

3.3b 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 six 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.

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.

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 ($p<0.0001$) (figure 8) but received the same amount of protein ($p=0.92$) (figure 9).

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. Non-isocaloric, isonitrogenous.	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 \geq 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. Non-isocaloric, isonitrogenous.	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.	28 day 18/60 (30%)	28 day 16/60 (27%)	NR	NR
6) Chapman 2018	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).	Hospital 470/1981 (23.7) 28 day 455/1976 (23) 90 day 505/1966 (25.7)	Hospital 468/1967 (23.8) 28 day 450/1961 (22.9) 90 day 523/1948 (26.8)	Positive blood cultures 221/1984 (11.1)	Positive blood cultures 228/1971 (11.6) RR 1.04 (0.87-1.24)
7) Rice 2018	Multicentre ICU adults, mechanically ventilated, BMI 26-45, requiring EN for \geq 5 days N=105	C.Random: Yes ITT: no Blinding: no (5)	Peptamen Intense VHP (1 kcal/ml, 37% protein, 29% CHO) started within 48h of randomization and advanced to reach protein goal of 1.5 g/kg IBW/d vs Replete (1 kcal/ml 25% protein, 45% CHO) also started within 48h of randomization and advanced to reach protein goal of 1.5 g/kg IBW/d	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 2. Randomized studies evaluating hypocaloric vs full feeding in critically ill patients

Study	LOS days	Ventilator days	Other
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	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 1252 ± 432, p=0.0002 Caloric Adequacy (%) 59 ± 16.1 71.4 ± 22.8, p=<0.0001 Protein adequacy (%) 65.2 ± 25.7 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 1338 ±92 Kcal/kg/d 12.3 ±0.7 17.1 ±1.1 Protein g/d 86 ±6 83 ±6 Protein g/kg/d 1.1 ±0.1 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 ± 29 110.8 ± 26.8 % Protein adequacy 88.2 ± 39.1 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 1299±467 % Caloric adequacy (p=<0.001) 46±14 71±22 Protein g/d (p=0.29) 57±24 59±25 % Protein adequacy (p=0.56) 68±24 69±25 No. feeding intolerance (p=0.26) 67/448 (15) 79/446 (17.7) No. Diarrhea p=0.11 97/448 (21.7) 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 20.5 ± 5.1 P<0.0001 Calories/kg/d at 96h 12.1 ± 2.6 19.2 ± 4.3 P<0.0001 Protein/g/d at 48h 1.4 ± 0.4 1.4 ± 0.3 Protein/g/d at 96h 1.3 ± 0.3 1.3 ± 0.3
6) Chapman 2018	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 81±17 (n=1971) 82±16 (n=1985) Kcal delivered (kcal/kg IBW) , mean and SD 30.2±7.5 (n=1971) 21.9±5.6 (n=1985) Protein delivered (g/kg IBW) , mean and SD 1.09±0.22 (n=1971) 1.08±0.23 (n=1985) Vomiting 370/1959 (18.9) 309/1966 (15.7) Highest blood glucose 225.2 (185.6-277.4) 212.6 (174.7-261.2) Duration of study intervention 6 days (3-11) 6 days (3-11) Time to start EN 15.8h (7.7-26.3) 15.9h (7.9-28.3)
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

† presumed hospital mortality unless otherwise specified

± () : mean ± Standard deviation (number)

ITT: intent to treat; NA: not available

*Data obtained from author in mean and standard deviation

‡ 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 3 fatty acids arm.

Figure 1. Overall Mortality

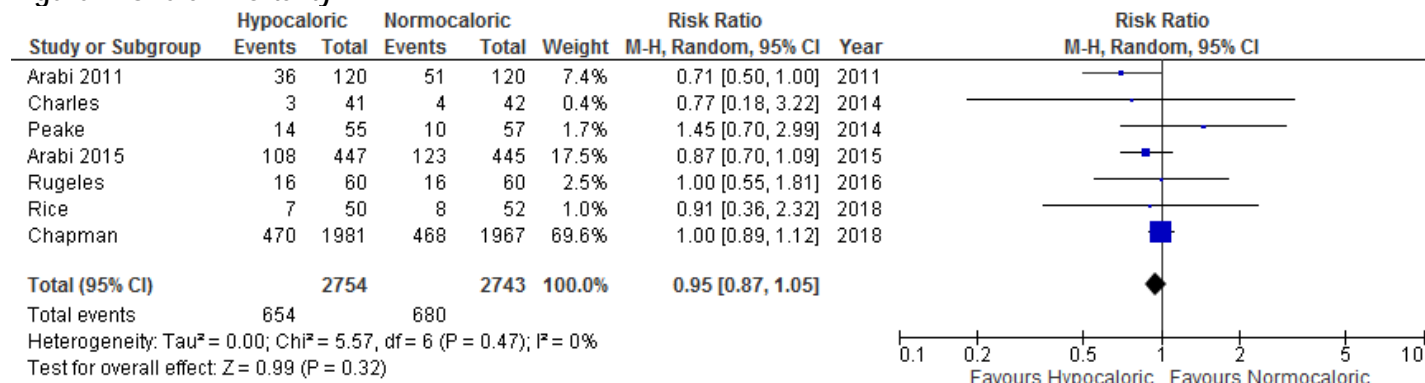


Figure 2: Hospital Mortality

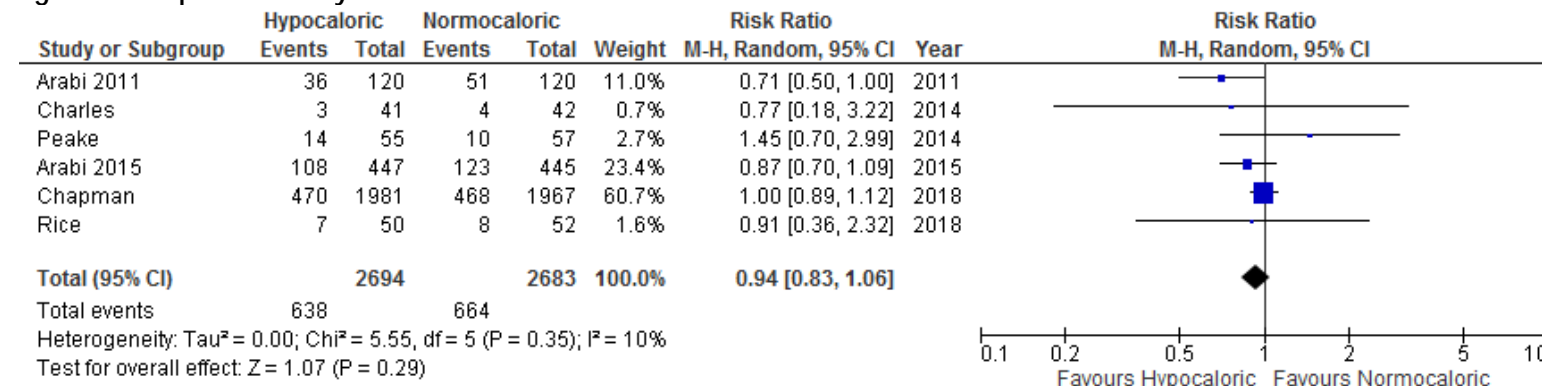


Figure 3: ICU Mortality

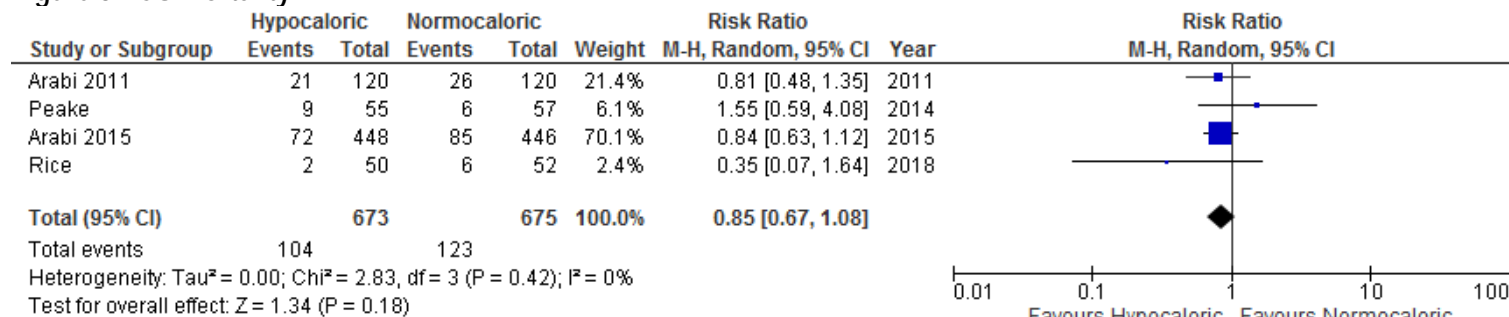


Figure 4: Infectious complications

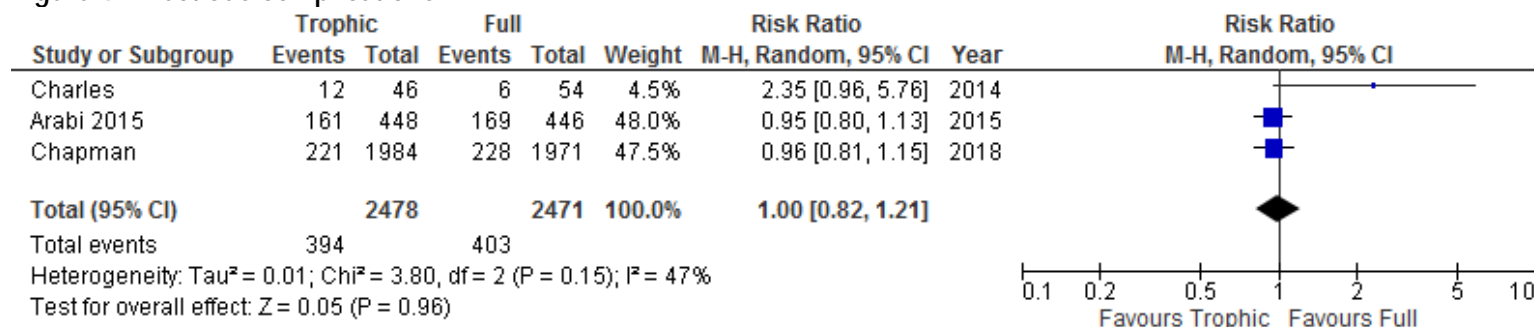


Figure 5. ICU LOS

Study or Subgroup	Hypocaloric		Normocaloric		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Random, 95% CI		
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: Tau ² = 0.00; Chi ² = 5.57, df = 6 (P = 0.47); I ² = 0%								
Test for overall effect: Z = 0.99 (P = 0.32)								

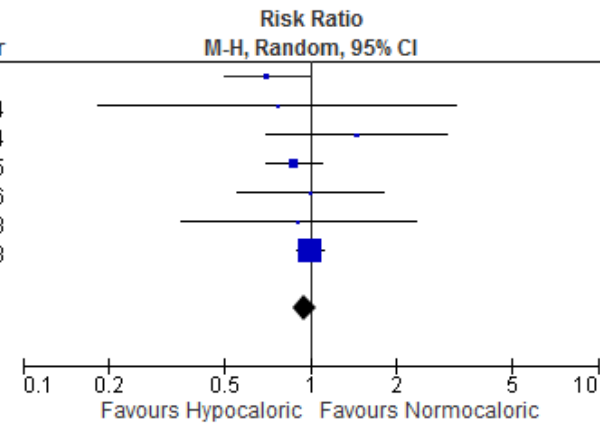


Figure 6. Hospital LOS

Study or Subgroup	Hypocaloric			Normocaloric			Weight	Mean Difference		Year
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI		
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)										

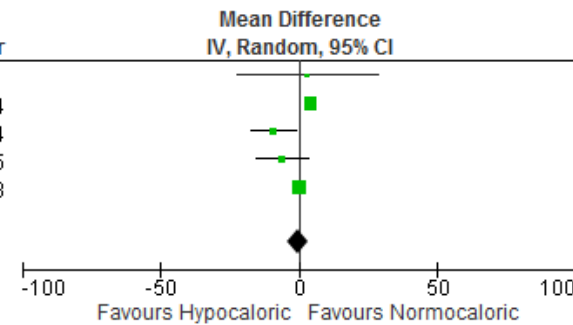


Figure 7. Ventilator Days

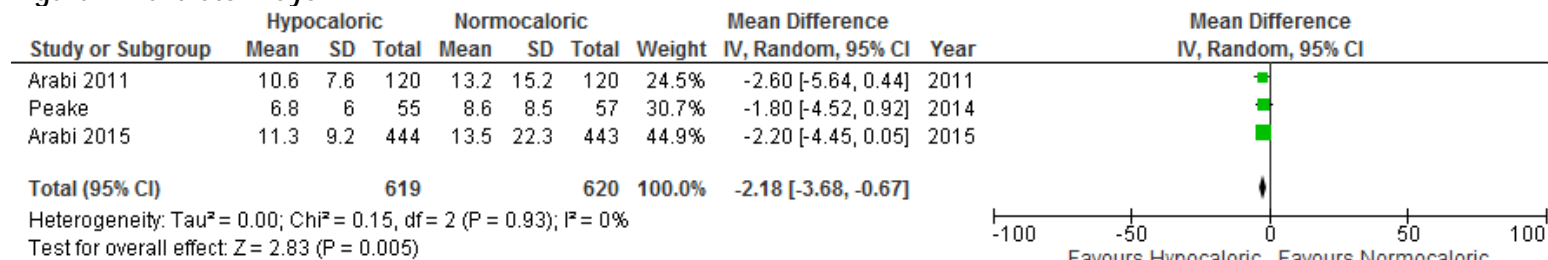


Figure 8. Caloric Adequacy

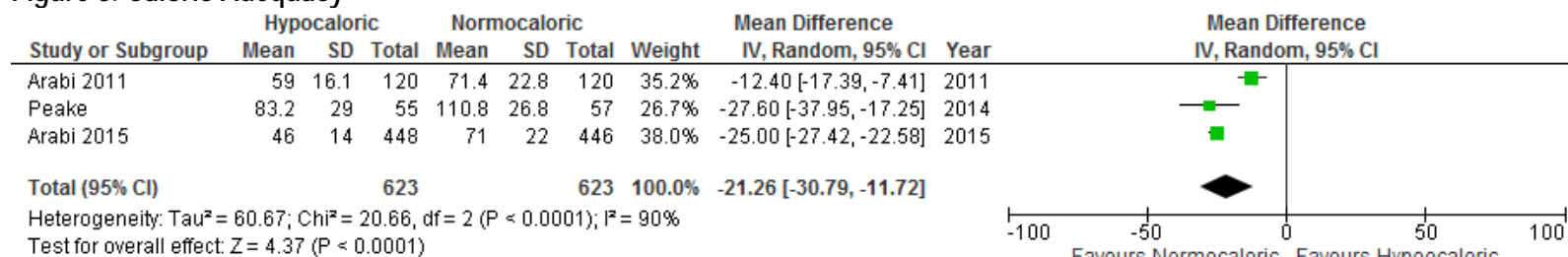


Figure 9. Protein Adequacy

