7.1 Combination Parenteral Nutrition and Enteral Nutrition

Question: Does the use of parenteral nutrition in combination with enteral nutrition result in better outcomes in the critically ill adult patient?

Summary of evidence: 12 randomized controlled trials were reviewed and meta-analysed[1-12].
Fifty percent (6/12) reported adequate generation of the random sequence, 46 % (5/12) of the RCTs reported adequate allocation sequence concealment and eight % (1/12) of the included RCTs reported adequate blinding of the outcome assessors. Nine trials compared EN+PN (an early combined enteral and parenteral nutrition) to EN, three trials compared SPN (where EN is supplemented by PN after some period, if full EN is impossible, or fails to reach nutrition targets) to EN. Five trials were published before 2000 and 7 trials after 2000. Seven trials included patients without nutritional risk assessment and five trials included patients evaluated to be at nutritional risk.

A priori defined subgroup analyses were:
1. Trials of patients receiving EN+PN or SPN vs. EN alone compared to trials of patients receiving SPN vs. EN alone, as these are different strategies regarding the timing of PN may have a different clinical effect.
2. Trials published until 2000 compared to trials published later than 2000, as "major relevant changes were implemented after new scientific data became available around the start of the new millennium"
3. Trials recruiting patients at increased risk for malnutrition or nutrition risk compared to trials that included heterogenous groups of patients without consideration of nutrition status as these different patient populations may respond differently to nutritional therapy.

Trials, where intravenous nutrients were given in both groups (Casaer and Chiarelli) were excluded in sensitivity analyses.

Mortality: All 12 studies reported on mortality (Figure 1). Data was collated to 30-day mortality. On average, no significant effect of any combination of EN with PN on "mortality within 30 days" was observed (Risk Ratio [RR] 1.0, 95% confidence intervals [CI], 0.79 to 1.28 p = 0.99) with low to moderate statistical heterogeneity (I^2 = 30%). A subgroup analysis in a single trial did demonstrate a tendency towards lower mortality in nutritionally high-risk patients when EN+PN was provided (p = 0.19 in patients with NUTRIC Score ≥5 and Body Mass Index <25 kg/m^2). In the sensitivity analysis, after excluding the Chiarelli and Casaer trials, the resultant effect was similar: RR 1.00., 95% CI, 0.70 to 1.44, p=1.00).

In our subgroup analyses, no difference in treatment effect was observed in RCTs using EN+PN vs. those using SPN (test for subgroup differences p = 0.72, Figure 1), in RCTs published until 2000 vs. those published after 2000 (test for subgroup differences, p = 0.18, Figure 2), nor in trials patients with or without a baseline nutrition risk assessment (test for subgroup differences, p = 0.28, Figure 3).

Infections: Seven trials reported on the outcome "infectious complications", but time window for its assessment as well as the definition of infection was too heterogeneous to perform meta-analysis. Differences between treatment groups were observed in three trials. An older RCT performed by

Chiarelli et al. observed different rates of pneumonia (50% infections in the EN+PN group [6/12] and 25% in the EN group [3/12]) as defined by positive bronchial aspirate and x-ray of the chest. Casaer et al. observed statistically significant more infections in the EN+PN group (p=0.008), which included airway, bloodstream, wound and urinary tract infections. Heidegger et al. reported a lower risk of nosocomial infection from days 9-18 in the SPN group in comparison to EN alone (hazard ratio 0.65, 95% CI 0.43–0.97; p=0.0338), and the SPN group had a lower mean number of nosocomial infections per patient (hazard ratio−0.42 CI −0.79 to −0.05; p=0.0248). With the data obtained from the authors for days 4 – 28, no differences between groups were found. No statistically significant differences regarding infection rates were observed in the other four trials that reported this outcome.

Hospital LOS: When the data from the 8 studies that reported hospital length of stay as a mean ± standard deviation were aggregated, on average, no significant effect of any combination of EN with PN on hospital LOS was observed (mean difference [MD]-1.44, CI -5.59 to 2.71, p = 0.50) with substantial statistical heterogeneity (I^2 = 88%) was observed (Figure 4). In the sensitivity analysis, after excluding the Chiarelli and Casaer trials, the resultant effect was greater: MD -3.00, 95% CI, -6.40 to 0.40, p=0.08.

There was no difference in the treatment effect in RCTs using EN+PN vs. those using SPN, RCTs published until 2000 vs. those published after 2000, nor in RCTs patients with or without a baseline nutrition risk assessment (test for subgroup differences, p = 0.88 [Figure 4], p = 0.97 [Figure 5] and p = 0.99 [Figure 6]).

ICU LOS: Seven studies reported this outcome (Figure 7)**.** On average, no significant effect of any combination of EN with PN on ICU LOS was observed (MD -0.15, CI -2.05 to 1.75, p = 0.88) with substantial statistical heterogeneity (I2 = 88%). Sensitivity analysis showed no difference when the trials by Casaer et al. and Chiarelli et al. were excluded (MD -0.81, 95% CI, -2.42 to 0.80, p=0.32).

There was no difference in the treatment effect in RCTs using EN+PN vs. those using SPN, RCTs published until 2000 vs. those published after 2000, nor in RCTs patients with or without a baseline nutrition risk assessment (test for subgroup differences, p = 0.94 [Figure 7], p = 0.91 [Figure 8] and p = 0.94 [Figure 9]).

Ventilation time: Eight studies reported this outcome (Figure 10). On average, no significant effect of any combination of EN with PN on the duration of mechanical ventilation (MD -0.43, CI -1.50 to 0.63, p = 0.42) with substantial statistical heterogeneity (I^2 = 79%) were observed. There was no difference in the sensitivity analyses (MD -0.59, 95% CI, -1.97 to 0.79, p=0.40).

There was no difference in the treatment effect in RCTs using EN+PN vs. those using SPN, RCTs published until 2000 vs. those published after 2000, nor in RCTs patients with or without a baseline nutrition risk assessment (test for subgroup differences, p = 0.83 [Figure 10], p = 0.31 [Figure 11] and p = 0.79 [Figure 12]), nor in sensitivity analysis.

Blood sugars: Blood sugar levels were reported by four trials. Glycaemia was significantly higher in the EN+PN group compared to the EN in the RCT by Bauer et al. on day 7 only ($p<0.05$). On the contrary, Chiarelli et al. observed no difference in glycemia between the groups, but no numbers were reported. Heidegger et al. reported similar glucose control in both groups and Berger et al. reported similar area under the curves of glycemia.

Nutrition delivery: Trials reported nutritional data in a non-uniform manner (Table 2) which precluded statistical aggregation. A combination of EN with PN compared EN alone significantly increased energy intake in six trials, while in two trials differences between groups were not observed. Regarding protein, significant increases of delivery in the combination of EN with PN groups were observed in four trials, while one trial reported no difference.

Physical and Quality of Life Outcomes: Four studies reported on these outcomes displayed in Table 3. None of the trials found significant differences between groups. However, Wischmeyer et al. found trends towards improved handgrip strength at hospital discharge, improved 6 Minute Walk Test and better Barthel index at hospital discharge, as well as improved SF-36 scores at 6 months in the nutritionally high-risk patients that received a combination of EN and PN. Berger et al. observed a trend for a lower loss of the quadriceps cross sectional area in those patients receiving SPN**.**

Conclusions: In critically ill patients, the combined use of EN and PN, compared to EN alone,

1) may be associated greater amounts of macronutrients administered
2) has no effect on mortality, infectious complications, duration of mechanical ventilation, ICU and Hospital LOS.
3) may be associated with some improvements in long-term physical function of surviving critically ill patients.
4) may be associated with a trend towards reduced mortality in nutritionally at-risk patients but data are too sparse to make any conclusions really.

Table 1. Randomized studies evaluating combined EN + PN in critically ill patients

Study	Population	Intervention	Co-Intervention	Study Period
Trials comparing EN+PN with EN				
Herndon 1987 [44]	28 patients with burns > 50 % TBSA	**EN+PN vs. EN**	Albumin and hourly feedings (milk or commercial EN) for all	Day 0-10 post-injury
Herndon 1989 [45]	39 patients with burns > 50 % TBSA	**EN+PN vs. EN**	Albumin and hourly feedings (milk or commercial EN) for all	NR, presumably day 0-14 post-injury
Dunham 1994 [42]	37 blunt trauma patients	**EN+PN vs. EN vs. PN#** PN made up 50% of given calories	NR	Randomized < 30 hours after injury
Chiarelli 1996 [33]	24 ICU patients medical and surgical	**EN+PN vs. EN** PN made up 50% of given calories, TPN for all patients on days 1-3	NR	Intervention starting day 4, duration NR
Bauer 2000 [40]	120 patients expected to eat less than 20 kcal/kg daily for 2 d	**EN+PN vs. EN+placebo** PN : 120 ml/h of 1 kcal/ml for 18-24 hours EN : bolus feeding up to 350 ml of 1kcal/mL standard formula	GRV > 300 ml : feeding delayed by 4 hours and cisapride was added	Started early, continued for 4-7 days
Abrishami 2010 [39]	20 SIRS patients with APACHE II > 10 and expected not to feed orally for ≥5 d	**EN+PN vs. EN** EN+PN : EN + 500 ml of 10% amino acid solution + 500 ml of dextrose 50% solution	Metocloparamide if GRV >300 ml	Days 1-7 after admission
Casaer 2011 [35, 48]	2312 ICU patients, NRS > 3, all patients who were unable to eat by day 2 received enteral nutrition and expected to remain on IU for more than 5 further days	**EN+PN vs. EN** EN+PN : 20% glucose solution (400 kcal day 1, 800 kcal day 2), day 3: PN+EN at 100%, when EN covered 80% or patient fed orally, PN was reduced / stopped. PN was restarted whenever enteral or oral intake fell to less than 50% of the calculated caloric needs.	Prokinetic agents	Days 1-7 but PN not started until day 3
Chen 2011 [32]	147 elderly patients in respiratory ICU	**EN+PN vs. EN vs. PN#** PN to make up kcal and nitrogen deficit; EN: 100ml/hr=goal rate	Metoclopramide if GRV>200mL, NJ if not tolerating NG	NR, comparison of groups on day 7
Wischmeyer 2017 [47]	125 adult (≥18 years) mixed ICU patients with BMI <25 or >35, mNUTRIC score <5 / >5	**EN+PN vs. EN** PN adjusted daily to reach 100% of goal calories. In extubated patients, until 50% of calories goal were tolerated orally	No	Days 1-7 or until death
Trials comparing SPN with EN				
Heidegger 2013 [43]	305 ICU-patients requiring treatment > 5 d, not achieving 60% of calculated energy target by end of day 3	**SPN vs. EN** EN progression encouraged in both groups.	Prokinetic agents (≥300 ml)	4-8 days post randomization 28 day follow-up
Ridley 2018 [46]	100 adult (≥16 years) mixed ICU patients not achieving 80% of target within first 48-72 hours of admission.	**SPN vs. EN** SPN to provide 80% of goal energy based on amount of EN received.	No	7 days or until ICU discharge/ oral nutrition s
Berger 2019 [41]	23 mechanically ventilated patients who by end of day 3 did not receive >60% of equation target	**SPN vs. EN** EN alone for all patients days 1-3	No	6 days post randomization and 15 and 28 days follow-up

Table 1. Randomized studies evaluating combination parenteral nutrition and enteral nutrition in critically ill patients (continued)

Study	Mortality # (%) †		Infections # (%) ‡		LOS in days		Ventilator days		Other	
	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN
Trials comparing EN+PN with EN										
Herndon 1987 [44]	8/13 (62)	8/15 (53)	NR	NR	NR	NR	NR	NR	NR	
Herndon 1989 [45]	**> Day 14** 10/16 (63)	**> Day 14** 6/23 (26)	NR	NR	NR	NR	NR	NR	NR	
Dunham 1994 [42]	3/10 (30)	1/12 (8.3)	NR	NR	NR	NR	NR	NR	**Nutrition related complications** 5/10 (50)	**3/12 (25)**
Chiarelli 1996 [33]	3/12 (25)	4/12 (33)	**Bloodstream** 5/12 (42) **Bronchial aspirate** 7/12 (58) **Positive chest X-ray** 6/12 (50)	**Bloodstream** 5/12 (42) **Bronchial aspirate** 6/12 (50) **Positive chest X-ray** 3/12 (25)	**Hospital** 37 ± 13	**Hospital** 41 ± 23	19 ± 6	19 ± 2	NR	
Bauer 2000 [40]	**< Day 4:** 3/60 (5) **90-day:** 17/60 (28)	**< Day 4:** 4/60 (6.7) **90-day:** 18/60 (30)	39/60 (65)	39/60 (65)	**ICU** 16.9 ± 11.8 **Hospital** 31.2 ± 18.5	**ICU** 17.3 ± 12.8 **Hospital** 33.7 ± 27.7	11 ± 9	10 ± 8	**Glycemia on day 7 (g/L)** 1.16 ± 0.36	1.31 ± 0.49
Abrishami 2010 [39]	2/10 (20)	1/10 (10)	NR	NR	**ICU** 25.7 **Hospital** 37.4	**ICU** 27.7 **Hospital** 36.5	NR	NR	NR	
Casaer 2011 [35, 48]	**ICU** 146/2312 (6.3) **Hospital** 251/2312 (10.9) **Within 90 post enrollment** 255/2312(11.2)	**ICU** 141/2328 (6.1) **Hospital** 242/2328 (10.4) **Within 90 post enrollment** 257/2328 (11.2)	**Any** 605/2312 (26.2) **Airway or lung** 447/2312 (19.3) **Bloodstream** 174/2312 (7.5) **Wound** 98/2312(4.2) **Urinary tract** 72/2312 (3.1)	**Any** 531/2328 (22.8) **Airway or lung** 381/2328 (16.4) **Bloodstream** 142/2328 (6.1) **Wound** 64/2328 (2.7) **Urinary tract** 60/2328 (2.6)	**ICU** 5.05 ±5.19 4 [2-9] **Hospital** 18.1 ±14.83 16 [9-29]	**ICU** 4.05 ±3.7 3 [2-7] **Hospital** 16.8 ± 13.35 14 [9-27]	2.7 ± 2.96 2 [1-5]	2.7 ± 2.96 2 [1-5]	**Kidney failure** **Median duration (days) of renal-replacement therapy** 10 [5-23]	7 [3-16]
Chen 2011 [32]	**20-day** 3/49 (6)	**20-day** 11/49 (22)	6/49 (12)	5/49 (10)	**ICU** 6.75 ± 1.8 **Hospital** 17.3 ± 2.5	**ICU** 9.1 ± 2.8 **Hospital** 23.32 ± 5.6	5.76 ± 1.56	8.0 ± 2.1	**"Other complications"** 8/49 (16)	10/49 (20)

Wischmeyer 2017 [47]	**ICU:** 7/52 (13.5) **Hospital:** 8/52 (15.4)	**ICU:** 13/73 (17.8) **Hospital:** 17/73 (23.3)	38/52	46/73	**ICU*** 16.7 ± 13.5 **Hospital*** 39.9 ± 61.9	**ICU*** 14.2 ± 9.2 **Hospital*** 29.6 ± 22.6	* 11.1 ± 11.3	* 10.4 ± 8.7	**NR**
Trials comparing SPN with EN									
Heidegger 2013 [43]	**ICU:** 8/153 (5) **28-day:** 20/153 (13)	**ICU:** 11/152 (7) **28-day:** 28/152 (18)	**Day 4 – 28*** 77/153 (50)	**Day 4 – 28*** 85/152 (56)	**ICU** 13 ± 10 **Hospital** 31 ± 23	**ICU** 13 ± 11 **Hospital** 32 ± 23	2.5 ± 4.6	2.8 ± 4.2	Similar glucose control in the EN+PN and EN groups, Target < 8 mmol/l
Ridley 2018 [46]	**ICU:** 15/51 **Hospital:** 16/51 **90-day:** 19/51 **180-day:** 19/51	**ICU:** 11/48 **Hospital:** 11/48 **90-day:** 13/48 **180-day:** 13/48	NR	NR	**ICU*** 13 ± 10 **Hospital** 22 ± 21	**ICU*** 13.9 ± 11.7 **Hospital** 23 ± 17	* 12.2 ± 8.3	* 12.8 ± 10.1	**Vomiting** 3/51 | 18/48
Berger 2019 [41]	0/11 /(0)	1/12 (8.3)	1 [1-1] n=11	1 [1-2] n=12	**ICU** 16.01 ± 8.09 15.3 [10.6-17.4] **Hospital** 45.36 ± 20.51 44 [30-57]	**ICU** 15.74 ± 12.74 9.5 [7.1-24.4] **Hospital** 46.91 ± 25.13 48 [25-59]	11 ± 7.66 8.9 [4.9-15.7]	9.5 ± 8.5 5.5 [4.2-14.5]	AUC of glycemia did not differ between groups Net protein breakdown similar to 0 in both groups

#only EN and PN vs. EN groups are included in this analysis; *data obtained from author in mean and SD, †presumed hospital mortality unless otherwise specified, + mean±standard deviation), ‡ refers to the # of patients with infections unless specified, , Abbreviations: AUC: area under the curve, APACHE II: Acute Physiology And Chronic Health Evaluation II, BMI: body mass index; EN: enteral nutrition, GRV: Gastric residual volume, ICU: intensive care unit, NG: nasogastric tube, NJ: nasojejunal tube, NR: not reported, NRS: Nutrition Risk Screening, mNUTRIC Score (modified NUTRIC score), PN: parenteral nutrition, SIRS: systemic inflammatory response syndrome, TBSA: Total body surface area

Table 2. Delivery of Nutrients

Study	Calorie target	Calories delivered			Protein target	Protein delivered		
		Combination EN and PN	EN	Comparison between groups: p-Value		Combination EN and PN	EN	Comparison between groups: p-Value
Trials comparing EN+PN with EN								
Herndon 1987 [44]	25 kcal/kg/d+ 40 kcal/%TBSA	Day 0-3: 3421 ± 336 kcal/d Days 4-7: 3997 ±304 kcal/d Days 8-10: 4191 ±485 kcal/d	Day 0-3: 321± 177 kcal/d Days 4-7: 1494 ±358 kcal/d Days 8-10: 1876 ±541 kcal/d	<0.05 for days 0-7; NS for days 8-10	NR	NR	NR	-
Herndon 1989 [45]	25 kcal/kg/d + 40 kcal/%TBSA	Survivors: 3080 ±177 kcal/d Nonsurvivors: 2952 ± 415 kcal/d	Survivors: 1994 ± 217 kcal/d Nonsurvivors: 498 ±422 kcal/d	*<0.05; between survivors and nonsurvivors	NR	NR	NR	-
Dunham 1994 [42]	1.3 x basal energy expenditure by HBE	Days 1-7: 2067 ± 499 (n=3)	Days 1-7: 2097 ± 552 (n=6)	NS	1.75 g/kg/day	Days 1-7: 222 ±31 (n=3)	Days 1-7: 129 ± 35 (n=6)	NS
Chiarelli 1996 [33]	No reported	31 ± 6 kcal/kg/d	33 ± 9 kcal/kg/d	NS difference of lost calories	NR	NR	NR	-
Bauer 2000 [40]	25 kcal/kg/d	Day 4: 11 ±3.3 kcal/kg Day 7†: 14.8±4.6 kcal/kg	Day 4: 9.9 ±3.9 Day 7: 13.2 ±4.3	Day 4: 0.25 Day 7: 0.6	1 gram of N per 100 kcal of carbohydrates-fat	NR	NR	-
Abrishami 2010 [39]	NR	NR	NR	-	NR	NR	NR	-
Casaer 2011 [35, 48]	Day 1: 400 kcal/ Day 2: 800 kcal/d Day 3: 100% kcal/d Max goal: 2880 kcal/d	NR	NR	-	NR	NR	NR	-
Chen 2011 [32]	NR	NR	NR	-	NR	NR	NR	-
Wischmeyer 2017 [47]	BMI <25: 25 kcal/actual BW/d; BMI >35 20 kcal/adjusted BW/d	Days 0-7: 95 ± 13%; Day 0-27: 90 ± 16%	Days 0-7: 69 ± 28%; Day Days 0-27: 72 ± 25%	Days 0-7: <0.001 Days 0-27: <0.001	BMI <25: 1.2 g/kg actual BW/d; BMI >35: 1.2/g kg adjusted BW/d	Days 0-7 : 86 ± 16% Day 0-27: 82 ± 19%	Days 0-7: 64 ± 26% Day 0-27: 68 ± 25 %	Days 0-7: <0.001 Days 0-27: <0.001

Table 3. Physical Outcomes

Study	Combination of EN + PN	EN alone	P Value
Chen 2011	Changes in respiratory muscle strength before and after nutrition support (cmH_2O) *		
	Before: 28.34 ± 9.49 Day 7: 34.32 ± 15.43 P=0.025	Before: 26.75 ± 11.6 Day 7: 32.3 ± 10.3 P=0.011	
Wischmeyer 2017	Handgrip strength in kg #		
	ICU discharge: 9 (43) [unable-25]	ICU discharge: Unable (62) [unable-18]	P=0.21
	Hospital discharge: 12 (36) [unable-33]	Hospital discharge: Unable (56) [unable-20]	P=0.14
	6-minute walk test at hospital discharge #		
	Unable (40) [unable-0]	Unable (60) [unable-unable]	P=0.2
	Barthel Index at hospital discharge *		
	61.1 ± 32.4 (28)	46.5 ± 32.1 (41)	P=0.08
	SF-36: standardized physical component scale *		
	3 months: 33.3 ± 10.1 (22) 6 months: 39.3 ± 10.2 (20)	3 months: 35.3 ± 10.8 (27) 6 months: 35.8 ± 11.2 (30)	P= 0.38 P=0.17
	SF-36: standardized mental component scale *		
	3 months: 51.5 ± 10.0 (22) 6 months: 49.0 ± 13.5 (20)	3 months: 50.0 ± 10.5 (27) 6 months: 43.2 ± 14.8 (30)	P=0.38 P=0.11
Ridley 2018	Hand grip at hospital discharge in kg *		
	19 ± 13.5 (19)	20 ± 8, (24)	P=0.71
	ICU mobility scale at hospital discharge #		
	9 [5-10], (25)	8 [4-10] (33)	P=0.58
	EQ-5D-3L *		
	Hospital discharge: 0.25 ± 0.34 (27) 90 days: 0.69 ± 0.24 (35) 180 days: 0.75 ± 0.26 (35)	Hospital discharge: 0.32 ± 0.36 (17) 90 days: 0.76 ± 0.23 (29) 180 days: 0.77 ± 0.2 (29)	P=0.54 P=0.29 P=0.76
Berger 2019	Difference of quadriceps cross sectional area between days 4 and 15 after admission		
	-16%	-21%	p=0.07
Abbreviations: ICU: Intensive Care Unit, SF-36: Short Form 36			

Figure 1. Mortality, Subgroup Analysis: Type of nutrition

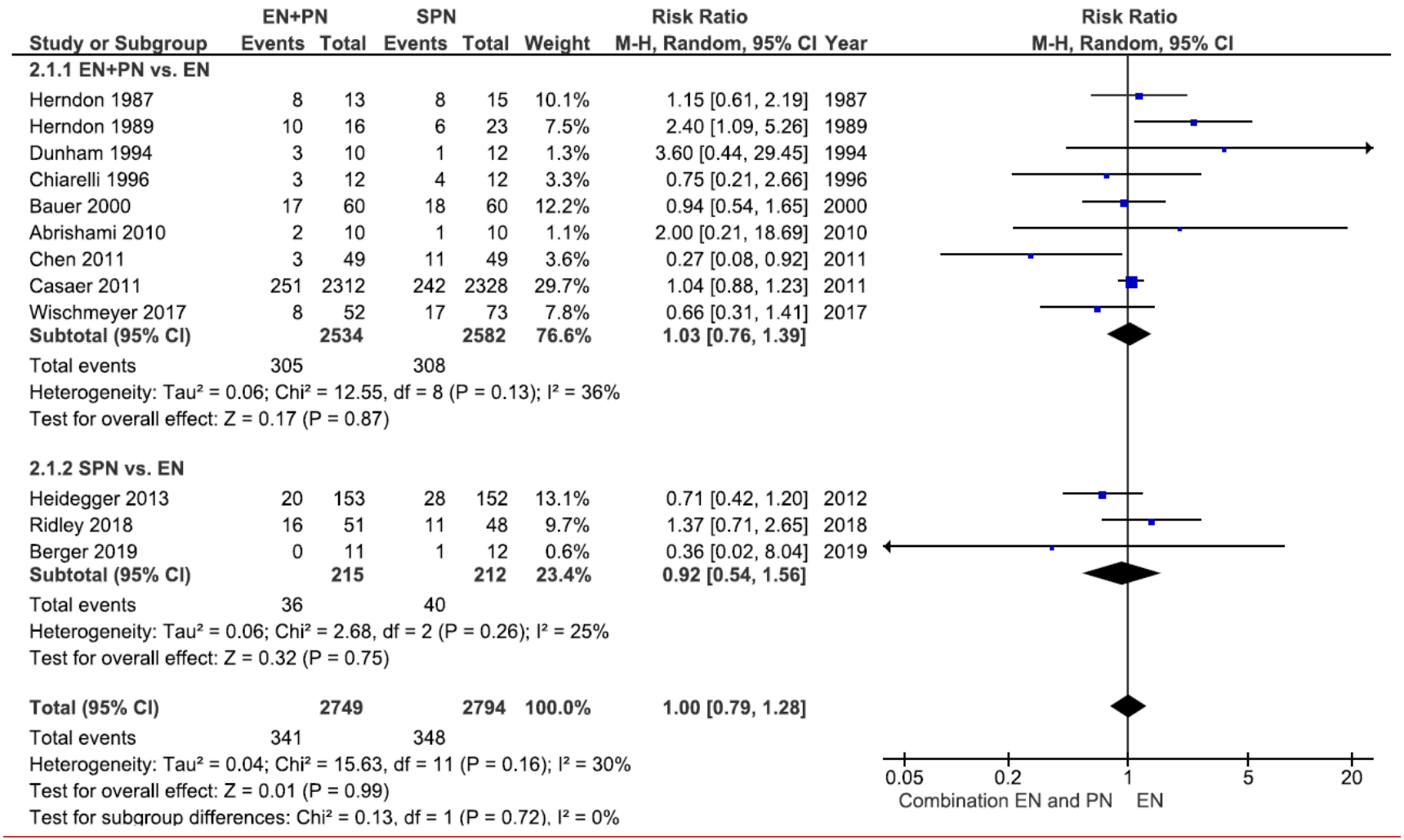

Figure 2. Mortality, Subgroup Analysis: Publication Year

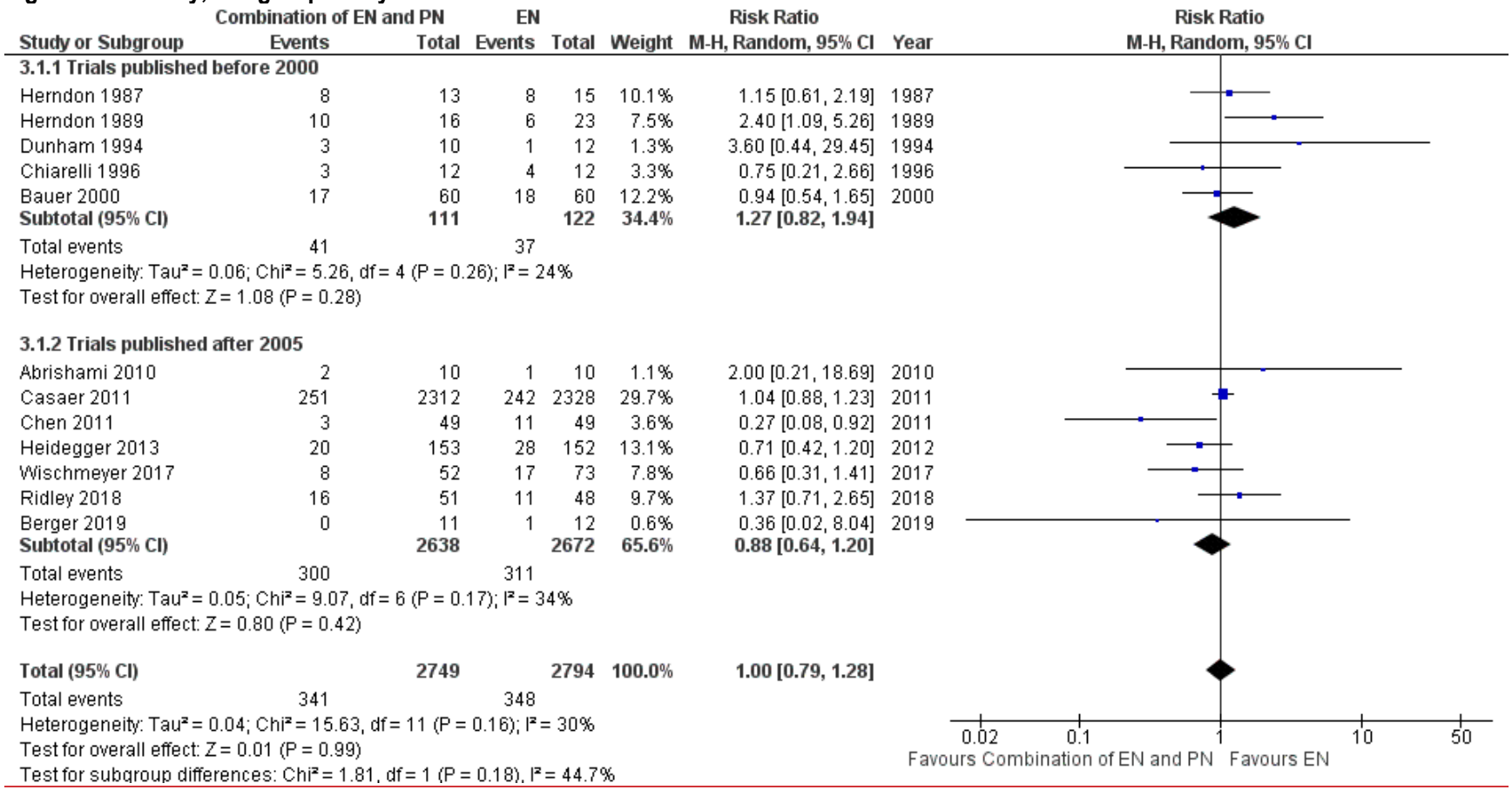

Figure 3. Mortality, Subgroup Analysis: Nutrition Risk Assessment

Study or Subgroup	Combination of EN and PN Events	Total	EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
4.1.1 Trials with nutritional assessment							
Bauer 2000	17	60	18	60	12.2%	0.94 [0.54, 1.65]	2000
Abrishami 2010	2	10	1	10	1.1%	2.00 [0.21, 18.69]	2010
Chen 2011	3	49	11	49	3.6%	0.27 [0.08, 0.92]	2011
Casaer 2011	251	2312	242	2328	29.7%	1.04 [0.88, 1.23]	2011
Wischmeyer 2017	8	52	17	73	7.8%	0.66 [0.31, 1.41]	2017
Subtotal (95% CI)		**2483**		**2520**	**54.4%**	**0.87 [0.62, 1.24]**	
Total events	281		289				
Heterogeneity: Tau² = 0.05; Chi² = 6.22, df = 4 (P = 0.18); I² = 36%							
Test for overall effect: Z = 0.75 (P = 0.45)							
4.1.2 Trials without nutritional assessment							
Herndon 1987	8	13	8	15	10.1%	1.15 [0.61, 2.19]	1987
Herndon 1989	10	16	6	23	7.5%	2.40 [1.09, 5.26]	1989
Dunham 1994	3	10	1	12	1.3%	3.60 [0.44, 29.45]	1994
Chiarelli 1996	3	12	4	12	3.3%	0.75 [0.21, 2.66]	1996
Heidegger 2013	20	153	28	152	13.1%	0.71 [0.42, 1.20]	2012
Ridley 2018	16	51	11	48	9.7%	1.37 [0.71, 2.65]	2018
Berger 2019	0	11	1	12	0.6%	0.36 [0.02, 8.04]	2019
Subtotal (95% CI)		**266**		**274**	**45.6%**	**1.17 [0.78, 1.77]**	
Total events	60		59				
Heterogeneity: Tau² = 0.09; Chi² = 8.99, df = 6 (P = 0.17); I² = 33%							
Test for overall effect: Z = 0.77 (P = 0.44)							
Total (95% CI)		**2749**		**2794**	**100.0%**	**1.00 [0.79, 1.28]**	
Total events	341		348				
Heterogeneity: Tau² = 0.04; Chi² = 15.63, df = 11 (P = 0.16); I² = 30%							
Test for overall effect: Z = 0.01 (P = 0.99)							
Test for subgroup differences: Chi² = 1.15, df = 1 (P = 0.28), I² = 12.9%							

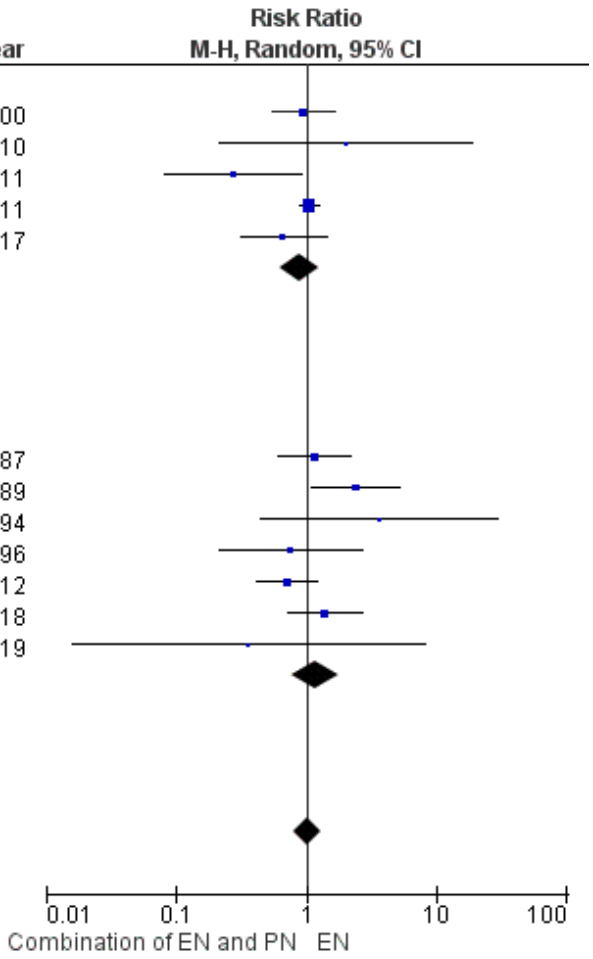

Figure 4. Hospital LOS, Subgroup Analysis: Type of nutrition

Study or Subgroup	EN+PN Mean	EN+PN SD	EN+PN Total	SPN Mean	SPN SD	SPN Total	Weight	Mean Difference IV, Random, 95% CI	Year
2.4.1 EN+PN vs. EN									
Chiarelli 1996	37	13	12	41	23	12	5.7%	-4.00 [-18.95, 10.95]	1996
Bauer 2000	31.2	18.5	60	33.7	27.7	60	11.7%	-2.50 [-10.93, 5.93]	2000
Chen 2011	17.3	2.47	49	23.32	5.6	49	21.8%	-6.02 [-7.73, -4.31]	2011
Casaer 2011	18.1	14.83	2312	16.8	13.35	2328	22.5%	1.30 [0.49, 2.11]	2011
Wischmeyer 2017	39.9	61.9	52	29.6	22.6	73	4.5%	10.30 [-7.30, 27.90]	2017
Subtotal (95% CI)			**2485**			**2522**	**66.2%**	**-1.56 [-7.08, 3.96]**	
Heterogeneity: Tau² = 24.22; Chi² = 59.16, df = 4 (P < 0.00001); I² = 93%									
Test for overall effect: Z = 0.55 (P = 0.58)									
2.4.2 SPN vs. EN									
Heidegger 2013	31	23	153	32	23	152	16.8%	-1.00 [-6.16, 4.16]	2012
Ridley 2018	22	21	51	23	17	48	13.0%	-1.00 [-8.51, 6.51]	2018
Berger 2019	45.36	20.51	11	46.91	25.13	12	4.1%	-1.55 [-20.23, 17.13]	2019
Subtotal (95% CI)			**215**			**212**	**33.8%**	**-1.03 [-5.17, 3.12]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%									
Test for overall effect: Z = 0.49 (P = 0.63)									
Total (95% CI)			**2700**			**2734**	**100.0%**	**-1.44 [-5.59, 2.71]**	
Heterogeneity: Tau² = 19.79; Chi² = 59.36, df = 7 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 0.68 (P = 0.50)									
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%									

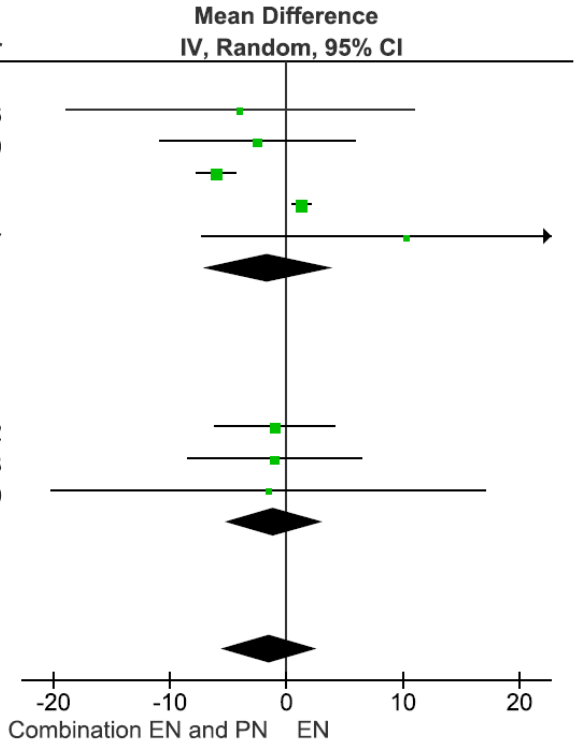

Figure 5. Hospital LOS, Subgroup Analysis: Publication Year

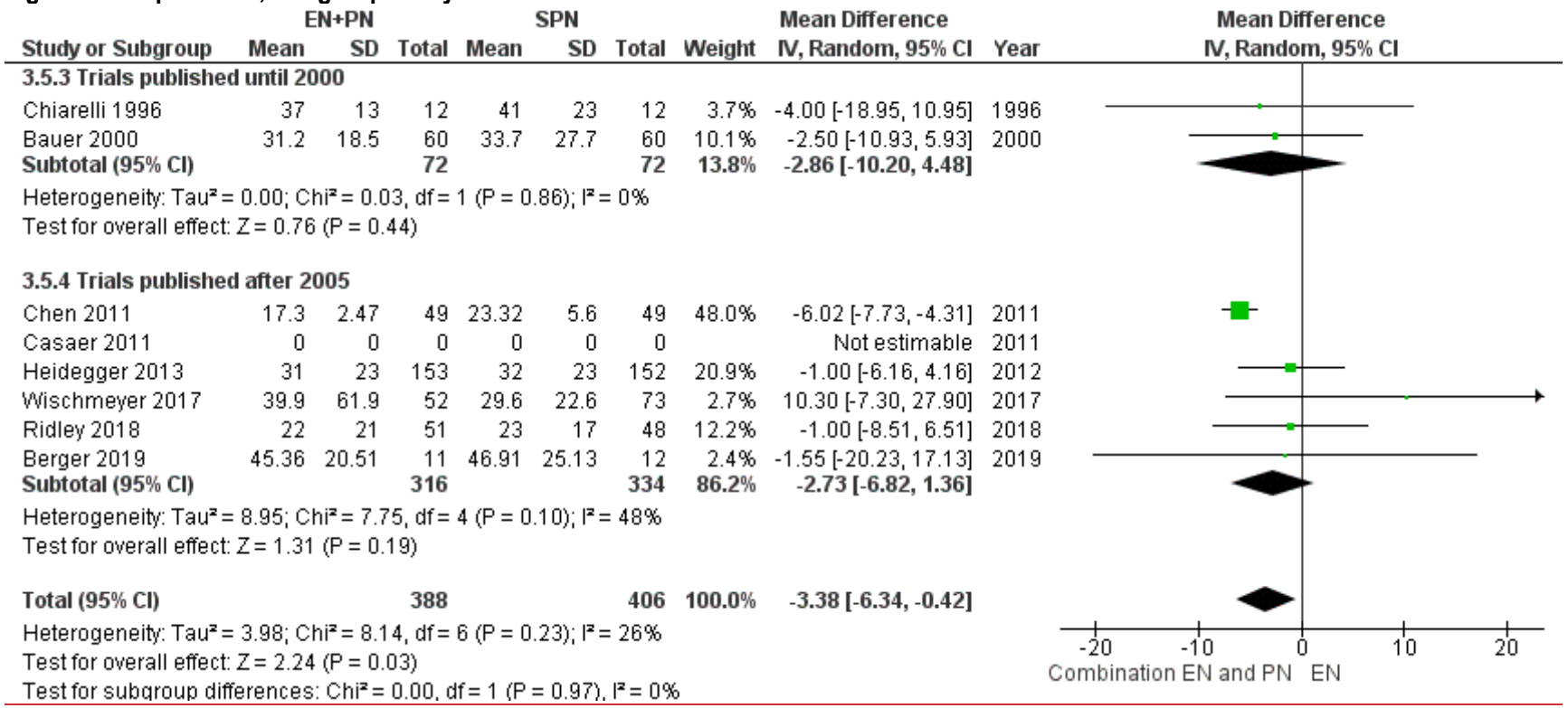

Figure 6. Hospital LOS, Subgroup Analysis: Nutrition Risk Assessment

Study or Subgroup	EN+PN Mean	EN+PN SD	EN+PN Total	SPN Mean	SPN SD	SPN Total	Weight	Mean Difference IV, Random, 95% CI	Year
4.5.3 Trials with nutritional assessment									
Bauer 2000	31.2	18.5	60	33.7	27.7	60	11.7%	-2.50 [-10.93, 5.93]	2000
Casaer 2011	18.1	14.83	2312	16.8	13.35	2328	22.5%	1.30 [0.49, 2.11]	2011
Chen 2011	17.3	2.47	49	23.32	5.6	49	21.8%	-6.02 [-7.73, -4.31]	2011
Wischmeyer 2017	39.9	61.9	52	29.6	22.6	73	4.5%	10.30 [-7.30, 27.90]	2017
Subtotal (95% CI)			**2473**			**2510**	**60.4%**	**-1.28 [-7.15, 4.59]**	
Heterogeneity: Tau² = 24.86; Chi² = 58.89, df = 3 (P < 0.00001); I² = 95%									
Test for overall effect: Z = 0.43 (P = 0.67)									
4.5.4 Trials without nutritional assessment									
Chiarelli 1996	37	13	12	41	23	12	5.7%	-4.00 [-18.95, 10.95]	1996
Heidegger 2013	31	23	153	32	23	152	16.8%	-1.00 [-6.16, 4.16]	2012
Ridley 2018	22	21	51	23	17	48	13.0%	-1.00 [-8.51, 6.51]	2018
Berger 2019	45.36	20.51	11	46.91	25.13	12	4.1%	-1.55 [-20.23, 17.13]	2019
Subtotal (95% CI)			**227**			**224**	**39.6%**	**-1.24 [-5.24, 2.76]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 3 (P = 0.99); I² = 0%									
Test for overall effect: Z = 0.61 (P = 0.54)									
Total (95% CI)			**2700**			**2734**	**100.0%**	**-1.44 [-5.59, 2.71]**	
Heterogeneity: Tau² = 19.79; Chi² = 59.36, df = 7 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 0.68 (P = 0.50)									
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%									

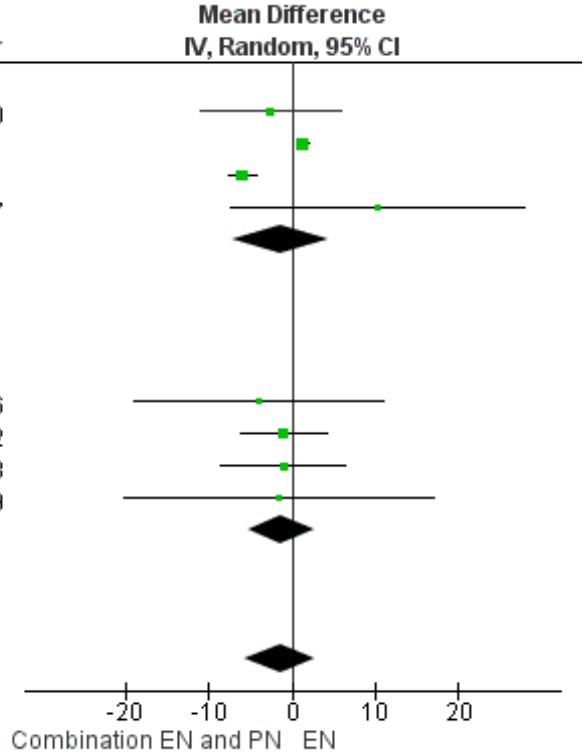

Figure 7. ICU LOS, Subgroup Analysis: Type of nutrition

Study or Subgroup	EN+PN Mean	EN+PN SD	EN+PN Total	SPN Mean	SPN SD	SPN Total	Weight	Mean Difference IV, Random, 95% CI	Year
2.3.1 EN+PN vs. EN									
Bauer 2000	16.9	11.8	60	17.3	12.8	60	10.5%	-0.40 [-4.81, 4.01]	2000
Chen 2011	6.75	1.75	49	9.09	2.75	49	22.6%	-2.34 [-3.25, -1.43]	2011
Casaer 2011	5.05	5.19	2312	4.05	3.7	2328	23.8%	1.00 [0.74, 1.26]	2011
Wischmeyer 2017	16.7	13.5	52	14.2	9.2	73	10.9%	2.50 [-1.73, 6.73]	2017
Subtotal (95% CI)			**2473**			**2510**	**67.8%**	**-0.05 [-2.58, 2.47]**	
Heterogeneity: Tau² = 4.90; Chi² = 48.52, df = 3 (P < 0.00001); I² = 94%									
Test for overall effect: Z = 0.04 (P = 0.97)									
2.3.2 SPN vs. EN									
Heidegger 2013	13	10	153	13	11	152	17.5%	0.00 [-2.36, 2.36]	2012
Ridley 2018	13	10	51	13.9	11.7	48	10.7%	-0.90 [-5.20, 3.40]	2018
Berger 2019	16.01	8.09	11	15.74	12.74	12	4.0%	0.27 [-8.38, 8.92]	2019
Subtotal (95% CI)			**215**			**212**	**32.2%**	**-0.18 [-2.19, 1.83]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 2 (P = 0.93); I² = 0%									
Test for overall effect: Z = 0.18 (P = 0.86)									
Total (95% CI)			**2688**			**2722**	**100.0%**	**-0.15 [-2.05, 1.75]**	
Heterogeneity: Tau² = 3.94; Chi² = 49.47, df = 6 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 0.15 (P = 0.88)									
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%									

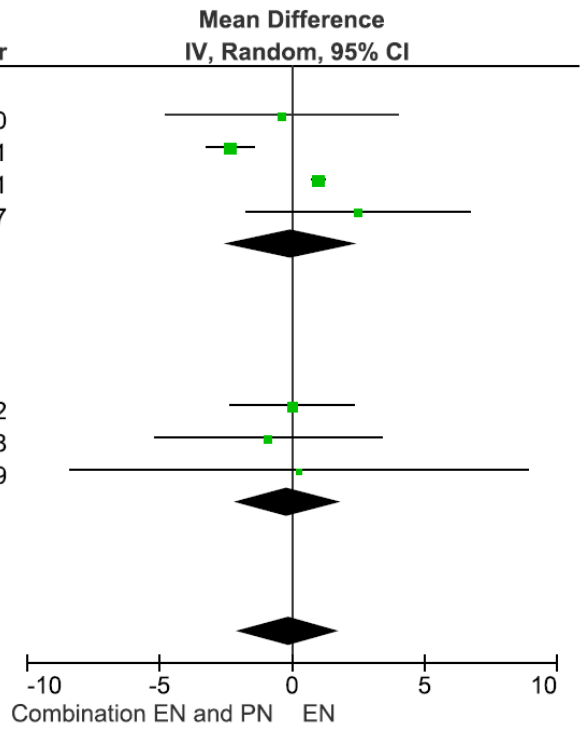

Figure 8. ICU LOS, Subgroup Analysis: Publication Year

Study or Subgroup	EN+PN Mean	EN+PN SD	EN+PN Total	SPN Mean	SPN SD	SPN Total	Weight	Mean Difference IV, Random, 95% CI	Year
3.4.3 Trials published until 2000									
Bauer 2000	16.9	11.8	60	17.3	12.8	60	10.5%	-0.40 [-4.81, 4.01]	2000
Subtotal (95% CI)			**60**			**60**	**10.5%**	**-0.40 [-4.81, 4.01]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.18 (P = 0.86)									
3.4.4 Trials published after 2005									
Casaer 2011	4	5.19	2312	3	3.7	2328	23.8%	1.00 [0.74, 1.26]	2011
Chen 2011	6.75	1.75	49	9.09	2.75	49	22.6%	-2.34 [-3.25, -1.43]	2011
Heidegger 2013	13	10	153	13	11	152	17.5%	0.00 [-2.36, 2.36]	2012
Wischmeyer 2017	16.7	13.5	52	14.2	9.2	73	10.9%	2.50 [-1.73, 6.73]	2017
Ridley 2018	13	10	51	13.9	11.7	48	10.7%	-0.90 [-5.20, 3.40]	2018
Berger 2019	16.01	8.09	11	15.74	12.74	12	4.0%	0.27 [-8.38, 8.92]	2019
Subtotal (95% CI)			**2628**			**2662**	**89.5%**	**-0.11 [-2.16, 1.94]**	
Heterogeneity: $Tau^2 = 4.14$; $Chi^2 = 49.22$, df = 5 (P < 0.00001); $I^2 = 90\%$									
Test for overall effect: Z = 0.11 (P = 0.92)									
Total (95% CI)			**2688**			**2722**	**100.0%**	**-0.15 [-2.05, 1.75]**	
Heterogeneity: $Tau^2 = 3.94$; $Chi^2 = 49.47$, df = 6 (P < 0.00001); $I^2 = 88\%$									
Test for overall effect: Z = 0.15 (P = 0.88)									
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.91), $I^2 = 0\%$									

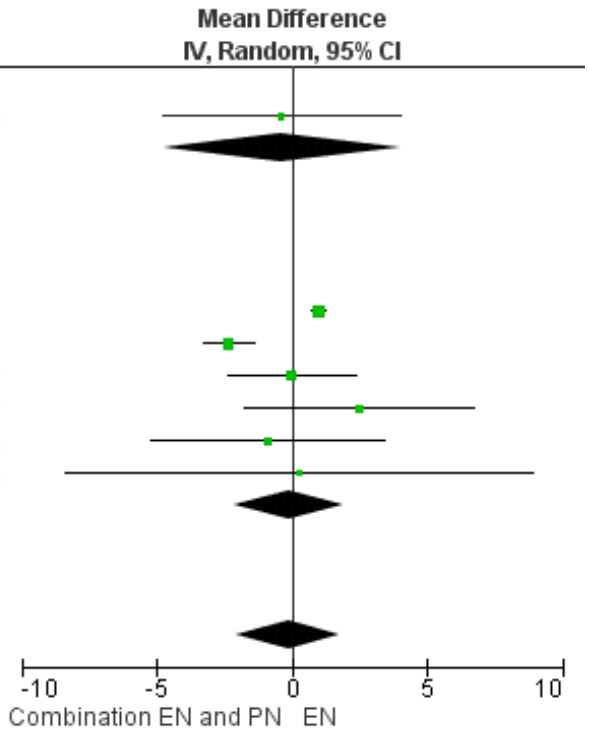

Figure 9. ICU LOS, Subgroup Analysis: Nutrition Risk Assessment

Study or Subgroup	EN+PN Mean	EN+PN SD	EN+PN Total	SPN Mean	SPN SD	SPN Total	Weight	Mean Difference IV, Random, 95% CI	Year
4.4.3 Trials with nutritional assessment									
Bauer 2000	16.9	11.8	60	17.3	12.8	60	10.5%	-0.40 [-4.81, 4.01]	2000
Chen 2011	6.75	1.75	49	9.09	2.75	49	22.6%	-2.34 [-3.25, -1.43]	2011
Casaer 2011	5.05	5.19	2312	4.05	3.7	2328	23.8%	1.00 [0.74, 1.26]	2011
Wischmeyer 2017	16.7	13.5	52	14.2	9.2	73	10.9%	2.50 [-1.73, 6.73]	2017
Subtotal (95% CI)			**2473**			**2510**	**67.8%**	**-0.05 [-2.58, 2.47]**	
Heterogeneity: Tau² = 4.90; Chi² = 48.52, df = 3 (P < 0.00001); I² = 94%									
Test for overall effect: Z = 0.04 (P = 0.97)									
4.4.4 Trials without nutritional assessment									
Heidegger 2013	13	10	153	13	11	152	17.5%	0.00 [-2.36, 2.36]	2012
Ridley 2018	13	10	51	13.9	11.7	48	10.7%	-0.90 [-5.20, 3.40]	2018
Berger 2019	16.01	8.09	11	15.74	12.74	12	4.0%	0.27 [-8.38, 8.92]	2019
Subtotal (95% CI)			**215**			**212**	**32.2%**	**-0.18 [-2.19, 1.83]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 2 (P = 0.93); I² = 0%									
Test for overall effect: Z = 0.18 (P = 0.86)									
Total (95% CI)			**2688**			**2722**	**100.0%**	**-0.15 [-2.05, 1.75]**	
Heterogeneity: Tau² = 3.94; Chi² = 49.47, df = 6 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 0.15 (P = 0.88)									
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%									

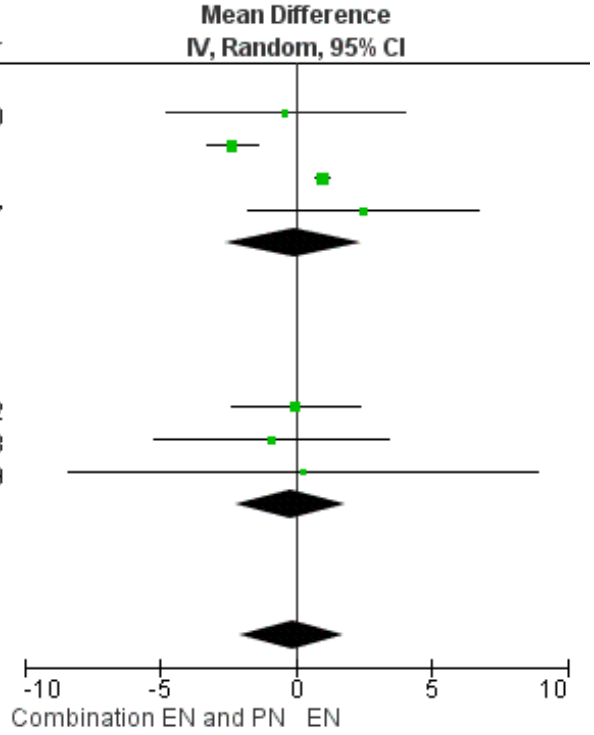

Figure 10. Ventilator days, Subgroup Analysis: Type of nutrition

Study or Subgroup	EN+PN Mean	EN+PN SD	EN+PN Total	SPN Mean	SPN SD	SPN Total	Weight	Mean Difference IV, Random, 95% CI	Year
2.2.1 EN+PN vs. EN									
Chiarelli 1996	19	6	12	19	2	12	6.6%	0.00 [-3.58, 3.58]	1996
Bauer 2000	11	9	60	10	8	60	8.3%	1.00 [-2.05, 4.05]	2000
Casaer 2011	2.7	2.96	2312	2.7	2.96	2328	25.8%	0.00 [-0.17, 0.17]	2011
Chen 2011	5.76	1.56	49	7.95	2.11	49	23.1%	-2.19 [-2.92, -1.46]	2011
Wischmeyer 2017	11.1	11.3	52	10.4	8.7	73	6.4%	0.70 [-2.96, 4.36]	2017
Subtotal (95% CI)			**2485**			**2522**	**70.1%**	**-0.44 [-1.98, 1.10]**	
Heterogeneity: Tau² = 1.89; Chi² = 33.09, df = 4 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 0.56 (P = 0.57)									
2.2.2 SPN vs. EN									
Heidegger 2013	2.5	4.625	153	2.75	4.21	152	21.2%	-0.25 [-1.24, 0.74]	2012
Ridley 2018	12.2	8.31	51	12.8	10.1	48	6.4%	-0.60 [-4.26, 3.06]	2018
Berger 2019	11	7.66	11	9.5	8.5	12	2.4%	1.50 [-5.10, 8.10]	2019
Subtotal (95% CI)			**215**			**212**	**29.9%**	**-0.24 [-1.19, 0.71]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 2 (P = 0.86); I² = 0%									
Test for overall effect: Z = 0.49 (P = 0.62)									
Total (95% CI)			**2700**			**2734**	**100.0%**	**-0.43 [-1.50, 0.63]**	
Heterogeneity: Tau² = 1.14; Chi² = 33.46, df = 7 (P < 0.0001); I² = 79%									
Test for overall effect: Z = 0.80 (P = 0.42)									
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%									

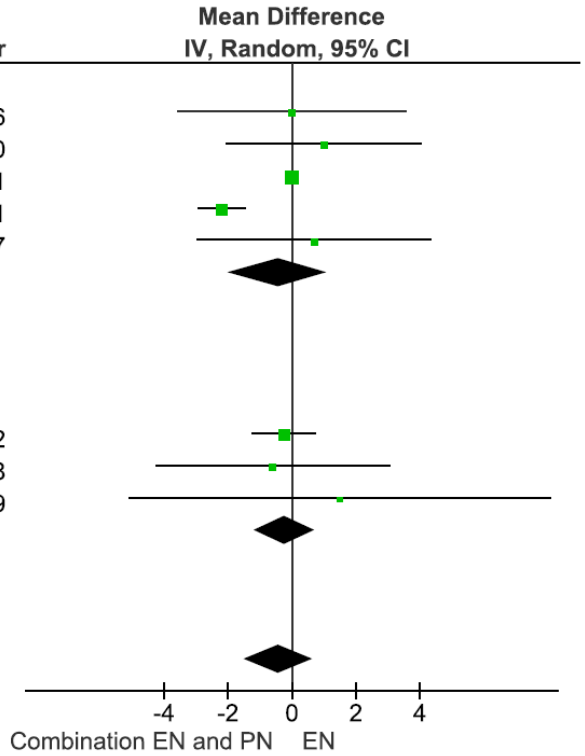

Figure 11. Ventilator Days, Subgroup Analysis: Publication Year

Study or Subgroup	EN+PN Mean	EN+PN SD	EN+PN Total	SPN Mean	SPN SD	SPN Total	Weight	Mean Difference IV, Random, 95% CI	Year
3.3.3 Trials published until 2000									
Chiarelli 1996	19	6	12	19	2	12	9.1%	0.00 [-3.58, 3.58]	1996
Bauer 2000	11	9	60	10	8	60	11.4%	1.00 [-2.05, 4.05]	2000
Subtotal (95% CI)			**72**			**72**	**20.5%**	**0.58 [-1.74, 2.90]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%									
Test for overall effect: Z = 0.49 (P = 0.62)									
3.3.4 Trials published after 2005									
Casaer 2011	2	2.96	2312	2	2.96	2328		Not estimable	2011
Chen 2011	5.76	1.56	49	7.95	2.11	49	30.5%	-2.19 [-2.92, -1.46]	2011
Heidegger 2013	2.5	4.625	153	2.75	4.21	152	28.1%	-0.25 [-1.24, 0.74]	2012
Wischmeyer 2017	11.1	11.3	52	10.4	8.7	73	8.8%	0.70 [-2.96, 4.36]	2017
Ridley 2018	12.2	8.31	51	12.8	10.1	48	8.8%	-0.60 [-4.26, 3.06]	2018
Berger 2019	11	7.66	11	9.5	8.5	12	3.3%	1.50 [-5.10, 8.10]	2019
Subtotal (95% CI)			**316**			**334**	**79.5%**	**-0.84 [-2.29, 0.60]**	
Heterogeneity: Tau² = 1.29; Chi² = 11.79, df = 4 (P = 0.02); I² = 66%									
Test for overall effect: Z = 1.14 (P = 0.25)									
Total (95% CI)			**388**			**406**	**100.0%**	**-0.57 [-1.83, 0.70]**	
Heterogeneity: Tau² = 1.22; Chi² = 14.61, df = 6 (P = 0.02); I² = 59%									
Test for overall effect: Z = 0.88 (P = 0.38)									
Test for subgroup differences: Chi² = 1.04, df = 1 (P = 0.31), I² = 3.8%									

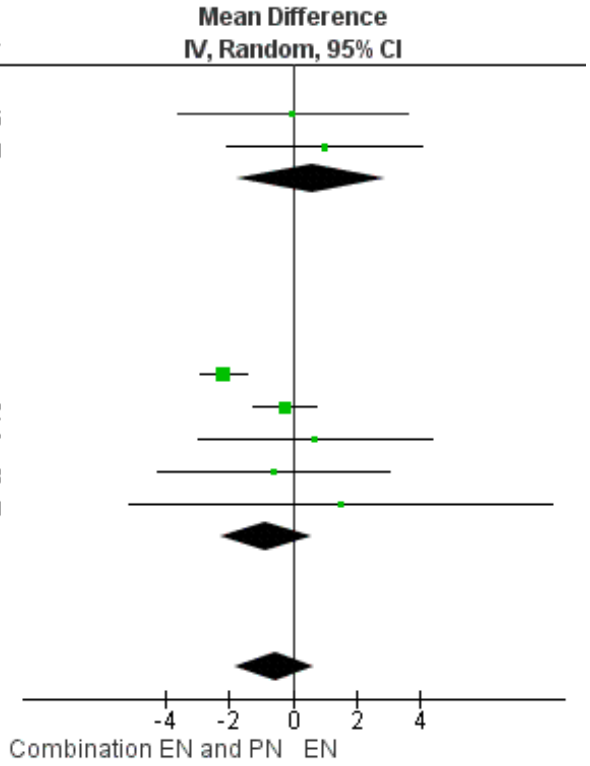

Figure 12. Ventilator Days, Subgroup Analysis: Nutrition Risk Assessment

Study or Subgroup	EN+PN Mean	EN+PN SD	EN+PN Total	SPN Mean	SPN SD	SPN Total	Weight	Mean Difference IV, Random, 95% CI	Year
4.3.3 Trials with nutritional assessment									
Bauer 2000	11	9	60	10	8	60	8.3%	1.00 [-2.05, 4.05]	2000
Chen 2011	5.76	1.56	49	7.95	2.11	49	23.1%	-2.19 [-2.92, -1.46]	2011
Casaer 2011	2.7	2.96	2312	2.7	2.96	2328	25.8%	0.00 [-0.17, 0.17]	2011
Wischmeyer 2017	11.1	11.3	52	10.4	8.7	73	6.4%	0.70 [-2.96, 4.36]	2017
Subtotal (95% CI)			**2473**			**2510**	**63.5%**	**-0.48 [-2.17, 1.20]**	
Heterogeneity: Tau² = 2.03; Chi² = 33.09, df = 3 (P < 0.00001); I² = 91%									
Test for overall effect: Z = 0.56 (P = 0.57)									
4.3.4 Trials without nutritional assessment									
Chiarelli 1996	19	6	12	19	2	12	6.6%	0.00 [-3.58, 3.58]	1996
Heidegger 2013	2.5	4.625	153	2.75	4.21	152	21.2%	-0.25 [-1.24, 0.74]	2012
Ridley 2018	12.2	8.31	51	12.8	10.1	48	6.4%	-0.60 [-4.26, 3.06]	2018
Berger 2019	11	7.66	11	9.5	8.5	12	2.4%	1.50 [-5.10, 8.10]	2019
Subtotal (95% CI)			**227**			**224**	**36.5%**	**-0.22 [-1.14, 0.69]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 3 (P = 0.96); I² = 0%									
Test for overall effect: Z = 0.47 (P = 0.64)									
Total (95% CI)			**2700**			**2734**	**100.0%**	**-0.43 [-1.50, 0.63]**	
Heterogeneity: Tau² = 1.14; Chi² = 33.46, df = 7 (P < 0.0001); I² = 79%									
Test for overall effect: Z = 0.80 (P = 0.42)									
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%									

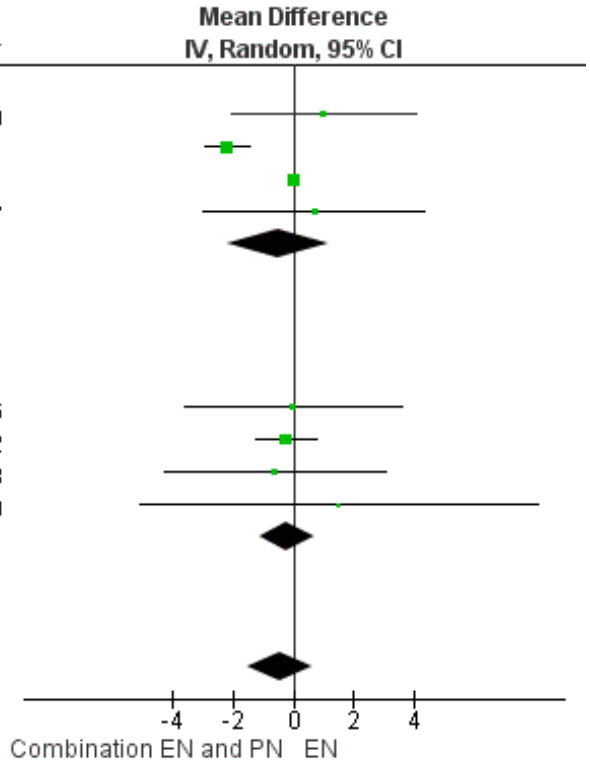

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Table 4. Excluded Articles

Author	Year	Reason for Exclusion
Altintas	2011	Intervention: no combination of EN and PN Methodological: no true randomization
Antebi	2004	Intervention: no combination of EN and PN, TPN for 5 days
Arabi	2011	Intervention/Control: no PN in either group, instead additional calories via propofol and dextrose in both groups
Arabi	2015	Intervention: only very small amount of calories received through PN (3-5 kcal/d)
Atkinson	1998	Intervention: no PN used in either group
Barbosa	2010	Intervention: EN started in both groups as soon as possible, but in no patient before day 6
Bastarache	2012	Intervention: no PN used in either group
Bost	2014	Type: Review
Boughton	2019	Patients: non-critically ill
Braunschweig	2015	Intervention: PN used in both groups (8/40 intervention group and 5/38 in control group)
Chapple	2019	Type: Review
Charles	2014	Intervention/Control: patients in both groups started on PN after 5-7 days if EN was not tolerated
Chelkeba	2017	Type: Systematic Review/ Meta-Analysis
Chuntrasakul	1996	Article missing, author contacted June 2019, May 2020 and June 2020 without response
Danielis	2019	Intervention: each patient enrolled in the study could undergo enteral and/or parenteral nutrition according to the clinical judgement and guidelines in the field
Dhaliwal	2004	Type: Systematic Review/ Meta-Analysis
Doig	2013	Intervention: only 40% of patients received EN Control: only 40.8% never received PN
Dvorak	2004	Intervention: no PN
Elke	2013	Secondary analysis, patients were divided into groups according to the types of nutrition used in the VISEP trial
Fan	2016	Type: Pseudo-randomized
Fetterplace	2019	Intervention: PN only used in case of feeding intolerance (2 patients in standard care group)
Fuentes Padilla	2019	Type: Systematic Review
Harvey	2014	Intervention: exlucsive PN, 6.8% crossover
Ibrahim	2002	Intervention: no PN used, Methodology: no true randomization
Kott	2019	Type: Review
Lewis	2018	Type: Systematic Review/ Meta-Analysis
Luo	2012	Article could not be obtained. Working group of meta-analysis mentioning this study was contacted June 2020, no response

Luo	2020	Type: Systematic Review/ Meta-Analysis
Mazaherpur	2016	Intervention: in the combination group, PN started at a mean of 15 days
Petros	2016	Intervention/ Control: hypocaloric vs. eucaloric, EN, PN and EN+PN used in both groups
Radpay	2016	Control group: total PN, no EN-only group
Schilling	1996	Fulltext not obtained
Shi	2018	Type: Systematic Review/ Meta-Analysis
Singer	2011	Intervention: though significantly more calories were given via PN in the intervention group, 34/56 patients received EN only. Comparison: PN was received by 8/56 patients
Wan	2015	Type: Systematic Review/ Meta-Analysis
Wernerman	2008	Type: Review
Wischmeyer	2012	Type: Editorial
Wu	2017	Patients: 0% mortality, ICU and mechanical ventilation not reported
Xi	2014	Full text could not be obtained, authors were contacted in May 2020 and June 2020 without response