3.2c Intentional Underfeeding: Hypocaloric Enteral Nutrition

Question: Does the use of hypocaloric enteral nutrition vs. full feeding result in better outcomes in the critically ill adult patient?

Summary of evidence: All of the trials included in this topic resulted in similar protein intake but less caloric intake in the intervention arm (hypocaloric EN) compared to the control arm (full feeds). Trials that resulted in different levels of calories and proteins are reviewed in section 3.2 Achieving Target Dose of EN. In this section, there was one level 1 and seven level 2 studies reviewed, and significant heterogeneity is present in the study designs:

- Arabi 2011: Hypocaloric group aimed to receive 60-70% of calorie goals and gave protein supplements vs. 90-100% of nutrition goals
- Charles 2014: Hypocaloric group aimed to receive 50% of calorie goals and 100% of protein goals vs. 100% of nutrition goals
- Peake 2014 and Chapman 2018: Hypocaloric group received a 1.0 kcal/ml EN formula at 1 ml/kg IBW/hr vs. a 1.5 kcal/ml EN formula provided at 1 ml/kg IBW/hr with both formulas having a comparable protein content per ml
- Arabi 2015: Hypocaloric group aimed to receive 40-60% of caloric goals and 1.2-1.5 g/kg/d protein vs. 70-100% of calorie goals 1.2-1.5 g/kg/d protein
- Rugeles 2016: Hypocaloric group aimed to receive 15 kcal/kg/d and 1.7 g/kg/d protein vs. 25 kcal/kg/d and 1.7 g/kg/d protein
- Rice 2018: Hypocaloric group aimed to receive 1.5 g/kg/d protein from a higher protein density formula vs. 1.5 g/kg/d from a lower protein density formula with both formulas having equal caloric density. The higher protein formula group intended to receive less calories.
- Deane 2020: was a 6 month follow up study of the Chapman 2018 study.

All studies were isonitrogenous but non-isocaloric. The Arabi 2011 study also compared intensive insulin therapy to control in a 2 X 2 factorial design (refer to section 10.4 Insulin therapy for data pertaining to these groups). In previous reviews, Petros 2014 was included in this section but due to its non-isonitrogenous study design it has been moved to section 3.2 Achieving Target Dose of EN. Peake 2014 was moved to this section from section 3.2 due to its isonitrogenous study design. Deane 2020 reported on unique 180 day mortality and quality of life data from the Chapman 2018 study which is shown in table 1 with the Chapman 2018 study.

Mortality: When the data from the trials were aggregated, hypocaloric enteral nutrition had no effect on overall (RR 0.95, 95% CI 0.87, 1.05, p =0.32, I^2= 0%; figure 1) or hospital mortality (RR 0.94, 95% CI 0.83, 1.06, p =0.29, I^2= 10%; figure 2). There was a trend towards a reduction in ICU mortality in the hypocaloric group (RR 0.85, 95% CI 0.67, 1.08, p =0.18, I^2= 0%; figure 3).

Infections: Hypocaloric enteral nutrition had no effect on the incidence of ICU-acquired infections (RR 1.00, 95% CI 0.82, 1.21, p=0.96, heterogeneity I^2= 47%) (figure 4).

LOS: When the data from the four studies (Arabi 2011, Charles 2014, Peake 2014, Arabi 2015) that reported results in mean and standard deviation were aggregated, hypocaloric enteral nutrition had no effect on ICU LOS (WMD 0.02, 95% CI -2.92, 2.96, p=0.99, I^2= 89%) (figure 5) or hospital LOS (-0.51, 95%CI -4.35, 3.33, p = 0.79, I^2= 85%) (figure 6).

Ventilator days: When the data from the 3 studies (Arabi 2011, Peake 2014, Arabi 2015) that reported this outcome in mean and standard deviation were aggregated, hypocaloric enteral nutrition was associated with a significant reduction in ventilator days (WMD -2.18, 95% CI -3.68, -0.67, p = 0.005, I^2= 0%) (figure 7). Rugeles et al reported mechanical ventilation duration in median and IQR and found no difference between groups (p=0.632) and Chapman et al reported the outcome as days alive and free of invasive ventilation (median and IQR) and found no difference between groups (p=NS).

Other: Due to the intended study designs, the hypocaloric enteral nutrition groups received significantly fewer calories than the full feeds groups (p<0.00001) (figure 8) but received the same amount of protein (p=0.29) (figure 9). In the 6 month follow up of the Chapman 2018 large multicentre study, the delivery of 70% compared to 100% calorie intake during critical illness did not improve quality of life or functional outcomes as measured by the Euro Quality of Life five dimensions five-level quality-of-life (EQ5D5L) visual analog scale (Deane 2020). EQ5D5L evaluates mobility, personal care, usual activities, pain/discomfort, and anxiety/depression and separates each of these health domains into five levels.

Conclusions:

1. The use of hypocaloric enteral nutrition vs. full feeds is not associated with a reduction in overall and hospital mortality but may be associated with a reduction in ICU mortality.
2. The use of hypocaloric enteral nutrition vs. full feeds has no effect on ICU or hospital LOS.
3. The use of hypocaloric enteral nutrition vs. full feeds has no effect on infectious complications.
4. The use of hypocaloric enteral nutrition vs. full feeds may be associated with a decrease in length of ventilator support.

Note: Risk ratios, mean differences, confidence intervals and p-values indicated above were calculated using Review Manager 5.3.

Level 1 study: *if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
Level 2 study*: If any one of the above characteristics are unfulfilled.*

Table 1. Randomized studies evaluating hypocaloric vs. full feeding in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				Hypocaloric Feeds	Full Feeds	Hypocaloric Feeds	Full Feeds
1) Arabi 2011*	ICU patients ~30% brain trauma 40% Type 2 diabetes N=240 **BMI (kg/m²)** Trophic feeds pts: 28.5±7.4 Full feeds pts: 28.5±8.4 **Age** Trophic feeds pts: 50.3±21.3 Full feeds pts: 51.9±22.1	C.Random: Yes ITT: Yes Blinding: No (9)	Underfed: 60-70% goal + protein supplements vs.90-100% goal Calories actually received 59.0% vs. 71.4% Protein actually received 65.2% vs. 63.7% Isonitrogenous, non-isocaloric	**ICU** 21/120 (18) **28 Day** 22/120 (18) **Hospital** 36/120 (30) **180 Day** 38/120 (32)	**ICU** 26/120 (22) **28 Day** 28/120 (23) **Hospital** 51/120 (43) **180 Day** 52/120 (43)	**All Infections/1000 days** 54.7 **VAP/1000 vent days** 14 **Sepsis** 53/120 (44)	**All infections/1000 days** 53.6 **VAP/1000 vent days** 10 **Sepsis** 56/120 (47)
2) Charles 2014	Adults admitted to surgical ICU, included operative and non-operative trauma pts, abdominal vascular liver transplant, and ortho non-trauma surgical pts. N=83	C.Random: Yes ITT: Yes Blinding: single (11)	50% of caloric goal (12.5-15 kcal/kg/d) and protein 1.5 g/kg/d vs. 100% of goal calories and protein 1.5 g/kg/d. Calories received 12.3 vs. 17.2 kcal/kg/d, protein 1.1 vs. 1.1 g/kg/d. Isonitrogenous, non-isocaloric	**Hospital** 3/41 (7.3)	**Hospital** 4/42 (9.5)	**Pts w ICU acquired** 23/41 (56.1) **Pneumonia** 18/41 (43.9) **Bloodstream** 10/41 (24.4) **Central Line** 2/41 (4.9) **UTI** 6/41 (14.6) **Wound** 5/41 (12.2)	**Pts w ICU acquired** 24/42 (57.1) **Pneumonia** 20/42 (47.6) **Bloodstream** 8/42 (19.1) **Central Line** 2/42 (4.8) **UTI** 6/42 (14.3) **Wound** 3/42 (7.1)
3) Peake 2014	Emergency operative and non-operative and elective operative admissions N=112	C. Random: yes ITT: yes Blinding: yes (9)	Fresubin 1000 Complete 1.0kcal/ml vs. Fresubin 2250 Complete 1.5kcal/ml. Goal rate of 1 ml/kg IBW/hr to a max of 100ml/hour to be achieved within 48 hours of feeding start in both groups. Comparable protein between formulas. Isonitrogenous, non-isocaloric,.	**ICU** 9/55 (16) **Hospital** 14/55 (27) **28 day** 18/55 (33) **90 day** 20/55 (27)	**ICU** 6/57 (11) **Hospital** 10/57 (19) **28 day** 11/57 (20) **90 day** 11/57 (20)	NR	NR

4) Arabi 2015	Multicenter. ICU adult patients with LOS >72 hrs, requiring EN. N=894	C.Random: Yes ITT: no Blinding: no (8)	40-60% of calorie goals x 14 days and 1.2-1.5 g/kg/d protein achieved with EN and protein supplements vs. 70-100% of calorie goals and 1.2-1.5 g/kg/d protein x 14 days. Calories received: 46.2% vs. 72% adequacy. No difference in protein. Isonitrogenous, non-isocaloric	**ICU** 72/448 (16.1) **Hospital** 108/447 (24.2) **28 day** 93/447 (20.8) **90 day** 121/445 (27.2) **180 day** 131/438 (29.9)	**ICU** 85/446 (19.1) **Hospital** 123/445 (27.6) **28 day** 97/444 (21.8) **90 day** 127/440 (28.9) **180 day** 140/436 (32.1)	**Infections** 161/448 (35.9) **VAP** 81/448 (18.1)	**Infections** 169/446 (37.9) **VAP** 90/446 (20.2)
5) Rugeles 2016	Single centre ICU adults expected to require EN for >96 hours N=187	C.Random: No ITT: no Blinding: double (8)	EN dosed at 15 kcal/kg, 1.7 g/kg protein for 7 days vs. 25 kcal/kg, 1.7 g/kg/d protein for 7 days. Same EN formula for each group. Isonitrogenous, non-isocaloric	**28 day** 18/60 (30)	**28 day** 16/60 (27)	NR	NR
6) Chapman 2018 and Deane 2020	Multicentre ICU adults, mechanically ventilated, expected to receive EN beyond the calendar day N=3997	C.Random: Yes ITT: no Blinding: double (11)	Fresubin 1000 Complete 1.0 kcal/ml vs. Fresubin Energy Fibre 1.5 kcal/ml. Goal rate in both groups was 1 ml/kg IBW/hr to a max of 100 ml/h to be achieved within 48h of starting EN. Protein content of formulas was comparable (55 vs. 56 g/L). Isonitrogenous, non-isocaloric	**Hospital** 470/1981 (23.7) **28 day** 455/1976 (23) **90 day** 505/1966 (25.7) **180 day** 539/1920 (28.1%)	**Hospital** 468/1967 (23.8) **28 day** 450/1961 (22.9) **90 day** 523/1948 (26.8) **180 day** 560/1895 (29.6%)	**Positive blood cultures** 221/1984 (11.1) **RR** 1.04 (0.87-1.24)	**Positive blood cultures** 228/1971 (11.6)
7) Rice 2018	Multicentre ICU adults, mechanically ventilated, BMI 26-45, requiring EN for > 5 days N=105	C.Random: Yes ITT: no Blinding: no (5)	Peptamen Intense VHP (1 kcal/ml, 37% protein, 29% CHO) vs. Replete (1 kcal/ml 25% protein, 45% CHO) vs. Both started within 48h of randomization and advanced to reach protein goal of 1.5 g/kg IBW/d. Isonitrogenous, non isolacoric	**Hospital mortality or entered palliative care** 7/50 **Feeding protocol duration** 2/50	**Hospital mortality or entered palliative care** 8/52 **Feeding protocol duration** 6/52	NR	NR

Table 1. Randomized studies evaluating hypocaloric vs. full feeding in critically ill patients (continued)

Study	LOS days		Ventilator days		Other	
	Hypocaloric Feeds	Full Feeds	Hypocaloric Feeds	Full Feeds	Hypocaloric Feeds	Full Feeds
1) Arabi 2011*	**ICU** 11.7 ±8.1 (120) **Hospital** 70.2 ±106.9 (120)	**ICU** 14.5 ±15.5 (120) **Hospital** 67.2 ±93.6(120)	10.6 ±7.6 (120)	13.2 ±15.2 (120)	**Kcal/day** 1067 ± 306 **Caloric Adequacy (%)** 59 ± 16.1 **Protein adequacy (%)** 65.2 ± 25.7	 1252 ± 432, p=0.0002 71.4 ± 22.8, p=<0.0001 63.7 ± 25, p=0.63
2) Charles 2014	**ICU** 16.7 ± 2.7 (41) **Hospital** 35.2 ± 4.9 (41)	**ICU** 13.5 ± 1.1 (42) **Hospital** 31.0 ± 2.5 (42)	NR	NR	**Kcal/d** 982 ± 61 **Kcal/kg/d** 12.3 ± 0.7 **Protein g/d** 86 ± 6 **Protein g/kg/d** 1.1 ± 0.1	 1338 ± 92 17.1 ± 1.1 83 ± 6 1.1 ± 0.1
3) Peake 2014	**ICU** 12.2 ± 8.3 **Hospital** 24 ± 17.6	**ICU** 12.8 ± 11.3 **Hospital** 33.3 ± 25.3	6.8 ± 6	8.6 ± 8.5	**% Energy adequacy** 83.2 ± 29 **% Protein adequacy** 88.2 ± 39.1	 110.8 ± 26.8 82 ± 23.6
4) Arabi 2015	**ICU**+ 15.8 ± 11.6 (444) **Hospital**+ 48.3 ± 67.5 (444)	**ICU**+ 16.4 ± 12.1 (443) **Hospital**+ 54.4 ± 73.9 (443)	11.3±9.2 (444) +	13.5±22.3 (443) +	**Kcal/d (p=<0.001)** 835.2±297 **% Caloric adequacy (p=<0.001)** 46±14 **Protein g/d (p=0.29)** 57±24 **% Protein adequacy (p=0.56)** 68±24 **No. feeding intolerance (p=0.26)** 67/448 (15) **No. Diarrhea p=0.11)** 97/448 (21.7)	 1299±467 71±22 59±25 69±25 79/446 (17.7) 117/446 (26.2)
5) Rugeles 2016	**ICU** 12 (7.3) Median (IQR) P=0.4132	**ICU** 10.5 (8.0) Median (IQR)	9 (8.3) Median (IQR) P=0.632	9 (8.3) Median (IQR)	**All reported as mean and SD** **Calories/kg/d at 48h** 12.6 ± 3.4 P<0.0001 **Calories/kg/d at 96h** 12.1 ± 2.6 P<0.0001 **Protein/g/d at 48h** 1.4 ± 0.4 **Protein/g/d at 96h** 1.3 ± 0.3	 20.5 ± 5.1 19.2 ± 4.3 1.4 ± 0.3 1.3 ± 0.3

6) Chapman 2018 and Deane 2020	**ICU free days** 17.4 (0-23.1) **Hospital Free days** 2.9 (0-15.3)	**ICU free days** 17.0 (0-23) **Hospital Free days** 2.9 (0-15.7)	**Median days alive and free of invasive ventilation (IQR)** 20.0 (0-25)	**Median days alive and free of invasive ventilation (IQR)** 20.0 (0-25)	**% of trial target rate delivered, mean and SD** 82±16 (n=1985) 81±17 (n=1971) **% trial target Kcals received** 69 ± 18 % (1296) 103 ± 28% (1291) Total **Kcal delivered (kcal/kg IBW) , mean and SD** 21.9±5.6 (n=1985) 30.2±7.5 (n=1971) **% target protein gms received** 77 ± 21 (1296) 78 ± 22 (1289) **Total Protein delivered (g/kg IBW) , mean and SD** 1.08±0.23 (n=1985) 1.09±0.22 (n=1971) **Vomiting** 309/1966 (15.7) 370/1959 (18.9) **Highest blood glucose mg/dL** 212.6 (174.7-261.2) 225.2 (185.6-277.4) **Duration of study intervention** 6 days (3-11) 6 days (3-11) **Time to start EN** 15.9h (7.9-28.3) 15.8h (7.7-26.3) **180 day Quality of Life outcomes, EQ5D5L score** 75 (60-85) (n=1222) 75 (60-85) (n=1270)
7) Rice 2018	**Hospital** 4.12 ±_2.32 (50)	**Hospital** 4.17 ±_2.37 (52)	NR	NR	**Protein intake, g/kg IBW/d, days 1-5** 1.1±0.3 1.2 ±0.4, p=0.83 **Calorie intake, kcal/kg IBW/d, days 1-5** 12.5±3.7 18.2 ±6.0, P<0.0001 **Carbohydrate load, g/d, days 1-5** 61±22 126±48, P<0.0001 **mean rate of glycemic events outside the range of >110 and _150 mg/dL between groups** 2.7%; 95% CI, −6% to 11.5%; p=0.54

C.Random: concealed randomization
ITT: intent to treat; NA: not available
† presumed hospital mortality unless otherwise specified
+Data obtained from author in mean and standard deviation
± ( ) : mean ± Standard deviation (number)
‡ refers to the # of patients with infections unless specified
* Data shown here for underfed group and full fed groups include patients randomized to the intensive insulin and conventional insulin therapy within these 2 groups. Refer to the intensive insulin therapy section for data on intensive insulin vs. conventional groups.
** Includes 272 patients that also randomized to an experimental arm of omega 3fatty acids arm.

Figure 1. Overall Mortality

Study or Subgroup	Hypocaloric Events	Hypocaloric Total	Normocaloric Events	Normocaloric Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Arabi 2011	36	120	51	120	7.4%	0.71 [0.50, 1.00]	2011
Charles	3	41	4	42	0.4%	0.77 [0.18, 3.22]	2014
Peake	14	55	10	57	1.7%	1.45 [0.70, 2.99]	2014
Arabi 2015	108	447	123	445	17.5%	0.87 [0.70, 1.09]	2015
Rugeles	16	60	16	60	2.5%	1.00 [0.55, 1.81]	2016
Rice	7	50	8	52	1.0%	0.91 [0.36, 2.32]	2018
Chapman	470	1981	468	1967	69.6%	1.00 [0.89, 1.12]	2018
Total (95% CI)		**2754**		**2743**	**100.0%**	**0.95 [0.87, 1.05]**	
Total events	654		680				

Heterogeneity: Tau² = 0.00; Chi² = 5.57, df = 6 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)

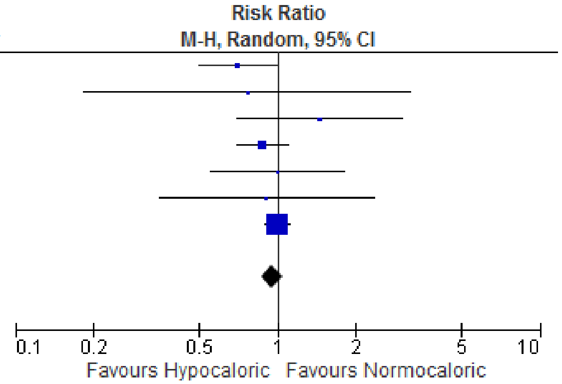


Figure 2: Hospital Mortality

Study or Subgroup	Hypocaloric Events	Hypocaloric Total	Normocaloric Events	Normocaloric Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Arabi 2011	36	120	51	120	11.0%	0.71 [0.50, 1.00]	2011
Charles	3	41	4	42	0.7%	0.77 [0.18, 3.22]	2014
Peake	14	55	10	57	2.7%	1.45 [0.70, 2.99]	2014
Arabi 2015	108	447	123	445	23.4%	0.87 [0.70, 1.09]	2015
Chapman	470	1981	468	1967	60.7%	1.00 [0.89, 1.12]	2018
Rice	7	50	8	52	1.6%	0.91 [0.36, 2.32]	2018
Total (95% CI)		**2694**		**2683**	**100.0%**	**0.94 [0.83, 1.06]**	
Total events	638		664				

Heterogeneity: Tau² = 0.00; Chi² = 5.55, df = 5 (P = 0.35); I² = 10%
Test for overall effect: Z = 1.07 (P = 0.29)

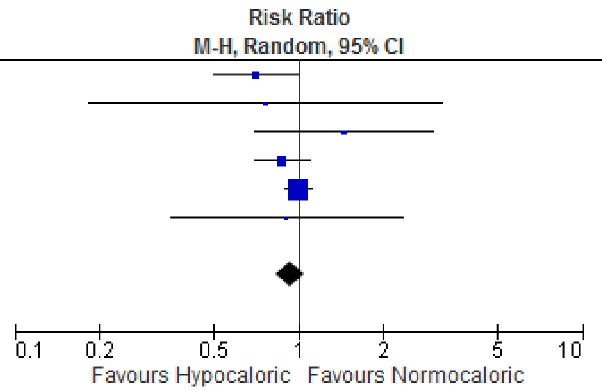


Figure 3: ICU Mortality

Study or Subgroup	Hypocaloric Events	Hypocaloric Total	Normocaloric Events	Normocaloric Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Arabi 2011	21	120	26	120	21.4%	0.81 [0.48, 1.35]	2011
Peake	9	55	6	57	6.1%	1.55 [0.59, 4.08]	2014
Arabi 2015	72	448	85	446	70.1%	0.84 [0.63, 1.12]	2015
Rice	2	50	6	52	2.4%	0.35 [0.07, 1.64]	2018
Total (95% CI)		**673**		**675**	**100.0%**	**0.85 [0.67, 1.08]**	
Total events	104		123				

Heterogeneity: Tau² = 0.00; Chi² = 2.83, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)

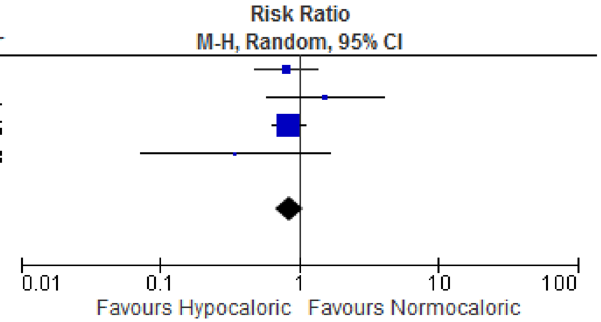


Figure 4: Infectious complications

Study or Subgroup	Trophic Events	Trophic Total	Full Events	Full Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Charles	12	46	6	54	4.5%	2.35 [0.96, 5.76]	2014
Arabi 2015	161	448	169	446	48.0%	0.95 [0.80, 1.13]	2015
Chapman	221	1984	228	1971	47.5%	0.96 [0.81, 1.15]	2018
Total (95% CI)		**2478**		**2471**	**100.0%**	**1.00 [0.82, 1.21]**	
Total events	394		403				

Heterogeneity: Tau² = 0.01; Chi² = 3.80, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 0.05 (P = 0.96)

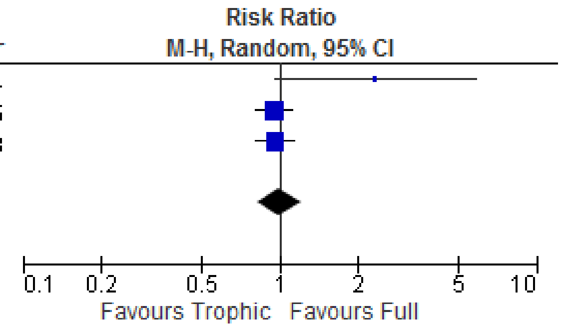


Figure 5. ICU LOS

	Hypocaloric			Normocaloric				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Arabi 2011	11.7	8.1	120	14.5	15.5	120	22.4%	-2.80 [-5.93, 0.33]	2011
Charles	16.7	2.7	41	13.5	1.1	42	29.3%	3.20 [2.31, 4.09]	2014
Peake	12.2	8.3	55	12.8	11.3	57	20.5%	-0.60 [-4.26, 3.06]	2014
Arabi 2015	15.8	11.6	444	16.4	12.1	443	27.7%	-0.60 [-2.16, 0.96]	2015
Total (95% CI)			**660**			**662**	**100.0%**	**0.02 [-2.92, 2.96]**	

Heterogeneity: $Tau^2 = 7.47$; $Chi^2 = 28.49$, df = 3 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: Z = 0.01 (P = 0.99)

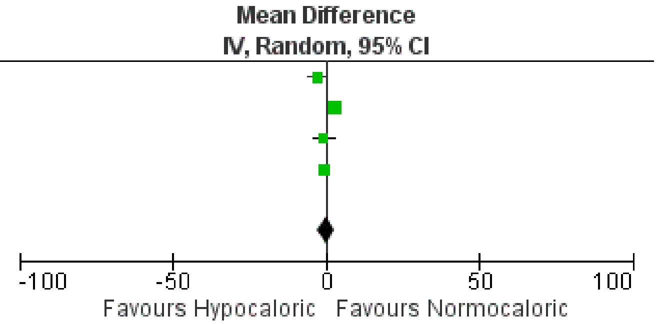


Figure 6. Hospital LOS

	Hypocaloric			Normocaloric				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Arabi 2011	70.2	106.9	120	67.2	93.6	120	2.1%	3.00 [-22.42, 28.42]	2011
Charles	35.2	4.9	41	31	2.5	42	35.1%	4.20 [2.52, 5.88]	2014
Peake	24	17.6	55	33.3	25.3	57	14.2%	-9.30 [-17.35, -1.25]	2014
Arabi 2015	48.3	67.5	444	54.4	73.9	443	11.7%	-6.10 [-15.42, 3.22]	2015
Rice	4.12	2.32	50	4.17	2.37	52	36.9%	-0.05 [-0.96, 0.86]	2018
Total (95% CI)			**710**			**714**	**100.0%**	**-0.51 [-4.35, 3.33]**	

Heterogeneity: $Tau^2 = 10.19$; $Chi^2 = 27.27$, df = 4 ($P < 0.0001$); $I^2 = 85\%$
Test for overall effect: Z = 0.26 (P = 0.79)

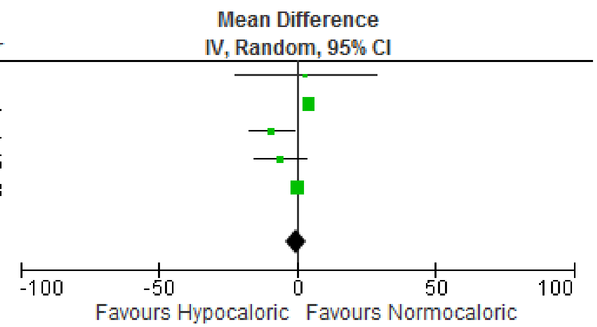


Figure 7. Ventilator Days

Study or Subgroup	Hypocaloric Mean	Hypocaloric SD	Hypocaloric Total	Normocaloric Mean	Normocaloric SD	Normocaloric Total	Weight	Mean Difference IV, Random, 95% CI	Year
Arabi 2011	10.6	7.6	120	13.2	15.2	120	24.5%	-2.60 [-5.64, 0.44]	2011
Peake	6.8	6	55	8.6	8.5	57	30.7%	-1.80 [-4.52, 0.92]	2014
Arabi 2015	11.3	9.2	444	13.5	22.3	443	44.9%	-2.20 [-4.45, 0.05]	2015
Total (95% CI)			**619**			**620**	**100.0%**	**-2.18 [-3.68, -0.67]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)

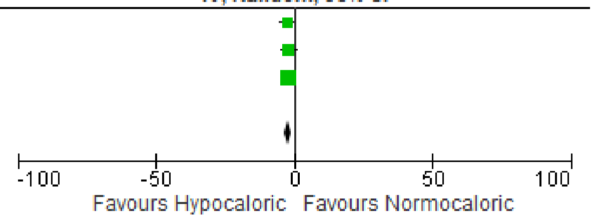


Figure 8. Caloric Adequacy

Study or Subgroup	Hypocaloric Mean	Hypocaloric SD	Hypocaloric Total	Normocaloric Mean	Normocaloric SD	Normocaloric Total	Weight	Mean Difference IV, Random, 95% CI	Year
Arabi 2011	59	16.1	120	71.4	22.8	120	25.4%	-12.40 [-17.39, -7.41]	2011
Peake	83.2	29	55	110.8	26.8	57	19.9%	-27.60 [-37.95, -17.25]	2014
Arabi 2015	46	14	448	71	22	446	27.2%	-25.00 [-27.42, -22.58]	2015
Chapman	69	18	1296	103	28	1291	27.4%	-34.00 [-35.81, -32.19]	2018
Total (95% CI)			**1919**			**1914**	**100.0%**	**-24.78 [-33.49, -16.07]**	

Heterogeneity: Tau² = 71.15; Chi² = 82.01, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 5.58 (P < 0.00001)

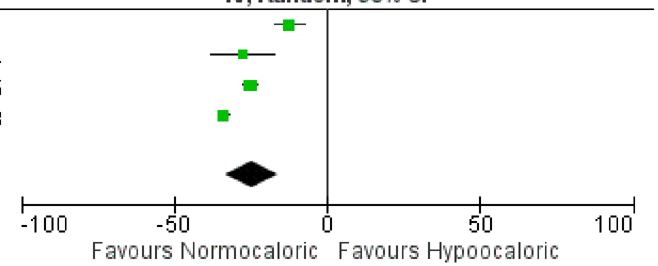
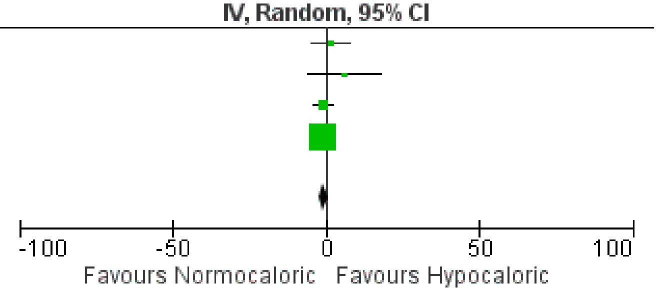


Figure 9. Protein Adequacy

Study or Subgroup	Hypocaloric Mean	Hypocaloric SD	Hypocaloric Total	Normocaloric Mean	Normocaloric SD	Normocaloric Total	Weight	Mean Difference IV, Random, 95% CI	Year
Arabi 2011	65.2	25.7	120	63.7	25	120	4.9%	1.50 [-4.91, 7.91]	2011
Peake	88.2	39.1	55	82	23.6	57	1.4%	6.20 [-5.81, 18.21]	2014
Arabi 2015	68	24	448	69	25	446	19.7%	-1.00 [-4.21, 2.21]	2015
Chapman	77	21	1296	78	22	1289	74.0%	-1.00 [-2.66, 0.66]	2018
Total (95% CI)			**1919**			**1912**	**100.0%**	**-0.78 [-2.20, 0.65]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.87, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.29)



References

Included Studies

1. Arabi YM, Tamim HM, Dhar GS, Al-Dawood A, Al-Sultan M, Sakkijha MH, Kahoul SH, Brits R. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr. 2011 Mar;93(3):569-77. Epub 2011 Jan 26. PubMed PMID: 21270385.
2. Charles EJ, Petroze RT, Metzger R, Hranjec T, Rosenberger LH, Riccio LM, McLeod MD, Guidry CA, Stukenborg GJ, Swenson BR, Willcutts KF, O'Donnell KB, Sawyer RG. 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. 2014 Nov;100(5):1337-43.
3. Peake SL, Davies AR, Deane AM, Lange K, Moran JL, O'Connor SN, Ridley EJ, Williams PJ, Chapman MJ; for the TARGET investigators the Australian New Zealand Intensive Care Society Clinical Trials Group. 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. 2014 Jul 2. [Epub ahead of print]
4. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, Mehta S, McIntyre L, Solaiman O, Sakkijha MH, Sadat M, Afesh L; PermiT Trial Group. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. N Engl J Med. 2015 Jun 18;372(25):2398-408.
5. Rugeles S, Villarraga-Angulo LG, Ariza-Gutiérrez A, Chaverra-Kornerup S, Lasalvia P, Rosselli D. High-protein hypocaloric vs normocaloric enteral nutrition in critically ill patients: A randomized clinical trial. J Crit Care. 2016 Oct;35:110-4. doi: 10.1016/j.jcrc.2016.05.004. PubMed PMID: 27481744.
6. TARGET Investigators, for the ANZICS Clinical Trials Group, Chapman M, Peake SL, et al. Energy-Dense versus Routine Enteral Nutrition in the Critically Ill. N Engl J Med. 2018;379(19):1823-1834. doi:10.1056/NEJMoa1811687
7. Rice TW, Files DC, Morris PE, Bernard AC, Ziegler TR, Drover JW, Kress JP, Ham KR, Grathwohl DJ, Huhmann MB, Gautier JBO. Dietary Management of Blood Glucose in Medical Critically Ill Overweight and Obese Patients: An Open-Label Randomized Trial. JPEN J Parenter Enteral Nutr. 2018 Sep 27.
8. Deane AM, Little L, Bellomo R, et al. Outcomes Six Months after Delivering 100% or 70% of Enteral Calorie Requirements during Critical Illness (TARGET). A Randomized Controlled Trial. Am J Respir Crit Care Med. 2020;201(7):814-822. doi:10.1164/rccm.201909-1810OC

Excluded Studies	**Reasons**
Owais AE, Kabir SI, Mcnaught C, Gatt M, MacFie J. A single-blinded randomised clinical trial of permissive underfeeding in patients requiring parenteral nutrition. Clin Nutr. 2014 Dec;33(6):997-1001.	Not critically ill patients
Petros S, Horbach M, Seidel F, Weidhase L. Hypocaloric vs Normocaloric Nutrition in Critically Ill Patients: A Prospective Randomized Pilot Trial. JPEN J Parenter Enteral Nutr. 2016 Feb;40(2):242-9.	See 3.2 Achieving target dose of EN
Theodorakopoulou M, Diamantakis A, Kontogiorgi M, Chrysanthopoulou E, Christodoulopoulou T, Frantzeskaki F, Lygnos M, Apostolopoulou O, Armaganidis A. Permissive underfeeding of mechanically ventilated septic ICU Patients. Intensive Care Medicine Experimental. Conference: 29th Annual Congress of the European Society of Intensive Care Medicine, ESICM 2016. aly. 4 (no pagination).	Abstract (page 131 of document)
Arabi YM, Aldawood AS, Al-Dorzi HM, Tamim HM, Haddad SH, Jones G, McIntyre L, Solaiman O, Sakkijha MH, Sadat M, Mundekkadan S, Kumar A, Bagshaw SM, Mehta S; PermiT trial group. Permissive Underfeeding or Standard Enteral Feeding in High- and Low-Nutritional-Risk Critically Ill Adults. Post Hoc Analysis of the PermiT Trial. Am J Respir Crit Care Med. 2017 Mar 1;195(5):652-662.	Post-hoc analysis
"Ochoa J, Huhmann M, Files DC, Drover J, Bernard A, Ziegler T, Kress J, Ham K.R, Grathwol D, Kulkarni H, Rice T. Hypocaloric high-protein enteral nutrition improves glucose management in critically ill patients. JPEN. 2017:41(2);289-90.	Abstract
Chelkeba L, Mojtahedzadeh M, Mekonnen Z. Effect of Calories Delivered on Clinical Outcomes in Critically Ill Patients: Systemic Review and Meta-analysis. Indian J Crit Care Med. 2017 Jun;21(6):376-390.	Systematic Review