Protein delivery and clinical outcomes in the critically ill: A systematic review and meta-analysis

Dr Michael Davies[1], Ms Lee-anne Chapple[2], Dr Marianne Chapman[1,2], Dr John Moran[2,3], Dr Sandra Peake[2,3]

1 Critical Care Services, Royal Adelaide Hospital, Adelaide, SA, Australia

2 Discipline of Acute Care Medicine, University of Adelaide, Adelaide, SA, Australia

3 Department of Intensive Care Medicine, Queen Elizabeth Hospital, Adelaide, SA, Australia

ONLINE APPENDIX

Example Search Strategy (PubMed - Medline)

(((((randomized controlled trial) OR controlled clinical trial)) AND ((((((critical care) OR critical illness) OR intensive care) OR mechanical ventilation) OR artificial ventilation) OR ventilator)) AND (((((((enteral nutrition) OR parenteral nutrition) OR nutrition support) OR protein) OR nitrogen balance) OR amino acid) OR caloric intake)) AND (((((((mortality) OR skeletal muscle) OR muscle strength) OR fatigue) OR endurance) OR infection) OR sepsis) AND (("1966/01/01"[PDat] : "2015/12/31"[PDat]) AND English[lang])

References of Included Studies

1. Braunschweig CA, Sheean PM, Peterson SJ, et al (2015) Intensive nutrition in acute lung injury: a clinical trial (INTACT). JPEN J Parenter Enteral Nutr 39(1):13-20.
2. Doig GS, Simpson F, Heighes PT, et al (2015) Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 3(12):943-952.
3. Doig GS, Simpson F, Bellomo R, et al. (2015) Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. Intensive Care Med 41(7):1197-1208.
4. Ferrie S, Allman-Farinelli M, Daley M, Smith K (2015) Protein Requirements in the Critically Ill: A Randomized Controlled Trial Using Parenteral Nutrition. JPEN J Parenter Enteral Nutr Dec 3. pii: 0148607115618449. [Epub ahead of print]
5. Goeters C, Wenn A, Mertes N, et al (2002) Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. Crit Care Med 30(9):2032-2037.
6. Heyland D, Muscedere J, Wischmeyer PE, et al (2013) A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 368(16):1489-1497.
7. 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(6):1866-1872.
8. Huang HH, Chang SJ, Hsu CW, Chang TM, Kang SP, Liu MY (2012) Severity of illness influences the efficacy of enteral feeding route on clinical outcomes in patients with critical illness. J Acad Nutr Diet 112(8):1138-1146.
9. Ibrahim EH, Mehringer L, Prentice D, et al. (2002) Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. JPEN J Parenter Enteral Nutr 26(3):174-181.
10. Kearns PJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM (2000) The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. Crit Care Med 28(6):1742-1746.
11. Ozgultekin A, Turan G, Durmus Y, Dincer E, Akgun N (2008) Comparison of the efficacy of parenteral glutamine and branched-chain amino acid solutions given as extra supplements in parallel to the enteral nutrition in head trauma. e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 3:e211 - e216.
12. Qiu C, Chen C, Zhang W, et al. (2015) A Fat-Modified Enteral Formula Improves Feeding Tolerance in Critically Ill Patients: A Multicenter, Single-Blind, Randomized Controlled Trial. JPEN J Parenter Enteral Nutr Sep 8. pii: 0148607115601858. [Epub ahead of print]
13. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP (2011) Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med 39(5):967-974.
14. 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(4):601-609.

Table S1: Characteristics of included studies

Lead author	**Braunschweig**
Year published	**2014**
Period of study	July 2009 to May 2013
Methods	Single centre randomised controlled trial.
Participants	78 adult patients with acute lung injury (American-European Consensus Conference definition) in medical or surgical ICUs
Interventions	1) Intensive medical nutrition therapy (IMNT). As for SNSC (below) with addition of rapid placement of feeding tubes and initiation of feeding. Additional measures to improve overall energy provision including closer monitoring and 24 hour feeding. (n=40)
	2) Standard nutrition support care (SNSC) using primarily EN, PN initiated if feeding via the enteral route not possible within 72-96 hours of intubation. Energy target 30kcal/kg, protein target 1.5g/kg. (n=38)
Outcomes	DMV, ICU LOS, Hospital LOS, Mortality (study), Nosocomial infections (total)
Notes	Trial ended prematurely by Data Safety Monitoring Board after interim analysis revealed significantly more deaths in the IMNT group.

Lead author	**Doig**
Year published	**2015**
Period of study	December 2010 to August 2014
Methods	Multicentre (13 ICUs) single blind, randomised clinical trial
Participants	331 adult critically ill patients with serum phosphate <0.65mmol/L within 72 hours of starting nutritional support
Interventions	1) Restricted caloric management, starting at 20kcal/h for at least 2 days before gradual escalation to 100% of caloric goal. (n=166)
	2) No caloric restriction (Standard care) (n=165)
Outcomes	ICU LOS, Hospital LOS, mortality (ICU, Hospital, day 60, day 90), major infections
Notes	

Lead author	**Doig**
Year published	**2015**
Period of study	December 2010 to February 2013
Methods	Multicentre (16 ICUs), unblinded, phase II randomised controlled trial.
Participants	472 adult ICU patients
Interventions	1) Continuous infusion of a standard mixture of 100g/L of L-amino acids providing a maximum of 100g of amino acids per day (with maximum total protein intake 2g/kg/d) for duration of ICU stay. (n=239)
	2) Standard care (n=235)
Outcomes	Renal dysfunction, Mortality (ICU, hospital, day 90), DMV, ICU LOS, Hospital LOS, Functional outcomes
Notes	

Lead author	**Ferrie**
Year published	**2015**
Period of study	2013 to 2014

Methods	Single centre randomised controlled trial.
Participants	119 patients older than 16 in a general medical/surgical ICU requiring PN
Interventions	1) PN with 0.8g/kg/day amino acids for 10 days or duration of ICU stay (Oli-Clinomel N7) (n=60) 2) PN with 1.2g/kg/day amino acids for 10 days or duration of ICU stay (Olimel N9) (n=59)
Outcomes	Handgrip strength, Fatigue score, Nitrogen balance, ICU LOS, Hospital LOS, Mortality (ICU, hospital, 6 months)
Notes	

Lead author	**Goeters**
Year published	**2002**
Period of study	April 1998 to January 2000
Methods	Single centre, prospective, open, randomised controlled trial
Participants	95 patients aged over 16 years admitted to a postoperative ICU expected to stay at least 5 days with an indication for PN. Nutritional and clinical outcomes only reported for per protocol group (n=68) treated for 9 days.
Interventions	1) PN containing 1.2g/kg/day standard amino acids plus 0.3g/kg/day L-alanyl-L-glutamine (Ala-Gln). Ala-Gln further supplied as long as central access maintained even once enteral nutrition established. (n=33) 2) PN containing 1.5g/kg/day standard amino acids. Transition to enteral nutrition once possible. (n=35)
Outcomes	ICU LOS, Hospital LOS, Mortality (ICU, day 30, 6 month)
Notes	Study analysed for "effects of long term glutamine supply" (study period of at least 9 days)

Lead author	**Heyland**
Year published	**2013**
Period of study	April 2005 to December 2011
Methods	Multicentre (40 ICUs) 2-by-2 factorial trial
Participants	1218 adult ICU patients receiving mechanical ventilation with two or more organ failures
Interventions	1) Glutamine supplementation (0.35g/kg/day parenteral glutamine as 0.5g/gk/day of dipeptide alanyl-glutamine plus 42.5g/day of alanyl-glutamine and glycine-glutamine dipeptides enterally, providing 30g/day of glutamine) (n=611) 2) Matching placebo (n=607)
Outcomes	Mortality (day 28, day 14, hospital, 6 month), DMV, ICU LOS, Hospital LOS, Infections
Notes	In addition patients were randomised to receive 500micrograms of selenium IV and enteral vitamins and minerals or matching placebos. Groups analysed for this meta-analysis according to allocation to glutamine or no glutamine.

Lead author	**Hsu**
Year published	**2009**
Period of study	January 2005 to December 2006
Methods	Single centre prospective randomised clinical study
Participants	121 medical ICU patients anticipated to enteral feeding for three days
Interventions	1) Nasogastric feeding (n=62) 2) Nasoduodenal feeding (n=59)

Outcomes	Nutrient intakes, ICU LOS, Hospital LOS, DMV, Feeding complications, bacteraemia, VAP, mortality (study)
Notes	

Lead author	**Huang**
Year published	**2012**
Period of study	2005 to 2006
Methods	Single centre, single-blind, randomised, prospective clinical study
Participants	101 medical ICU patients aged over 20 expected to require mechanical ventilation for more than 24 hours
Interventions	1) Nasogastric feeding (n=51) 2) Nasoduodenal feeding (n=50)
Outcomes	Nutrient intake, Feeding complications, ICU LOS, Mortality (hospital), Nitrogen balance
Notes	

Lead author	**Ibrahim**
Year published	**2002**
Period of study	May 1999 to December 2000
Methods	Single centre, prospective, controlled clinical trial
Participants	150 medical ICU patients requiring mechanical ventilation
Interventions	1) Target 100% of estimated total daily enteral nutritional requirements from day 1 (n=75) 2) 20% of estimated total daily enteral nutrition requirements ("trophic feeding")for day 1 to 4, then 100% of requirement from day 5 (n=75)
Outcomes	VAP, DMV, ICU LOS, Hospital LOS, Mortality (hospital)
Notes	

Lead author	**Kearns**
Year published	**2000**
Period of study	Unspecified 15 month period
Methods	Single centre, prospective randomised clinical trial
Participants	44 medical ICU patients receiving mechanical ventilation and anticipated to require enteral nutrition for three days
Interventions	1) Gastric feeding (n=23) 2) Small intestinal feeding (n=21)
Outcomes	Nutrient intakes, VAP, ICU LOS, Hospital LOS, Mortality (study), Feeding complications
Notes	

Lead author	**Ozgultekin**
Year published	**2008**
Period of study	January 2003 to January 2005
Methods	Single centre randomised clinical trial
Participants	60 mechanically ventilated ICU patients aged more than 15, with GCS 4 to 10 expected to stay more than 2 days
Interventions	1) Standard EN (n=20) 2) Standard EN plus supplemental parenteral branched-chain enriched amino acids (30.7g protein) (n=20) 3) Standard EN plus supplemental parenteral glutamine (20g L-alanine-L-glutamine) (n=20)

Outcomes	Nutrient intake, SIRS, Sepsis, DMV, ICU LOS, GCS, mortality (30 days)
Notes	Groups 2 and 3 combined for analysis in this meta-analysis.

Lead author	**Qiu**
Year published	**2015**
Period of study	June 2012 to September 2013
Methods	Multicentre (7 ICUs), prospective, single-blind randomised clinical trial
Participants	144 adult ICU patients anticipated to require EN for at least 5 days
Interventions	1) EN with fat modified enteral formula containing medium-chain triglycerides, carnitine and taurine (TPF-FOS) (n=71) 2) EN with standard enteral formula (TPF-TP) (n=73)
Outcomes	Nutrient intake, Feeding complications, ventilator free days in 28, ICU LOS, hospital LOS, mortality (hospital)
Notes	

Lead author	**Rice**
Year published	**2011**
Period of study	August 2003 to July 2009
Methods	Single centre (2 ICUs) randomised open-label study
Participants	200 patients with acute respiratory failure expected to require mechanical ventilation for at least 72 hours
Interventions	Full energy enteral nutrition (n=102) Trophic enteral nutrition (10ml/hr) for initial 6 days then advancement to full-energy (n=98)
Outcomes	Ventilator free days in 28, mortality (day 28, hospital, ICU free days, hospital free days, infections
Notes	

Lead author	**Singer**
Year published	**2011**
Period of study	Started May 2007, completion date unclear
Methods	Single centre pilot randomised clinical study
Participants	130 adult mechanically ventilated ICU patients, expected to have an ICU stay longer than 3 days
Interventions	1) Nutritional support guided by repeated measures of resting energy expenditure using indirect calorimetry (ITT = 65, PP = 56) 2) Nutritional support guided by a single weight based equation (ITT = 65, PP = 56)
Outcomes	Mortality (hospital, ICU), DMV, ICU LOS, Hospital LOS, infections
Notes	Nutritional intakes only reported for per protocol group (n=112) and therefore only clinical outcomes reported for this group used in this meta-analysis.

DMV = duration of mechanical ventilation, EN = enteral nutrition, GCS = Glasgow coma scale, ICU = intensive care unit, ITT = intention to treat, LOS = length of stay, PN = parenteral nutrition, PP = per protocol, VAP = ventilator associated pneumonia.

Table S2: Clinical outcomes from included studies

Lead author	Year published	Group	DMV, d; mean (SD)	ICU LOS, d; mean (SD)	Hospital LOS, d; mean (SD)	Mortality, n (%)	Mortality, time point[1]	VAP/Pneumonia, n (%)	Bacteraemia, n (%)
Braunschweig	2014	Lower	8 (8.5)	16.1 (11.5)	22.8 (14.3)	6 (15.8)	Study		
		Higher	6.7 (4.6)	15.5 (12.8)	27.2 (18.2)	16 (40.0)			
Doig (refeeding)[2]	2015	Lower		11.4 (6.2)	27.9 (15.1)	15 (9.1)	60 days	25 (15.1)	2 (1.2)
		Higher		10 (5.6)	21.7 (11.5)	35 (21.5)		34 (20.6)	8 (4.8)
Doig (IV AA)	2015	Lower	7.3 (2.6)	10.7 (5.9)	24.8 (14.1)	43 (18.3)	Hospital		
		Higher	7.3 (2.7)	11.6 (6.7)	26 (15.0)	37 (15.5)			
Ferrie	2015	Lower	2.7 (3.0)	6.6 (4.7)	28.4 (41)	9 (15.0)	Hospital		
		Higher	2 (1.5)	5.3 (3.8)	27.7 (18.6)	12 (20.3)			
Goeters[3]	2002	Lower		20.8 (9.1)	39.4 (31.1)	11 (31.4)	30 days		
		Higher		21.3 (13.5)	46 (49.1)	7 (21.2)			
Heyland[2]	2013	Lower	6.9 (6.7)	9.8 (7.6)	20.5 (20.6)	165 (27.2)	28 days	78 (12.9)	21 (3.5)
		Higher	7.2 (7.4)	9.6 (8.6)	19.3 (19.3)	198 (32.4)		88 (14.4)	11 (1.8)
Hsu	2009	Lower	23.8 (18.2)	18.2 (11.2)	31.7 (21.1)	24 (38.7)	Study	15 (24.2)	3 (4.8)
		Higher	28.5 (24.9)	18.2 (11.8)	36 (24.4)	26 (44.1)		5 (8.5)	3 (5.1)
Huang	2012	Lower		16.9 (9.1)		17 (35.4)	Hospital		
		Higher		17.2 (11.4)		20 (41.7)			
Ibrahim	2002	Lower	8.1 (7.4)	9.8 (7.4)	16.7 (12.5)	20 (26.7)	Hospital	23 (30.7)	8 (10.7)
		Higher	12.9 (15.7)	13.6 (14.2)	22.9 (19.7)	15 (20.0)		37 (49.3)	9 (12.0)
Kearns	2000	Lower		16 (9.6)	43 (52.8)	6 (26.1)	Study	3 (13.0)	
		Higher		17 (9.2)	39 (45.8)	5 (23.8)		4 (19.0)	
Ozgultekin[4]	2008	Lower	14.4 (14.0)	17.3 (16.4)		12 (60.0)	30 days		
		Higher	11.0	12.7		23 (57.5)			
Qiu	2015	Lower	16 (7.8)[5]	15.3 (8.6)	32.1 (15.3)	20 (27.4)	Hospital		
		Higher	16.3 (8.3)[5]	16.5 (8.5)	35.8 (16.2)	17 (23.9)			
Rice	2011	Lower	17.9 (10.4)[5]			22 (22.4)	Hospital	14 (14.3)	
		Higher	17.8 (10.5)[5]			20 (19.6)		18 (17.6)	
Singer[2]	2011	Lower				27 (48.2)	Hospital		
		Higher				16 (28.6)			

1. 'Analytic' mortality for each study – see text. 2. Studies where mortality was the primary outcome. 3. Nutritional and clinical outcomes only reported for the per protocol group (received treatment for 9 days). 4. Data from two higher protein groups (groups II, III) combined to make 'higher' protein group. 5. Ventilator free days in 28. DMV=duration of mechanical ventilation. ICU=intensive care unit. IV AA = Intravenous Amino Acids. LOS=length of stay. VAP=Ventilator associated pneumonia.

FIGURE S1. Effect of protein delivery on mortality – subgroup analysis according to mortality time-point

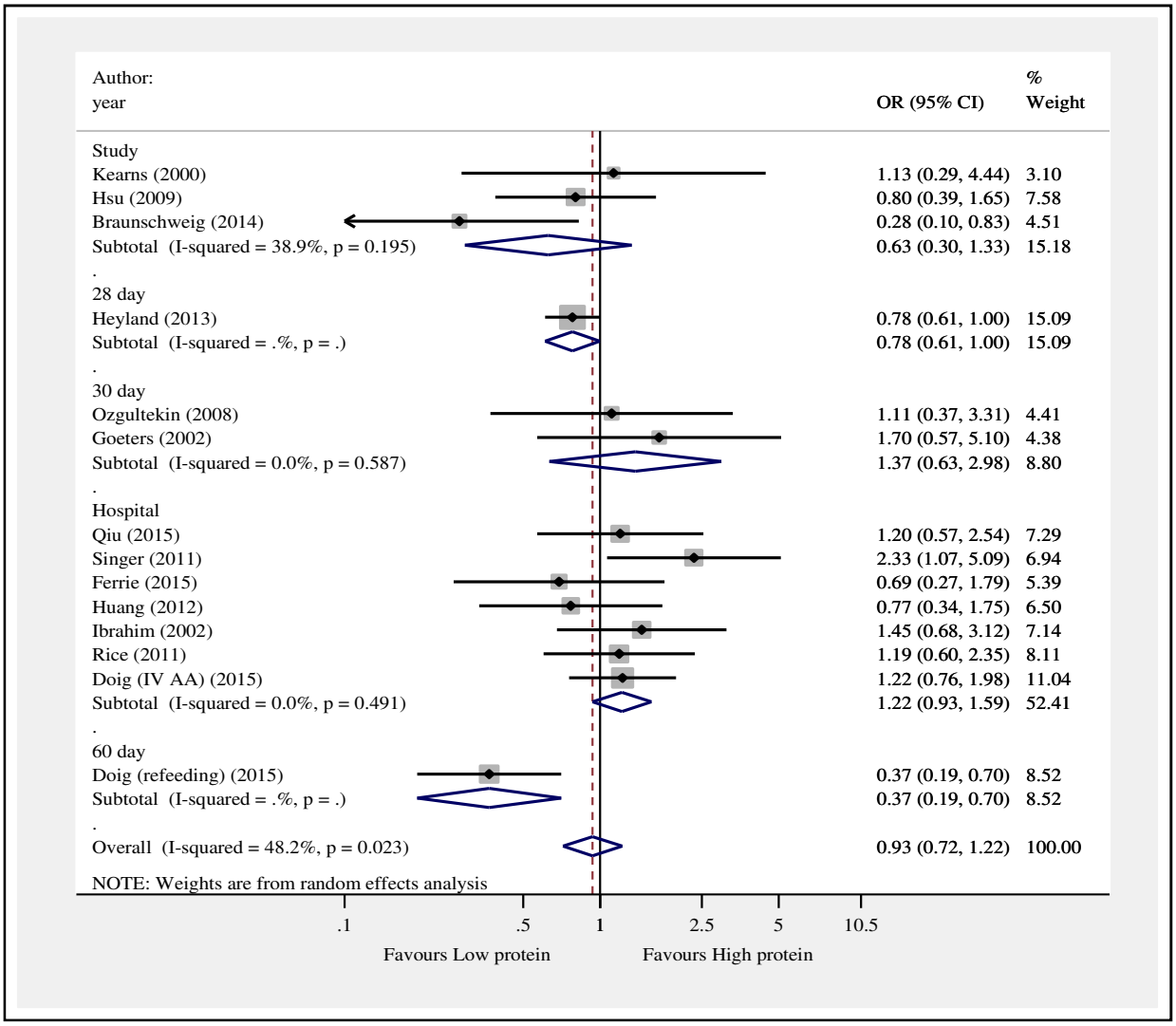

Fig. S1 OR = odds ratio. Random effects model. Individual (square) points denote OR of each study; the lines either side denote 95% confidence intervals; size of the square is proportional to the study size. Vertical line = null effect. Dashed line = meta-analytic point estimate

FIGURE S2. Effect of protein delivery on mortality – subgroup analysis according to study intervention

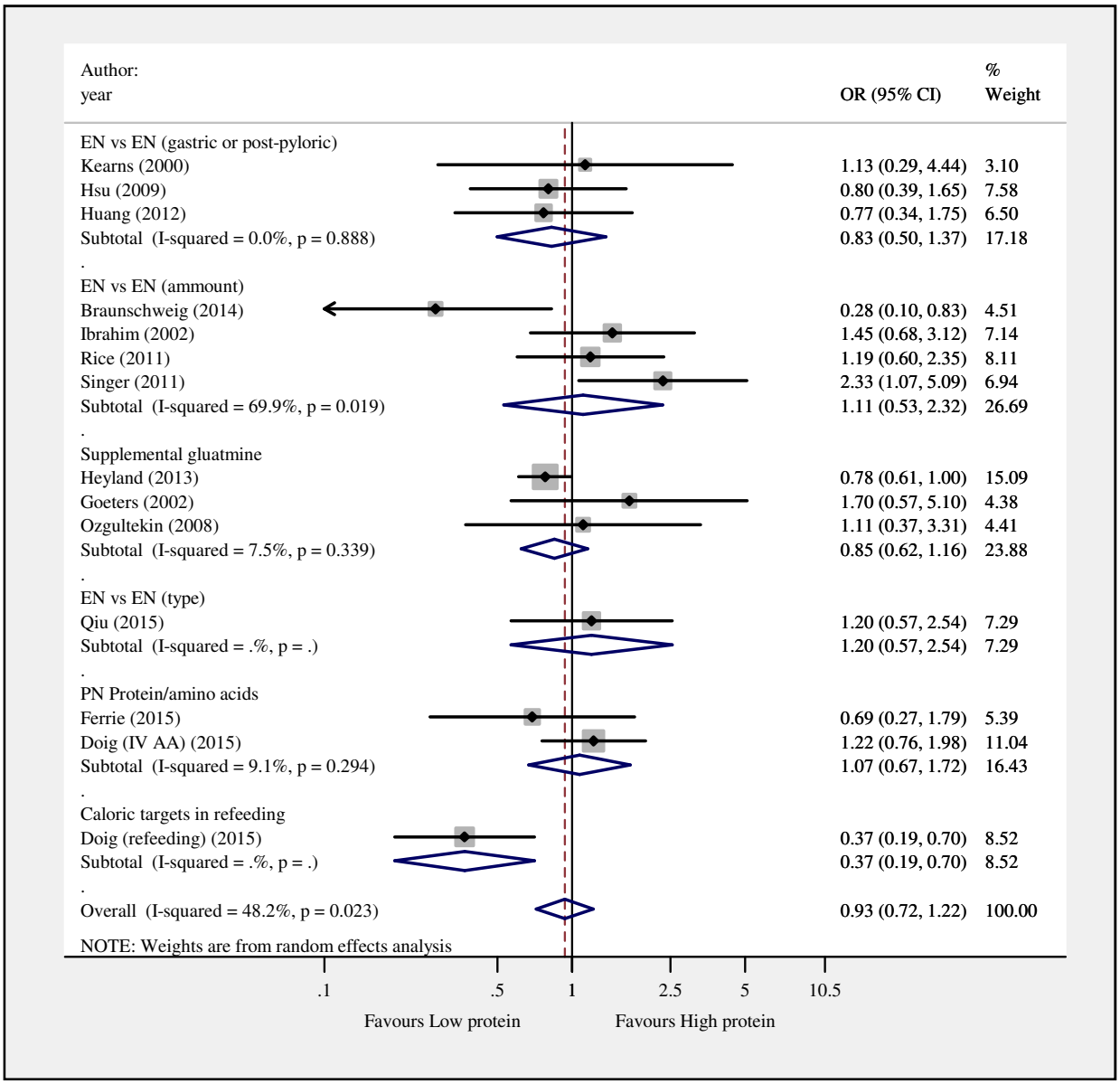

Fig. S2 OR = odds ratio. Random effects model. Individual (square) points denote OR of each study; the lines either side denote 95% confidence intervals; size of the square is proportional to the study size. Vertical line = null effect. Dashed line = meta-analytic point estimate

FIGURE S3. Sensitivity analysis for varying random effects distributions

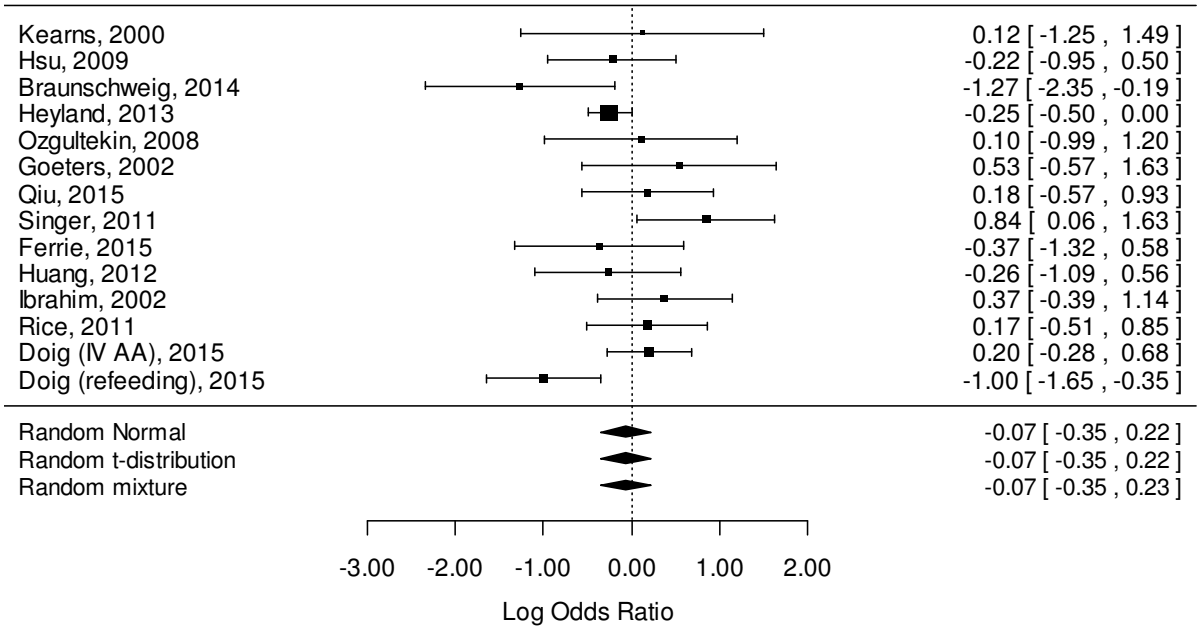

Fig. S3 Random effects distributions (Normal, *t*, mixed). OR = odds ratio. Log ORs for mortality. Individual (square) points denote log OR of each study; the lines either side denote 95% confidence intervals; size of the square is proportional to the study size. Vertical dashed line = null effect. Diamonds denote log OR summary estimates using different random effects distributions (using the metaplus R package[25])

FIGURE S4. Outlier probability for included studies

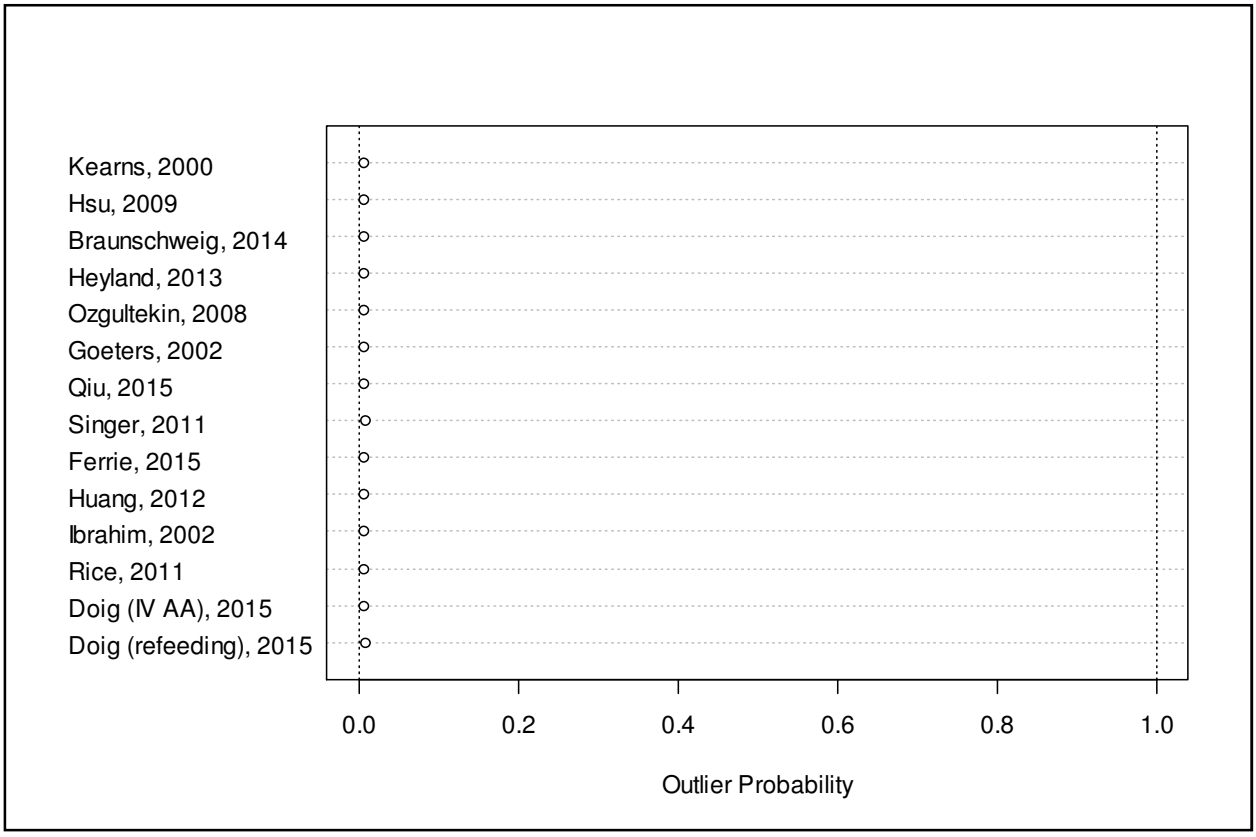

Fig. S4 Dots indicated outlier probability for each study (using the metaplus R package[25])

FIGURE S5. Galbraith Plot

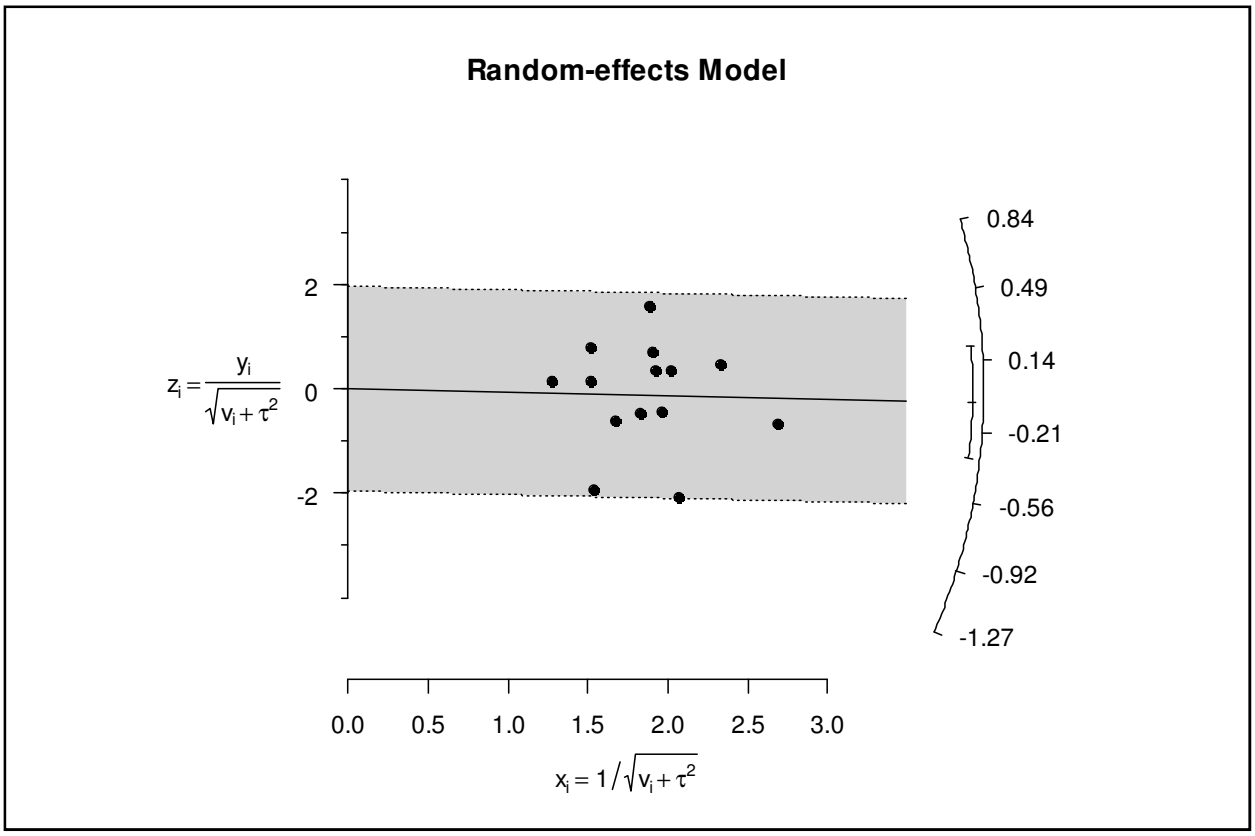

Fig. S5 For a random-effects model, the function uses $1/\left(v_i + \tau^2\right)$ for the horizontal axis, where v_i is the sampling variance of the observed effect size or outcome and τ^2 is the amount of heterogeneity as estimated based on the model. For the z-(vertical)axis, $\sqrt{\left(v_i + \tau^2\right)}$ is used to standardize the individual observed effect sizes or outcomes. On the right hand side of the plot, an arc is drawn (referred to as the y-axis within this function) corresponding to the individual observed effect sizes or outcomes. A line projected from (0,0) through a particular point within the plot onto this arc indicates the value of the individual observed effect size or outcome for that point[21]

FIGURE S6. Meta-regression analysis of effect of within trial protein difference on mortality

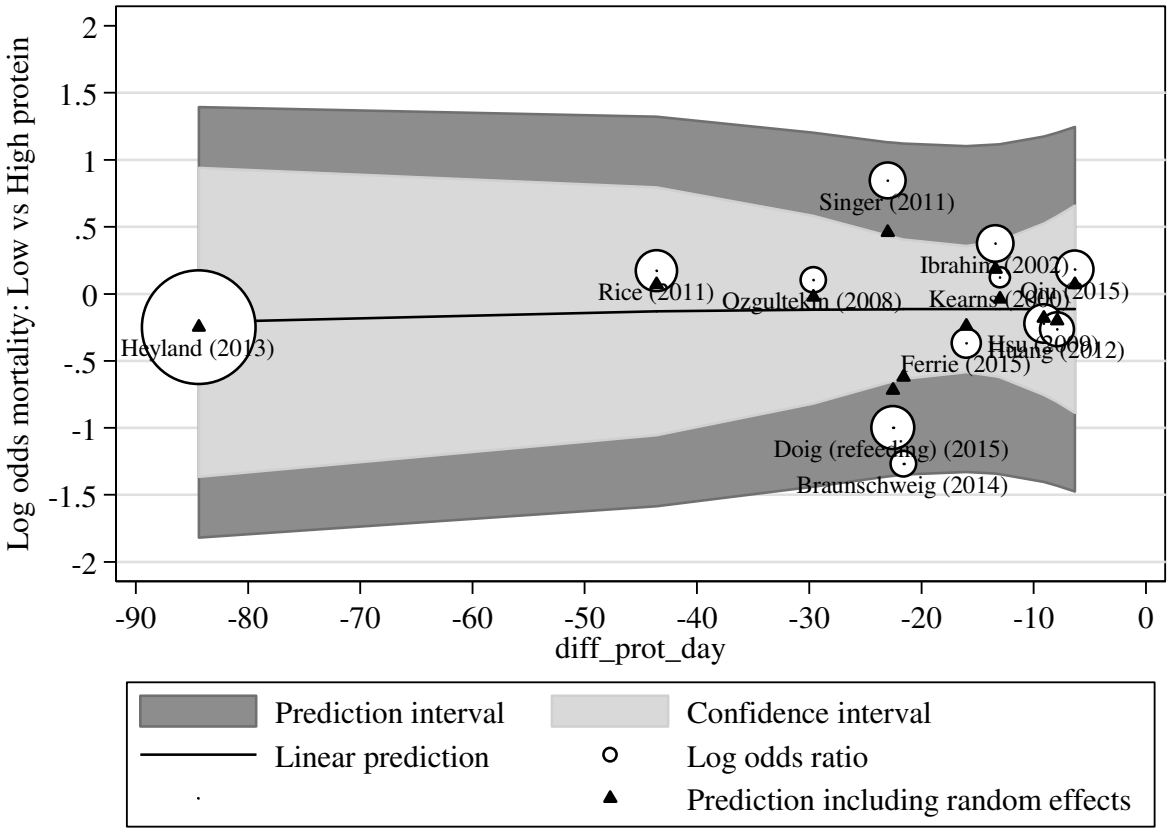

Fig. S6 Random effects meta-regression analysis. Diff_prot_day = difference in daily absolute protein provision between groups within each trial. Using log-odds scale with linear prediction effect-line, 95% confidence intervals and point estimates with circles that reflect study size. Triangles represent 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. A prediction interval is shown in dark grey and may be interpreted as the region within which one may realistically hope to find the next large study[41]. A quadratic effect was modelled for average daily protein as being more clinically plausible and supported by reduction in τ^2