3.2 Nutritional Prescription of Enteral Nutrition: Enhanced Dose of Enteral Nutrition May 2015

2015 Recommendation: ***Based on 1 level 1 study, 3 level 2 studies and 2 cluster randomized controlled trials, when starting enteral nutrition in critically ill patients, strategies to optimize delivery of nutrients (starting at target rate, volume-based feeding strategies, higher threshold of gastric residual volumes, use of prokinetics, concentrated feeding solutions and small bowel feedings) should be considered.***

2015 Discussion: The committee agreed that despite the studies being disparate with respect to the interventions, since they all aimed at providing more enteral nutrition, their inclusion in this section was appropriate. They also noted the consistent signal for significantly increased calorie and protein adequacy and a significant reduction in infections with the use of enhanced enteral nutrition with the inclusion of the 2 new trials (INTACT Braunschweig 2014 and Peake 2014). There were concerns about increased mortality being associated with early enteral nutrition as seen in the INTACT trial (Braunschweig 2014) however this is to be regarded with caution as it could be attributed to the overfeeding in a normo-nourished or low risk patients and excessive use of IV lipids in the early phase of critical illness in a small pilot trial that was terminated prematurely, as highlighted by recent correspondence (1, 2). This increased mortality disappeared when the data from this study was combined with the other non cluster trials. The evidence from the ACCEPT study was also considered as better fed patients had reduced mortality in that trial. The significant increase in hospital length of stay in the INTACT study (no statistical heterogeneity despite wide confidence intervals) with enhanced enteral nutrition was acknowledged but noted to conflict with the direction of reduced ICU LOS in the same meta-analysis and the earlier findings from the ACCEPT trial. Given these conflicting findings, the committee decided not to upgrade the recommendation, despite the stronger signal for reducing infections and improving intake. However, the committee noted that all the trials in this section studied heterogeneous groups of ICU patients and these recommendations to enhance EN may be more applicable to nutritionally high-risk patients (3).

(1) Heyland DK, Dhaliwal R, Lemieux M. More Questions Than Answers. JPEN. 2015;39(2):143.
(2) Braunschweig C, Sheean P, Peterson SJ, Perez SG, Freels S, Lateef O, Gurka D, Fantuzzi G. Response to Berger and Pichard and Heyland et al. JPEN. 2015 Feb;39(2):144-5.
(3) Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initialvalidation of a novel risk assessment tool. Crit Care. 2011;15(6):R268.

2013 and 2009 Recommendation: ***Based on 2 level 2 studies and 2 cluster randomized controlled trials , when starting enteral nutrition in critically ill patients, strategies to optimize delivery of nutrients (starting at target rate, higher threshold of gastric residual volumes, use of prokinetics and small bowel feedings) should be considered.***

Discussion: The committee noted that across the four disparate studies, there were large improvements in calorie/protein intake/calorie deficit, decreased complications and reduced mortality with the use of enhanced enteral nutrition. Cost and feasibility concerns were also favourable. These favourable signals are tampered by the probability of harm associated with aggressive enteral nutrition as illustrated by non-randomized studies[1,2] . Given the recent mixed signals from observational studies on the association of calorie deficit and outcomes[3,4], the committee felt that a stronger recommendation could not be made at this time.

1) Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. Crit Care Med 2001; 29(10):1955-61.
2) Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, Fraser V, Kollef M. Early versus late enteral feeding of mechanically ventilated patients: Results of a clinical trial. JPEN 2002;26:174-181.
3) Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. *Chest* 2003;124:297-305
4) Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr* 2005;24:502-9

Semi Quantitative Scoring

Values	Definition	Score 2013 (0,1,2,3)	Score 2015 (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	**2**	**Infections 2**
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	**2**	**Infections 3**
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	**2**	**2**
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	**2**	**2**
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	**3**	**3**
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	**3**	**3**
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings =3.	**2**	**2**
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	**3**	**3**
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	**2**	**2**
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	**1**	**1**

3.2 Nutritional Prescription of Enteral Nutrition: Enhanced Dose of Enteral Nutrition

Question: Does achieving target dose of enteral nutrition result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 3 level 2 studies (Taylor 1999, Desachy 2008, Braunschweig 2014) and 1 level 1 study (Peake 2014) that compared the use of early enhanced enteral nutrition to standard early enteral nutrition and two cluster randomized controlled trials that evaluated the effect of a enhanced feeding protocol as one of several interventions geared towards optimizing nutrition (Martin 2004, Doig 2008). In both the cluster randomized controlled trials, the effect of evidence based nutrition algorithms (plus an educational intervention) geared at improving nutrition on patient outcomes was tested. These algorithms assessed gastrointestinal tolerance and promoted the use of prokinetics, post pyloric feeding tubes and supplemental parenteral nutrition to meet at least 80% caloric goal. Two of the randomized trials started enteral nutrition at 15ml/hour to 25ml/hr on day 1 and increased gradually (Taylor 1999, Desachy 2008), one study evaluated the use of a nutritionally denser formula to achieve greater nutrition delivery (Peake 2014) and one study compared feeding at >75% of nutrient goals vs standard care (Braunschweig 2014). Gastric residual volume thresholds varied from 200 mls (Taylor 1999) to 300 mls (Desachy 2008) and other strategies such as HOB elevation and prokinetics were employed. In the Taylor study, 34% patients received small bowel feedings. The Taylor 1999 study included patients > 10 years of age but was not excluded from this review as the median age was 28 (95% C.I. 22-37) for the control and 34 (95% C.I. 24-43) for the experimental group. Given the disparate nature of the cluster trials, the data from these were not aggregated with the other trials.

Mortality: Five studies reported on ICU and hospital mortality while one study reported on 6 month mortality (Taylor 1999). In the ACCEPT trial (Martin 2004) there was a trend towards a reduction in hospital mortality in the ICUs that received the evidence based algorithms/education (p=0.058 and p=0.017 respectively) whereas o such difference was observed in the Doig 2008 cluster randomized trial. In the INTACT trial (Braunschweig 2014) was stopped early due to a significant increase in mortality in the intensive medical nutrition therapy group (40% vs 16%, p=0.017). When the 2 studies that reported on ICU mortality were aggregated, enhanced dose of EN was associated with no effect on overall mortality (RR 0.69, 95% CI 0.35, 1.38, p = 0.30, test for heterogeneity I^2 = 0%) (figure 1). When the 3 studies that reported on hospital mortality were aggregated, this lack of an effect remained (RR 1.28 95% CI 0.63,2.58, p = 0.50, test for heterogeneity I^2 = 63%) (figure 2).

Infections: Only two studies reported on infectious complications. In Taylor 1999, the goal rate fed group had significantly less infections (p 0.02), whereas no difference was seen in the INTACT trial (Braunschweig 2014) (p=0.29). When the data from these studies was aggregated, achieving enhanced dose of EN was associated with a significant reduction in infections (RR 0.71, 95% CI 0.54, 0.92, p = 0.01, test for heterogeneity I^2 = 0 (figure 3).

LOS: In the Desachy 2008, Braunschweid 2014 and Peake 2014 studies, there were no differences in ICU and hospital length of stay between the two groups. In one study, length of stay was only reported on a sub group of patients and hence was not included. In the two cluster randomized controlled trials, no differences in ICU length of stay was observed, however, the hospital length of stay was significantly lower in the ICUs that received the evidence based algorithms/education in one trial (p=0.003, Martin 2004). When the data from the 4 studies was aggregated, early EN has no effect on ICU LOS (Weighted Mean Difference WMD -1.01, 95% CI -2.59, 0.56, p = 0.21, test for test for heterogeneity I^2 =) but was associated with a significant increase in hospital LOS (WMD 6.96. 95% CI 0.90, 11.22, p = 0.02, test for heterogeneity I^2 =0) (figures 4, 5).

Ventilator duration: When the 2 trials that reported on ventilation days were combined, early EN had no effect on duration of ventilation (WMD -0.02, 95% CI -3.13, 3.08, p = 0.99, test for heterogeneity I^2 = 76%) (figure 6).

Other complications and nutritional outcomes: The # days 100% goal calories were met was higher in the ICUs that were randomized to the practice change group in the Doig cluster trial (p=0.03). The time from ICU admission to start of enteral nutrition was lower in the ICUs that were randomized to the algorithm group/practice change group in both cluster trials (Martin 2004 p=0.17, Doig 2008 p<0.001). In one study (Taylor 1999), early enhanced enteral nutrition was associated with a trend towards fewer major complications and better neurological outcome at 3 months (p =0.08). The enhanced feeding group also received significantly more calories in four studies and had a significantly lower cumulative caloric deficit than the slowly fed group in one study (Desachy 2008 p < 0.0001). Braunschweig 2014 showed significantly improved protein delivery in the enhanced feeding group (p < 0.0001). When the data from the 3 non cluster trials were aggregated, enhanced dose EN was associated with a significant increase in calories (RR 26.18, 95% CI 20.37, 32.00, p = <0.00001) (figure 7) and a trend in increased protein adequacy (RR 12.18, 95%CI -4.45, 28.81, p = 0.15) (figure 8).

Conclusions:

1) Early enhanced EN compared to slower rate of advancement of EN has no effect on mortality in the critically ill patient
2) Early enhanced EN compared to slower rate of advancement of EN has no effect on ICU LOS but is associated with a significant increase in hospital lengths of stay in the critically ill patient
3) Early enhanced EN compared to a slower rate of advancement of EN is associated with a significant reduction in the # infections and a trend towards a reduction in complications in head injured patients. Early enhanced EN compared to a slower rate of advancement of EN results in a significantly higher calorie and protein intake/lower calorie deficit in head injured patients and other critically ill patients.

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 target dose of enteral nutrition in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡		LOS days		Other outcomes	
				Goal rate	Standard	Goal rate	Standard	Goal rate	Standard	Goal rate	Standard
1) Taylor 1999	Head injured ventilated > 10 yrs n = 82	C.Random: not sure ITT: yes Blinding: no (10)	EN at Goal rate on Day 1 vs. 15 ml/hr day 1 and gradual increase. Both on standard formula	**6 months** 5/41(12.2)	**6 months** 6/41 (14.6)	25/41 (61) **Pneumonia** 18/41 (44)	35/41 (85) **Pneumonia** 26/41 (63)	NR*	NR*	**% Energy needs met (mean)** 59.2 **Nitrogen needs met (mean)** 68.7 **Major complications** 37 % **Better neurological outcome at 3 mo** 61% **Better neurological outcome at 6 mo** 68%	36.8 37.9 61% 39% 61%
2)Martin 2004	Cluster RCT of 14 mixed ICU's N = 492	C.Random: no ITT: no Blinding:no (NA)**	Nutrition algorithms with prokinetics+post pyloric feeding+ supplemental parenteral nutrition to meet at least 80% caloric goal vs. none	**Algorithms** 72/269 (27)	**No ne** 82/223 (37)	**Algorithms** NR	**No ne** NR	**Algorithms** **Hospital** 25 **ICU** 10.9	**None** **Hospital** 35 **ICU** 11.8	**Algorithms** **Days from ICU admit to start of EN** 1.61 **Days to 80% goal rate of EN** 4.80 **Calorie intake per patient day (cals)** 1269	**None** 2.16 5.10 1002
3) Desachy 2008	Patients from two mixed ICUs N =100	C.Random: not sure ITT: yes Blinding: no (8)	Goal rate EN on day 1vs. 25 ml/hr day 1 and gradual increase. Both on standard formula, goal rate 25 kcal/kg	**Hospital** 14/50 (28) **ICU** 6/50 (12)	**Hospital** 11/50 (22) **ICU** 8/50 (16)	NR	NR	**ICU** 15 ± 11 **Hospital** 56 ± 59	**ICU** 15 ± 11 **Hospital** 51 ± 75	**Energy intake (mean)** 1715 ± 331 **Cumulative calorie Deficit** 406 ±729 **% Energy needs met (mean)** 95	1297 ± 331 p < 0.001 2310 ± 1340 p < 0.0001 76
4) Doig 2008	Cluster RCT of 27 ICUs. Patients expected to remain in ICU >2 days N = 1118	C.Random: No ITT: yes Blinding: no (NA)**	Guideline development and practice change strategy of 18 guideline interventions vs. standard	**Hospital** 172/561 (28.9) **ICU** 137/561 (24.5)	**Hospital** 153/557 (27.4) **ICU** 121/561 (21.5)	NR	NR	**ICU** 9.1 (8.2 – 10.1) **Hospital** 24.2 (22.2 – 26.8)	**ICU** 9.9 (8.9 – 11.1) **Hospital** 24.3 (22.3 – 26.4)	**Time (days) from ICU admission to EN or PN (mean)** 0.75 (0.64 – 0.87) **Energy (kcal) intake (mean)** 1241 (1121 – 1374) **Protein (g) intake (mean)** 50.1 (45.4 – 55.3) **100% Goal of kcal intake (days)**	1.37 (1.17 – 1.60) 1065 (961 – 1179) 44.2 (40.0 – 48.9)

										6.1 (5.6 – 6.65) 5.02 (4.61 – 5.48)
5) Braunschweig 2014	Acute lung injury, single center ICU N= 78	C. Random: yes ITT: yes Blinding: No (7)	Intensive Medical Nutrition Therapy >75% of energy and protein goal (continuous feed), vs standard nutrition support (bolus, intermittent or continuous feed). Goal 30 kcal/kg/d, 1.5g/kg/d protein	**Hospital** 16/40 (40)	**Hospital** 6/38 (15.8)	5/40 (12)	8/38 (21)	**ICU** 15.5 ± 12.8 **Hospital** 27.2 ± 18.2	**ICU** **16.1** ± 11.5' **Hospital** 22.8 ± 14.3	**Ventilator days (mean)** 6 (4-10) 7 (3-14) p<0.25 **Caloric adequacy** 84.7 ± 22 55.4 ± 19 **Protein adequacy** 76.1 ± 18 54.4 ± 21
6) Peake 2014	Emergency operative and non-operative and elective operative admissions N=112	C. Random: yes ITT: yes Blinding: yes (9)	Fresubin 2250 Complete 1.5kcal/ml vs Fresubin 1000 Complete 1.0kcal/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.	**ICU** 6/57 (11) **Hospital** 10/57 (19) **28 day** 11/57 (20) **90 day** 11/57 (20)	**ICU** 9/55 (16) **Hospital** 14/55 (27) **28 day** 18/55 (33) **90 day** 20/55 (27)	NR	NR	**ICU** 12.8 ± 11.3 **Hospital** 33.3 ± 25.3	**ICU** 12.2 ± 8.3 **Hospital** 24 ± 17.6	**% Energy adequacy** 110.8 ± 26.8 83.2 ± 29 **% Protein adequacy** 82 ± 23.6 88.2 ± 39.1 **Ventilator days** 8.6 ± 8.5 6.8 ± 6

C.Random: concealed randomization ITT: intent to treat NR: not reported ‡ refers to the # of patients with infections unless specified * only reported on a subgroup of patients hence not included
**NA : methodological scoring not applicable as cluster RCTs

Figure 1: ICU Mortality

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Desachy 2008	6	50	8	50	49.0%	0.75 [0.28, 2.00]	2008
Peake 2014	6	57	9	55	51.0%	0.64 [0.25, 1.69]	2014
Total (95% CI)		**107**		**105**	**100.0%**	**0.69 [0.35, 1.38]**	
Total events	12		17				

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)

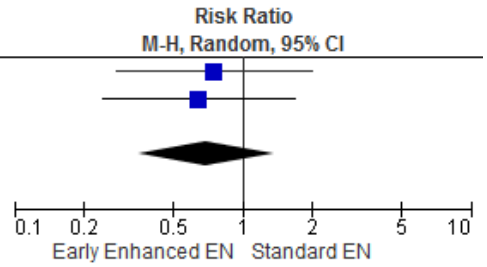

Figure 2: Hospital Mortality

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Desachy 2008	14	50	11	50	35.3%	1.27 [0.64, 2.53]	2008
Peake 2014	10	57	14	55	34.1%	0.69 [0.33, 1.42]	2014
Braunschweig 2014	16	40	6	38	30.7%	2.53 [1.11, 5.79]	2014
Total (95% CI)		**147**		**143**	**100.0%**	**1.28 [0.63, 2.58]**	
Total events	40		31				

Heterogeneity: Tau² = 0.25; Chi² = 5.42, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 0.68 (P = 0.50)

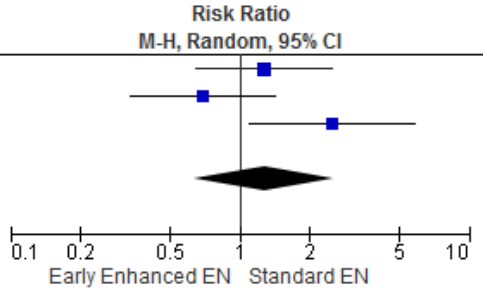

Figure 3: Infectious complications

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Taylor 1999	25	41	35	41	93.3%	0.71 [0.54, 0.94]	1999
Braunschweig 2014	5	40	8	38	6.7%	0.59 [0.21, 1.66]	2014
Total (95% CI)		**81**		**79**	**100.0%**	**0.71 [0.54, 0.92]**	
Total events	30		43				

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)

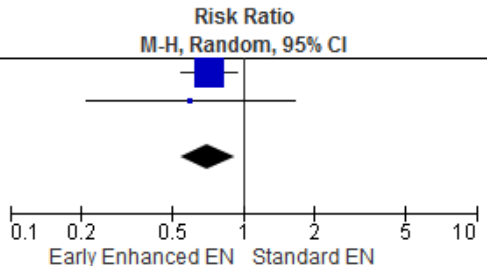

Figure 4 ICU LOS

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	4	3.6	41	5.8	5.6	41	59.7%	-1.80 [-3.84, 0.24]	1999
Desachy 2008	15	11	50	15	11	50	13.3%	0.00 [-4.31, 4.31]	2008
Peake 2014	12.8	11.3	57	12.2	8.3	55	18.5%	0.60 [-3.06, 4.26]	2014
Braunschweig 2014	15.5	12.8	40	16.1	11.5	38	8.5%	-0.60 [-5.99, 4.79]	2014
Total (95% CI)			**188**			**184**	**100.0%**	**-1.01 [-2.59, 0.56]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

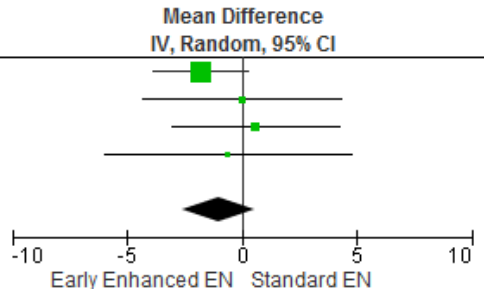

Figure 5 Hospital LOS

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	56.3	59.5	41	60.8	55.7	41	4.3%	-4.50 [-29.45, 20.45]	1999
Desachy 2008	56	59	50	51	75	50	3.8%	5.00 [-21.45, 31.45]	2008
Peake 2014	33.3	25.3	57	24	17.6	55	41.1%	9.30 [1.25, 17.35]	2014
Braunschweig 2014	27.2	18.2	40	22.8	14.3	38	50.8%	4.40 [-2.84, 11.64]	2014
Total (95% CI)			**188**			**184**	**100.0%**	**6.06 [0.90, 11.22]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.52, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)

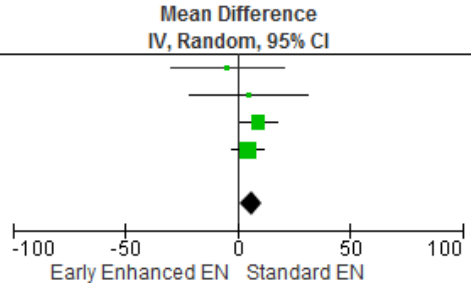

Figure 6 Ventilator Days

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	3.8	2.4	41	5.2	3.8	41	57.0%	-1.40 [-2.78, -0.02]	1999
Peake 2014	8.6	8.5	57	6.8	6	55	43.0%	1.80 [-0.92, 4.52]	2014
Total (95% CI)			**98**			**96**	**100.0%**	**-0.02 [-3.13, 3.08]**	

Heterogeneity: Tau² = 3.91; Chi² = 4.24, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 0.01 (P = 0.99)

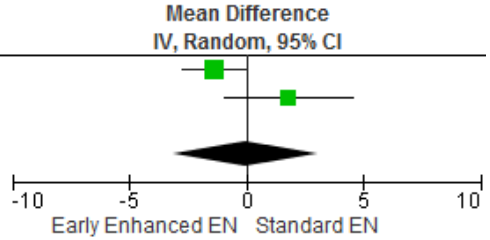

Figure 7 Caloric Adequacy

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	60	30	41	40	20	41	27.7%	20.00 [8.96, 31.04]	1999
Braunschweig 2014	84.7	22	40	55.4	19	38	40.7%	29.30 [20.19, 38.41]	2014
Peake 2014	110.8	26.8	57	83.2	29	55	31.5%	27.60 [17.25, 37.95]	2014
Total (95% CI)			**138**			**134**	**100.0%**	**26.18 [20.37, 32.00]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 8.83 (P < 0.00001)

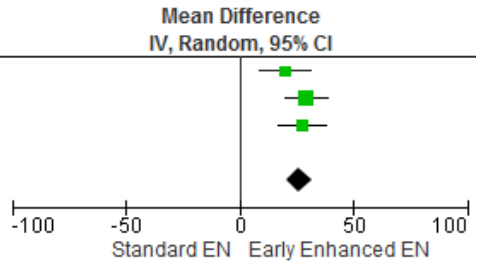

Figure 8 Protein Adequacy

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	60	30	41	40	20	41	33.0%	20.00 [8.96, 31.04]	1999
Peake 2014	82	23.6	57	88.2	39.1	55	32.1%	-6.20 [-18.21, 5.81]	2014
Braunschweig 2014	76.1	18	40	54.4	21	38	34.9%	21.70 [13.00, 30.40]	2014
Total (95% CI)			**138**			**134**	**100.0%**	**12.18 [-4.45, 28.81]**	

Heterogeneity: Tau² = 186.58; Chi² = 14.99, df = 2 (P = 0.0006); I² = 87%
Test for overall effect: Z = 1.44 (P = 0.15)