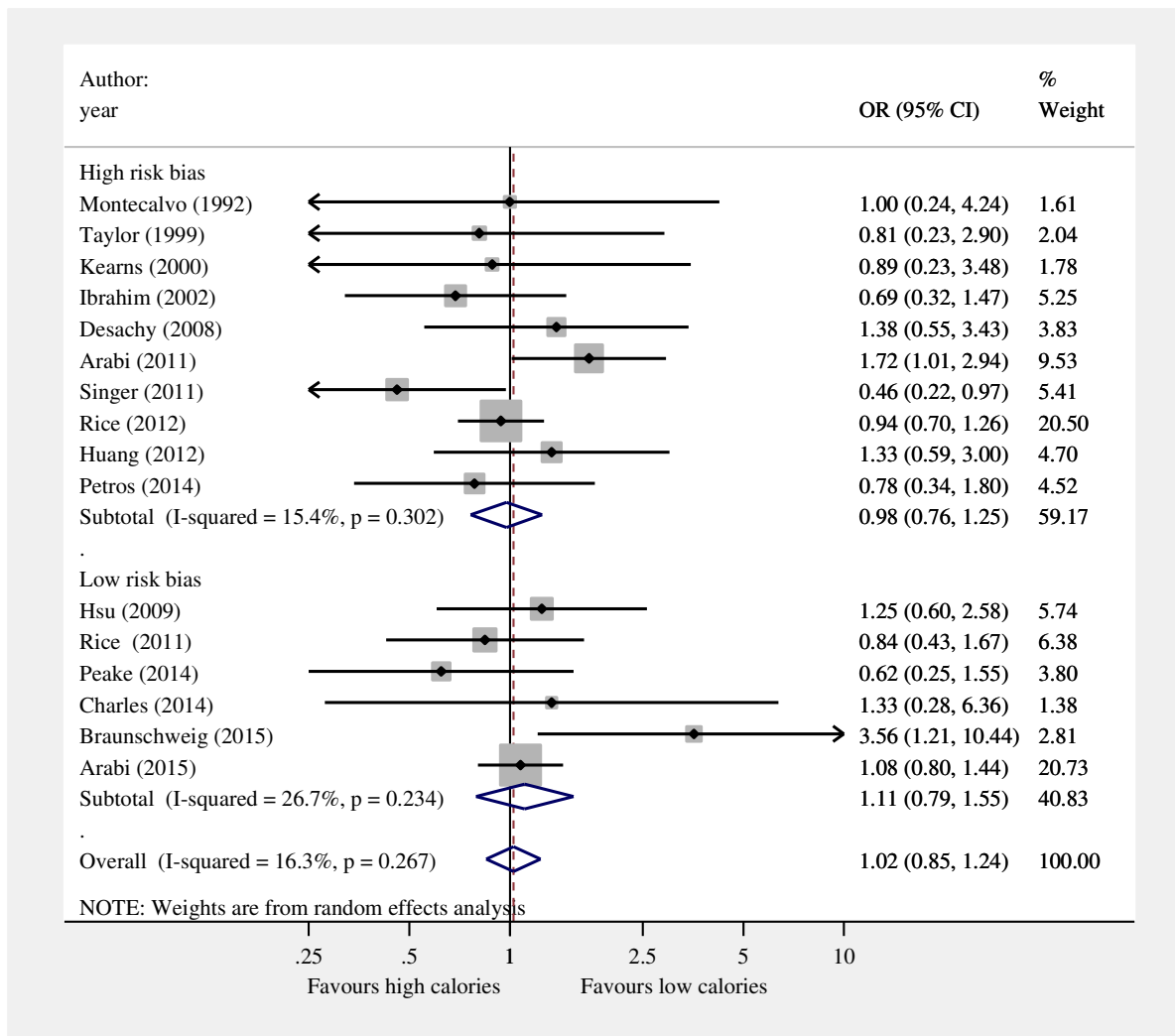
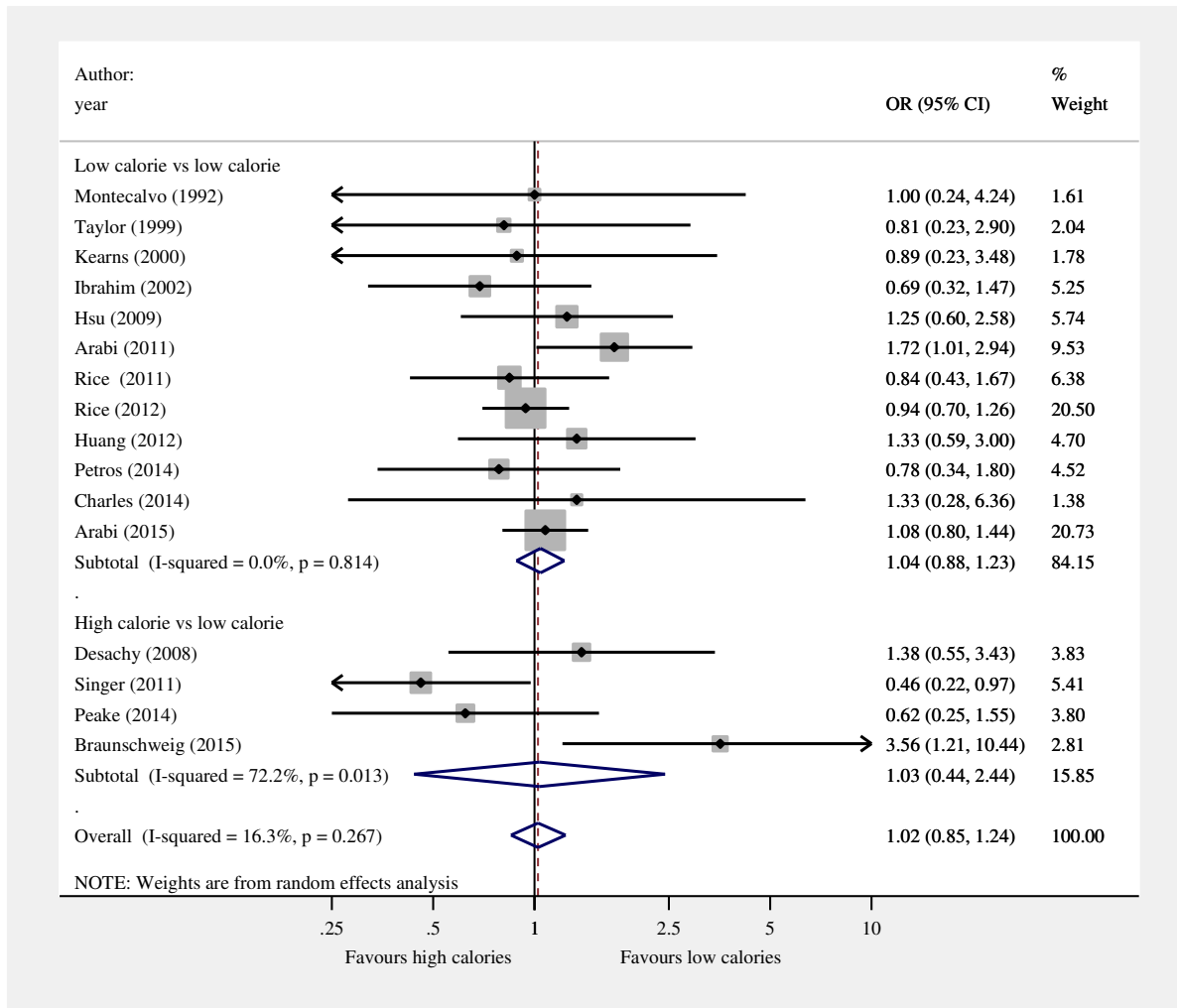


Figure S4. Subgroup analysis “high calorie” vs “low calorie”



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

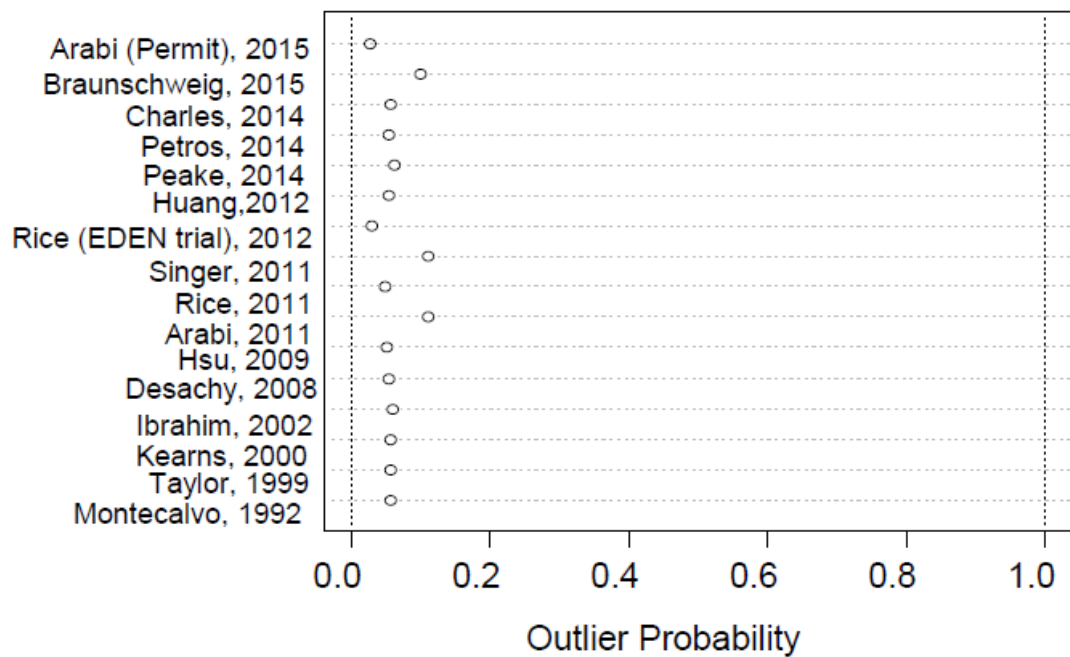


Figure S6. Effect of different RE distributions

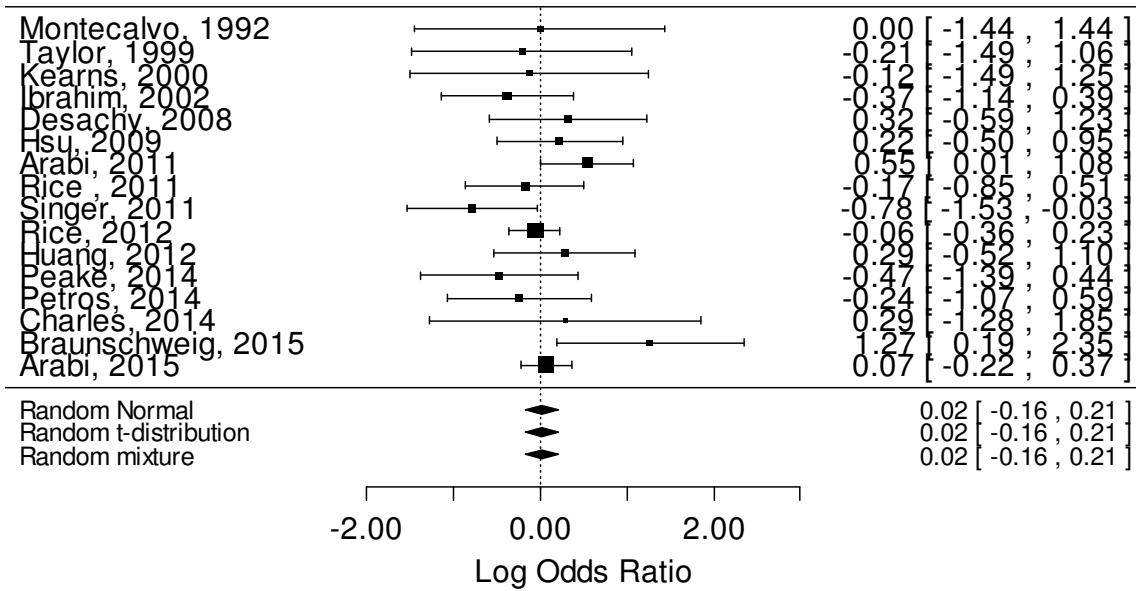
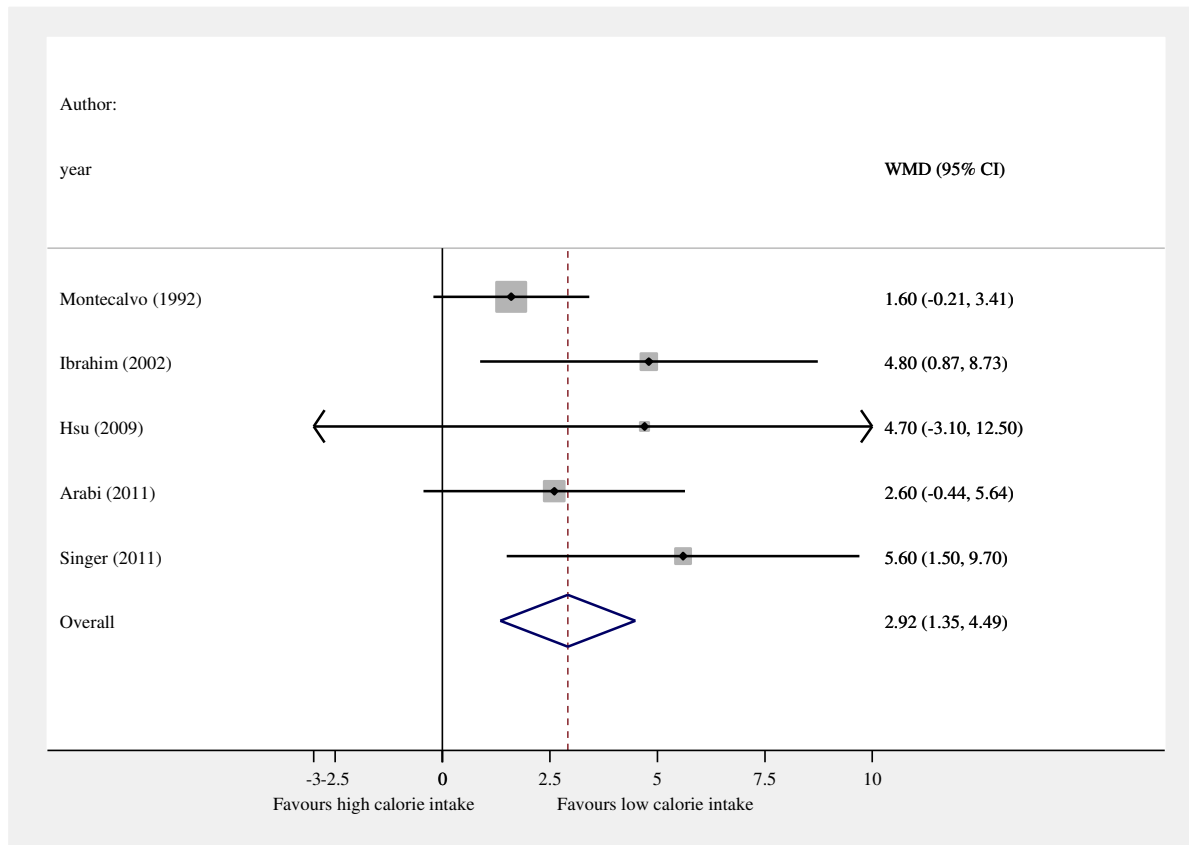


Figure S7. Random effect model of duration of mechanical ventilation



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 ^o	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 (<i>supplemental PN</i>)
		Higher	65	Target calorie according to 25 kcal/kg/day (<i>supplemental PN</i>)
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 (<i>supplemental PN</i>)
		Higher	54	100%of daily energy expenditure (<i>supplemental PN</i>)
Charles (26)	2014	Lower	41	12.5-15 kcal/kg/day via EN (<i>supplemental PN</i>)
		Higher	42	25-30 kcal/kg/day via EN (<i>supplemental PN</i>)
Braunschweig (17)	2015	Lower	38	Standard nutrition support via EN (<i>supplemental PN</i>)
		Higher	40	Greater than 75% of estimated energy and protein via EN (<i>supplemental PN</i>)
Arabi (18)	2015	Lower	448	40-70% estimated caloric requirements (<i>supplemental PN</i>)
		Higher	446	70-100% estimated caloric requirements (<i>supplemental PN</i>)

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.