

2.0 Early vs. Delayed Nutrient Intake

Question: Does early enteral nutrition compared to delayed nutrient intake result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 17 randomized controlled trials (level 2 studies) comparing early enteral nutrition vs. delayed nutrient intake (i.e. delayed enteral nutrition, parenteral nutrition or oral diet). In all the trials except one, enteral nutrition in the intervention group was started within 24-48 hours of admission/resuscitation. There were 10 studies comparing early vs. delayed EN and 7 studies where early EN was compared to no EN/IV fluids.

Mortality: When the data from the 17 studies that looked at the effect of early EN on mortality were aggregated, when compared to delayed nutrient intake, early enteral nutrition was associated with a trend towards a reduction in mortality (RR 0.73, 95% CI 0.51, 1.04, $p=0.08$, heterogeneity $I^2=0\%$; figure 1). In a subgroup analysis, early EN vs. no EN/IV fluids was associated with a trend towards a reduction in mortality (RR 0.62, 95% CI 0.37, 1.05, $p=0.08$, heterogeneity $I^2=0\%$; figure 1), whereas early vs. delayed EN had no effect on mortality (RR 0.84, 95% CI 0.51, 1.37, $p=0.47$, heterogeneity $I^2=0\%$; figure 1). The difference between the two subgroups was not significant ($p=0.41$; figure 1).

Infections: Eleven studies reported on infections and of these only 9 studies reported on the number of patients with infections and when these were aggregated, early enteral nutrition when compared to delayed nutrient intake was associated with a significant reduction in infectious complications (RR 0.81, 95% CI 0.68, 0.97, $p=0.02$, heterogeneity $I^2=14\%$; figure 2). In a subgroup analysis, early EN vs. no EN/IV fluids was associated with a trend towards a reduction in infections (RR 0.70, 95% CI 0.48, 1.02, $p=0.06$, heterogeneity $I^2=26\%$; figure 2), whereas early vs. delayed EN had no effect on infections (RR 0.86, 95% CI 0.69, 1.08, $p=0.20$, heterogeneity $I^2=12\%$; figure 2). The difference between the two subgroups was not significant ($p=0.36$; figure 2).

LOS and Ventilator days: Sixteen studies looked at LOS (6 reported on ICU LOS only, 4 reported on hospital LOS only and 6 reported on both ICU and hospital LOS). When the results were meta-analyzed, early enteral nutrition had no effect on ICU stay (WMD -0.78, 95% CI -3.56, 2.00, $p=0.58$, heterogeneity $I^2=46\%$; figure 3) or hospital length of stay (WMD -1.34, 95% CI -7.69, 5.02 $p=0.68$, heterogeneity $I^2=51\%$; figure 4). A total of 8 studies reported on ventilator days and all showed no significant differences between the early vs. delayed fed groups (WMD 0.03, 95% CI -3.01, 3.06 $p=0.99$, heterogeneity $I^2=42.6\%$; figure 5).

Other: All fifteen studies that reported nutritional endpoints showed a significant improvement in the groups receiving early enteral nutrition (calorie intake, protein intake, % goal achieved, faster nitrogen balance achieved). There were no differences in other complications between the groups.

Conclusions:

- 1) Early enteral nutrition compared to delayed nutrient intake may be associated with a trend towards a reduction in mortality in critically ill patients.
- 2) Early enteral nutrition compared to delayed nutrient intake is associated with a decrease in infectious complications.

- 3) Early enteral nutrition compared to delayed nutrient intake has no effect on ICU or hospital length of stay.
- 4) Early enteral nutrition compared to delayed nutrient intake is associated with improved nutritional intake.

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 early EN vs. delayed nutrient intake in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				Early EN	Delayed	Early EN	Delayed
1) Moore 1986	Trauma with abdominal trauma index > 15 N=43	C.Random: not sure ITT: no Blinding: no (6)	Vivonex post op (< 24 hrs) via jejunostomy vs. D5W then progressed to parenteral nutrition if not on regular diet (both groups got PN)	1/32 (3)	2/31 (6)	3/32 (9)	9/31 (29)
2) Chiarelli 1990	Burns N=20	C.Random: not sure ITT: yes Blinding: no (6)	Immediate EN (4.4 ± 0.49 hrs) vs > 48 hrs (57.7 ± 2.6 hrs) (gastric feeding)	0/10 (0)	0/10 (0)	3/10 (30) positive blood cultures	7/10 (70) positive blood cultures
3) Eyer 1993	Trauma, ICU N=52	C.Random: not sure ITT: no Blinding: no (8)	EN < 24 hrs (31 ± 13 hrs from ICU admission) vs > 72 hrs (82 ± 11 hrs from ICU admission) (small bowel feeding)	2/19 (11)	2/19 (11)	29/19 per group	14/19 per group
4) Chuntrasakul 1996	Trauma patients with injury severity score 20-40 N=38	C.Random: not sure ITT: yes Blinding: no (6)	Traumacal via gastric route (early i.e. immediately after resuscitation) + PN if needed vs IV fluids and oral diet when bowel function detected	1/21 (5)	3/17 (18)	NR	NR
5) Singh 1998	Non traumatic intestinal perforation and peritonitis BMI 21-22 N=37	C.Random: no ITT: yes Blinding: no (8)	Low residue blenderized diet via jejunostomy 12-24 hrs post laparotomy vs. IV fluids/lytes, oral diet started once bowel activity resumed	4/21 (19)	4/22 (18)	7/21 (33)	12/22 (55)
6) Kompan 1999	Multiple trauma in shock N=28	C.Random: yes ITT: no Blinding: no (9)	EN ~4.4 hrs after admission to ICU, 9.2 hrs after trauma vs ~ 36.5 hrs from ICU admission, 41.4 hrs after trauma. Gastric feeding, both groups got PN	ICU 0/14 (0) Hospital 0/14 (0)	ICU 0/14 (0) Hospital 1/14 (7)	NR	NR
7) Minard 2000	Closed head injuries N=27	C.Random: not sure ITT: no Blinding: no (7)	EN < 60 hrs (33 ± 15 hrs) (small bowel) vs late (84 ± 41 hrs) (gastric)	1/12 (8)	4/15(27)	6/12 (50)	7/15 (47)

8) Pupelis 2000	Severe pancreatitis patients undergoing emergency surgery N=29	C.Random: not sure ITT: yes Blinding: no (6)	EN < 24 hrs post-op via jejunum + IV fluids vs. IV fluids until reintroduction of normal diet	1/11 (9)	5/18 (28)	NR	NR
9) Pupelis 2001	Post laporotomy for severe pancreatitis and peritonitis N=60	C.Random: not sure ITT: yes Blinding: no (6)	EN < 12 hrs post-op via jejunum + IV fluids vs. IV fluids until reintroduction of normal diet	1/30 (3)	7/30 (23)	Unresolved Peritonitis 1/30 (3) 8/30 (27) Wound Septic Complications 10/30 (33) 8/30 (27)	
10) Kompan 2004	Multiple trauma patients, ICU N=52	C.Random: not sure ITT: yes Blinding: no (6)	EN ~10.6 hrs after injury vs ~ 36.5 hrs from ICU admission. Gastric feeding, both groups got PN	0/27 (0)	1/25 (4)	9/27 (33)	16/25 (64)
11) Malhotra 2004	Post-op for peritonitis N=200	C.Random: not sure ITT: yes Blinding: no (6)	EN post-op < 48 hrs via nasogastric+ IV fluids (oral feeds if ready by day 8 post-op) vs. IV fluids for 7 days (oral feeds if ready on day 5 post-op)	12/100 (12)	16/100 (16)	54/100 (54)	67/100 (67)
12) Peck 2004	Burns N=27	C.Random: not sure ITT: no Blinding: no (6)	Crucial < 24 hrs from burn injury vs. 7 days. Both groups received oral diet as tolerated (4-9% calories) (gastric feeding)	4/14 (28)	5/13 (38)	12/14 (86)	11/13 (85)
13) Dvorak 2004	Acute spinal cord injury patients BMI=26-29 N=17	C.Random: yes ITT: yes Blinding: no (10)	Continuous enteral feeding via nasogastric route within 72 hours of injury vs. after 120 hrs of injury. Both groups followed feeding protocol (head of bed, starting rate 25 ml/hr, gastric residual volumes checked, etc).	0/7 (0)	0/10 (0)	2.4 ± 1.5 per group	1.7 ± 1.1 per group
14) Nguyen 2008	Mixed ICU BMI=27-28 N=28	C.Random: no ITT: yes Blinding: no (9)	EN < 24 hrs of ICU admission vs. after day 4. No motility agents given	ICU 4/14 (29) Hospital 6/14 (43)	ICU 4/14 (29) Hospital 6/14 (43)	Pneumonia 3/14 (21)	Pneumonia 6/14 (43)
15) Moses 2009	Organophosphate poisoned, mechanically ventilated ICU patients N=59	C.Random: No ITT: No Blinding: No (5)	Hypocaloric EN within 48hr of intubation + IV glucose (Day 1 20 ml/hr (0.5 kcal/ml), day 2 20 ml/hr (1 kcal/ml) day 3 40 ml/hr (1 kcal/ml) feeds), max 1000 kcals/day vs. EN post tracheostomy placement + IV glucose	3/29 (10)	3/30 (10)	14/29 (48)	15/30 (50)

16) Chourdakis 2012	Traumatic brain injury requiring mechanical ventilation in ICU N=59	C.Random: No ITT: Yes Blinding: No (6)	Early enteral feed within 24-48 hrs post ICU admission (hrs in ICU prior to first feeding: 31.2 ± 11.2 hrs) vs. delayed enteral feed within 48-120hrs post ICU admission (hrs in ICU prior to first feeding: 76.5 ± 22.6 hrs)	3/34 (9)	2/25 (8)	VAP 13/34 (38)	VAP 12/25 (43)
17) Ostadrahimi 2016	Burn pts with TBSA 20-90% N=41	C.Random: No ITT: No Blinding: No (6)	Early enteral feeding within the first hour of admission, reaching goal EN by day 3 vs hospital routine diet ad libitum (liquid food for 2 days after injury followed by chow diet)	2-days (excluded from analysis in publication) 3/21	2-days (excluded from analysis in publication) 3/20	NR	NR

Table 1. Randomized studies evaluating early EN vs. delayed nutrient intake in critically ill patients (continued)

Study	LOS days		Ventilator days		Cost		Other	
	Early EN	Delayed	Early EN	Delayed	Early EN	Delayed	Early EN	Delayed
1) Moore 1986	NR	NR	NR	NR	\$16,280 ± 2146	\$19,636 ± 3396	Complications 14/32 (44)	15/31 (48)
2) Chiarelli 1990	Hospital 69.2 ± 10.4 (10)	Hospital 89 ± 18.9 (10)	NR	NR	NR	NR	Days to positive Nitrogen Balance 8.8 ± 4.1	24.1 ± 6.9 p<0.05
3) Eyer 1993	ICU 11.8 ± 7.9 (19)	ICU 9.9 ± 6.7 (19)	10.2 ± 8.1 (19)	8.1 ± 6.8 (19)	NR	NR	Calorie Intake (kcal/kg/day) 30 ± 6	19 ± 5 p<0.001
4) Chuntrasakul 1996	ICU 8.1 ± 6.3 (21)	ICU 8.35 ± 4.8 (17)	5.29 ± 6.3 (21)	6.12 ± 5.3 (17)	NR	NR	Protein Intake (gm/kg/day) 1.3 ± 0.3	0.9 ± 0.2 p<0.001
							Organ System Failure 2/19 (10.5)	2/19 (10.5)
							Calories Received in Week 1 1885.2 ± 38.3	633.4 ± 83.7
							Calories Received in Week 2 1850.3 ± 248.4	717.31 ± 142

5) Singh 1998	Hospital 14 ± 6.9 (19)	Hospital 13 ± 7.0 (18)	NR	NR	NR	NR	Complications 11/21 (52) 13/22 (59) Calorie Intake by Day 7 2610 ± 337 516 ± 156 Nitrogen Balance by Day 7 5.1 ± 0.7 10.8 ± 3.1
6) Kompan 1999	ICU 11 (10.5-24.7)	ICU 14 (10.5-24.7)	13 (6.7-18)	11.9 (6-7.7)	NR	NR	EN Received on Day 4 (mls) 1340 ± 473 703 ± 701 p=0.009
7) Minard 2000	ICU 18.5 ± 8.8 (12) Hospital 30 ± 14.7 (12)	ICU 11.3 ± 6.1 (15) Hospital 21.3 ± 13.7 (15)	15.1 ± 7.5 (12)	10.4 ± 6.1 (15)	NR	NR	Calorie Intake 1509 ± 45 1174 ± 425 p< 0.02 Feed Infusion Complications 22/12 28/15
8) Pupelis 2000	ICU 7 ± 41 (11) Hospital 45 ± 96 (11)	ICU 6 ± 34 (18) Hospital 29 ± 103 (18)	NR	NR	NR	NR	NR
9) Pupelis 2001	ICU 13.9 ± 14.6 (30) Hospital 35.3 ± 22.9 (30)	ICU 16 ± 20.5 (30) Hospital 35.8 ± 32.5 (30)	NR	NR	NR	NR	Total kcals After Surgery 1295 ± 327 473 ± 156
10) Kompan 2004	ICU 15.9 ± 9.7 (27)	ICU 20.6 ± 18.5 (25)	12.9 ± 8.1 (27)	15.6 ± 16.1 (25)	NR	NR	EN Received on Day 4 (mls) 1175 ± 485 803 ± 545 p=0.012
11) Malhotra 2004	ICU 1.59 (mean) Hospital 10.59 (mean)	ICU 2.10 (mean) Hospital 10.70 (mean)	NR	NR	NR	NR	Patients Receiving > 1500 cals Post-op Day 4 65% 0% p<0.001 Patients Receiving > 2500 cals Post-op Day 8 84% 0% p<0.001

12) Peck 2004	ICU 40 ± 32 (14) Hospital 60 ± 44 (14)	ICU 37 ± 33 (13) Hospital 60 ± 38 (13)	32 ± 27 (14)	23 ± 26 (13)	NR	NR	Mean Calorie Intake 2234 2207 Mean Calorie Intake Change/Week 156 166
13) Dvorak 2004	Hospital 53 ± 34.4	Hospital 37.9 ± 14.6	31.8 ± 35	20.9 ± 14.4	NR	NR	Number of Feeding Complications 39 59 Hours to Reach Energy Goals 113 166 Energy Intake 1938 ± 1100 1588 ± 983 Protein Intake 86.8 ± 59 67.6 ± 54
14) Nguyen 2008	ICU 11.3 ± 3.0	ICU 15.9 ± 7.1	9.2 ± 3.4 (14)	13.7 ± 7.1 (14)	NR	NR	Mean Calorie Intake from Day 0-4 2894 ± 198 0
15) Moses 2009	ICU 10.6 (6-13) Hospital 15 (9.5-20)	ICU 8 (5-17.5) Hospital 12 (7.5-15)	12 (5.5-14)	10 (4-12)	NR	NR	Total Calories 604 (500-713) 447 (424-484) p<0.0001
16) Chourdakis 2012	ICU 24.8 ± 7.6 (34)	ICU 28.5 ± 8.9 (25)	NR	NR	NR	NR	Hyperglycemia 5/34 (15) 4/25 (16) Feed Intolerance 3/34 (9) 3/25 (12) Diarrhea 4/34 (12) 3/25 (12) Constipation 1/34 (3) 1/25 (4) Day 10 of Intake (kcal/day) 1432.0 ± 156.3 813.0 ± 235.1
17) Ostadrahimi 2016	Hospital 17.64±8.2 (15)	Hospital 23.07±11.89 (15)	NR	NR	NR	NR	NR

C.Random: Concealed randomization

ITT: Intent to treat

NR: Not reported

‡ Refers to the # of patients with infections unless specified

† Presumed hospital mortality unless otherwise specified

± () : Mean ± SD =Standard deviation (number); (-) : mean (range) * SEM converted to SD

Figure 1. Studies comparing early EN vs delayed nutrient intake: Mortality

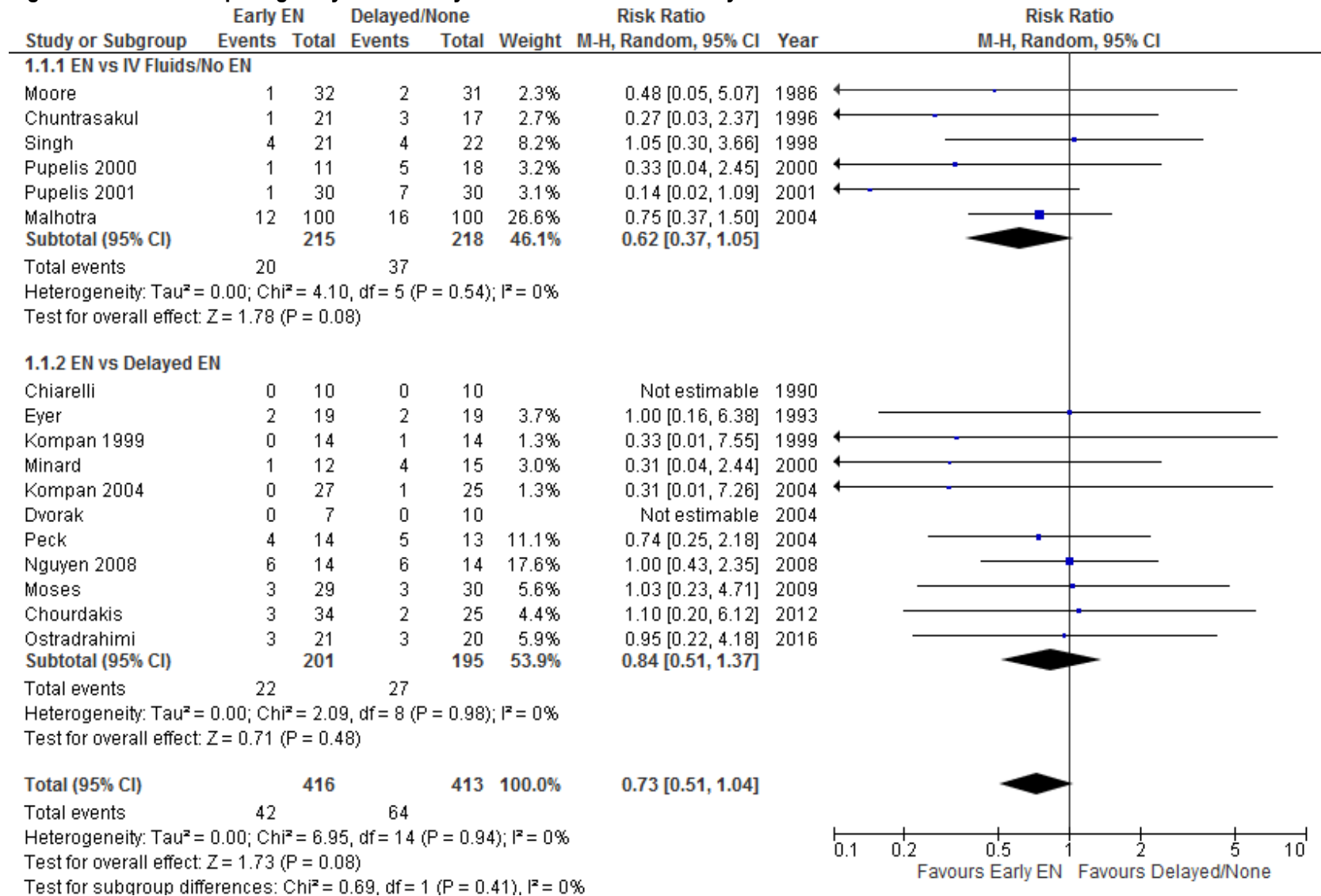


Figure 2. Studies comparing early EN vs delayed nutrient intake: Infectious complications

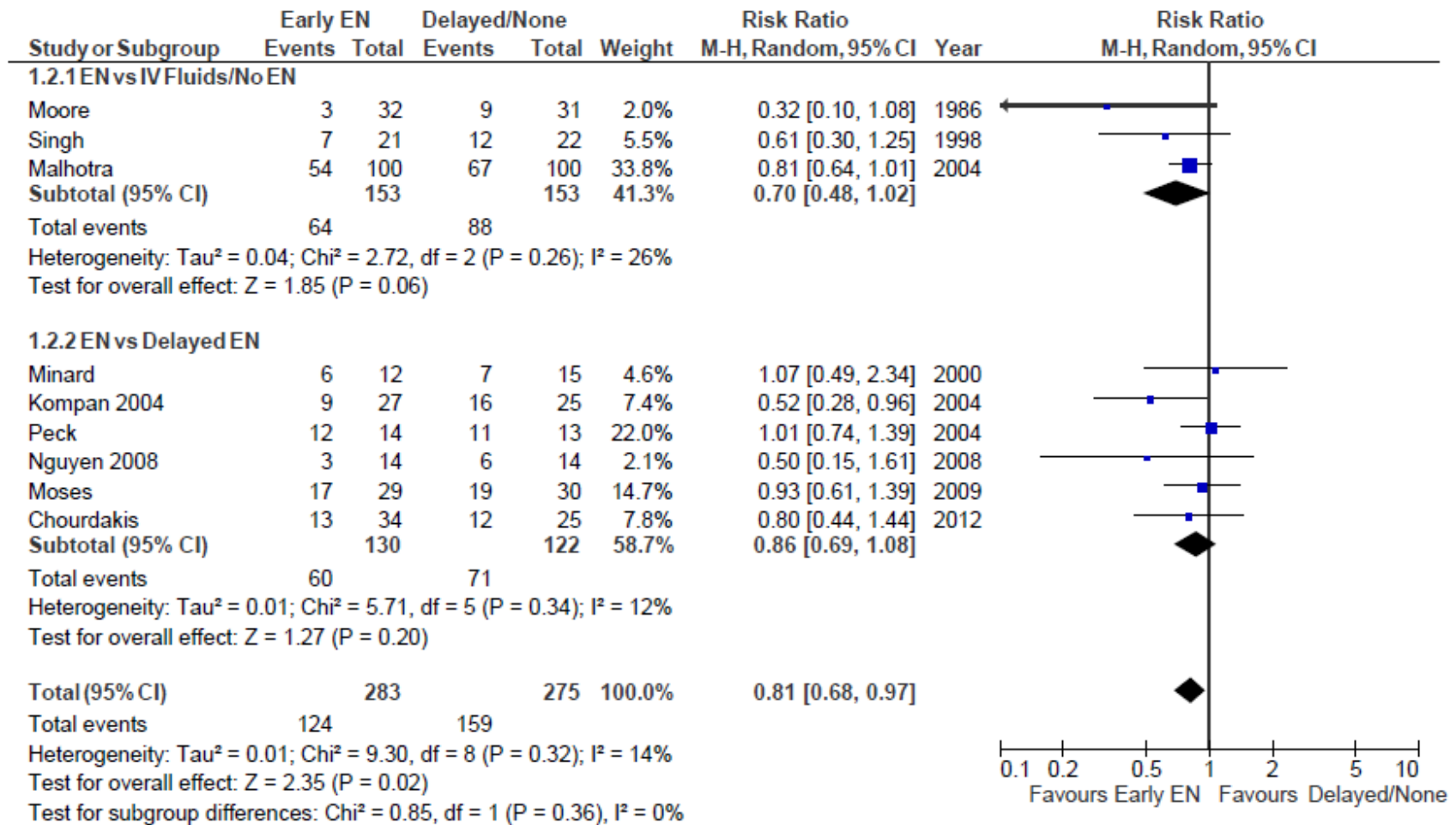


Figure 3. Studies comparing early EN vs delayed nutrient intake: ICU LOS

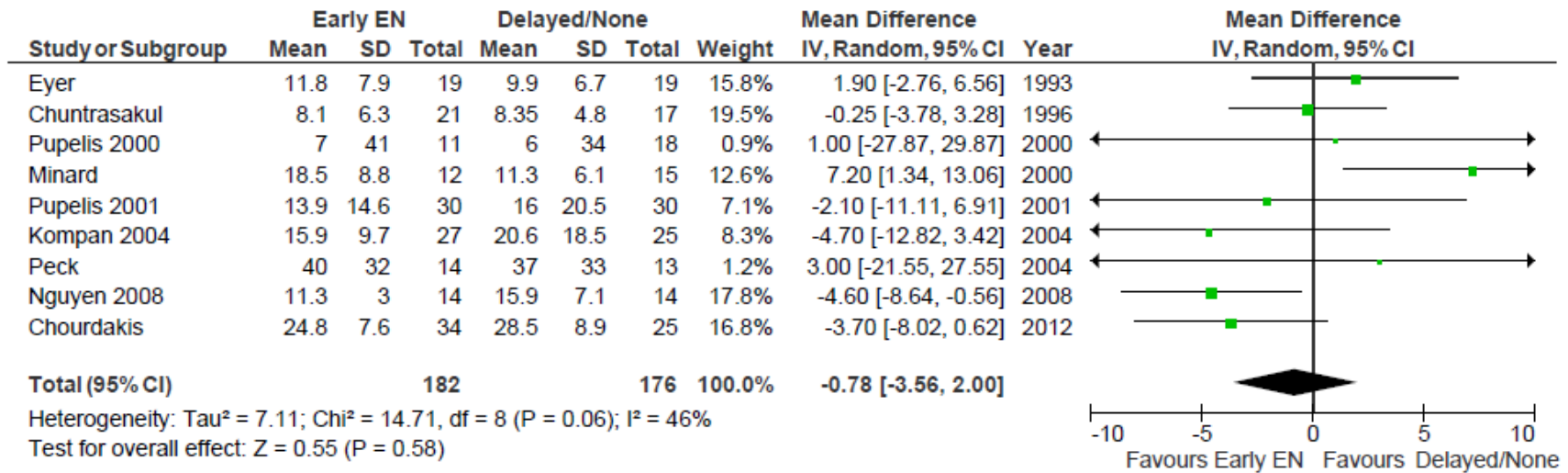


Figure 4. Studies comparing early EN vs delayed nutrient intake: Hospital LOS

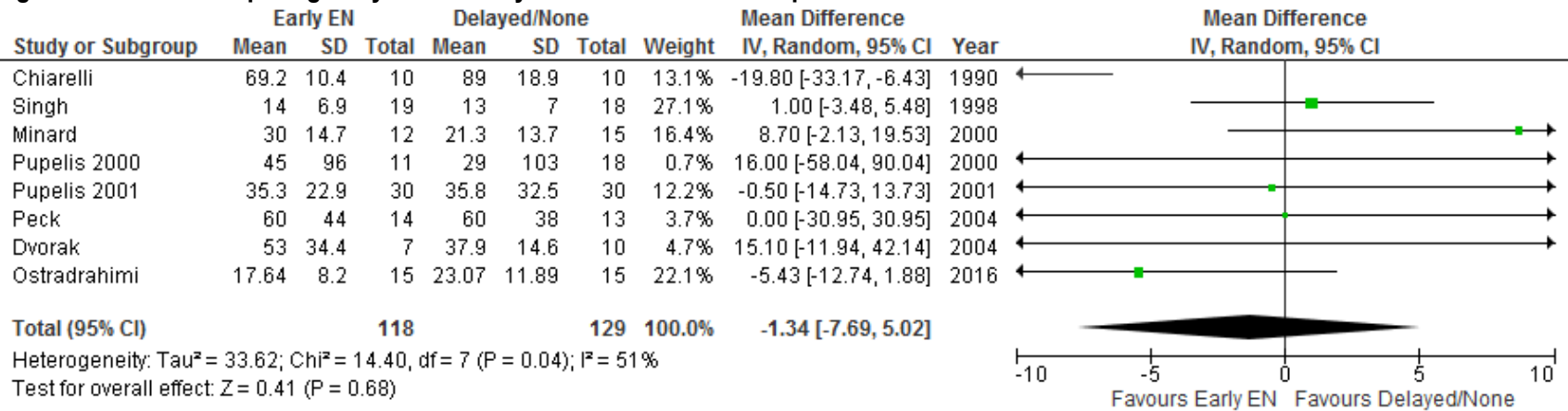


Figure 5. Studies comparing early EN vs delayed nutrient intake: Ventilator days

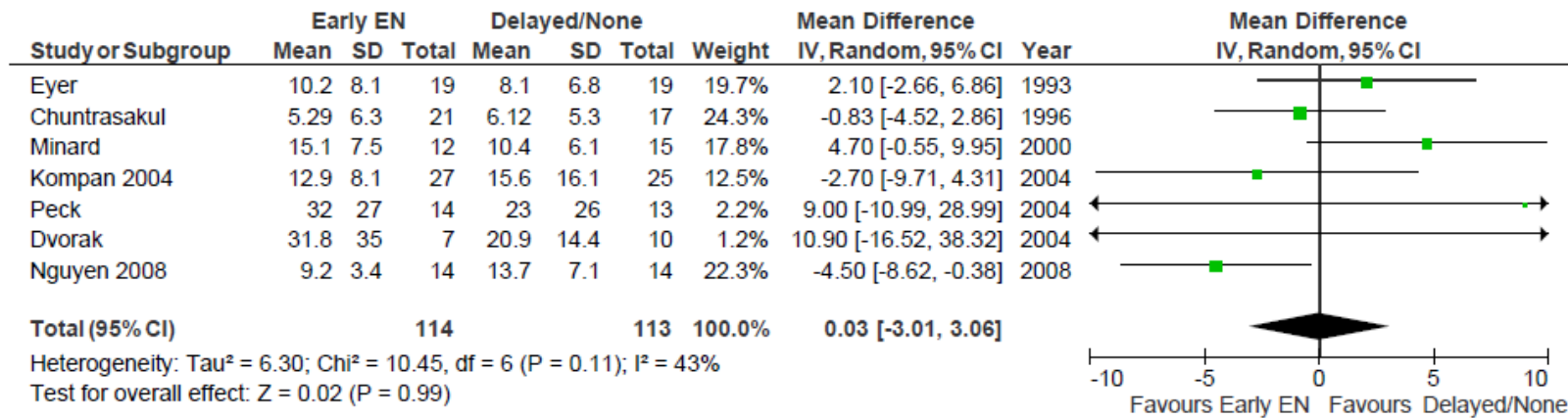


Table 2. Excluded Articles

#	Reason excluded	Citation
1	Elective surgery pts	Ryan JA Jr, Page CP, Babcock L. Early postoperative jejunal feeding of elemental diet in gastrointestinal surgery. Am Surg. 1981 Sep;47(9):393-403.
2	Not ICU pts	Seri S, Aquilio E. Effects of early nutritional support in patients with abdominal trauma. Ital J Surg Sci. 1984;14(3):223-7.
3	Pseudo-randomized	Grahm TW, Zadrozny DB, Harrington T. The benefits of early jejunal hyperalimentation in the head-injured patient. Neurosurgery 1989 Nov;25(5):729-35.
4	No clinical outcomes	Jones TN, Moore FA, Moore EE, McCroskey BL. Gastrointestinal symptoms attributed to jejunostomy feeding after major abdominal trauma – a critical analysis. Crit Care Med 1989 Nov;17(11):1146-50.
5	Elective surgery pts	Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma--reduced septic morbidity. J Trauma. 1989 Jul;29(7):916-22; discussion 922-3.
6	Elective surgery pts	Schroeder D, Gillanders L, Mahr K, Hill GL. Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. JPEN J Parenter Enteral Nutr. 1991 Jul-Aug;15(4):376-83.
7	Elective surgery pts	The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med. 1991 Aug 22;325(8):525-32.
8	Elective surgery pts	Binderow SR, Cohen SM, Wexner SD, Noguerras JJ. Must early postoperative oral intake be limited to laparoscopy? Dis Colon Rectum. 1994 Jun;37(6):584-9.
9	Paediatric population	Jenkins ME, Gottschlich MM, Warden GD. Enteral feeding during operative procedures in thermal injuries. J Burn Care Rehabil 1994 Mar-Apr;15(2):199-205.
10	Elective surgery pts	Braga M, Vignali A, Gianotti L, Cestari A, Profili M, Di Carlo V. Benefits of early postoperative enteral feeding in cancer patients. Infusionsther Transfusionsmed 1995 Oct;22(5):280-4.

11	Elective surgery pts	Brown DN, Miedema BW, King PD, Marshall JB. Safety of early feeding after percutaneous endoscopic gastrostomy. <i>J Clin Gastroenterol.</i> 1995 Dec;21(4):330-1.
12	Elective surgery pts	Hasse JM, Blue LS, Liepa GU, Goldstein RM, Jennings LW, Mor E, Husberg BS, Levy MF, Gonwa TA, Klintmalm GB. Early enteral nutrition support in patients undergoing liver transplantation. <i>JPEN J Parenter Enteral Nutr.</i> 1995 Nov-Dec;19(6):437-43.
13	Elective surgery pts	Reissman P, Teoh TA, Cohen SM, Weiss EG, Noguera JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. <i>Ann Surg.</i> 1995 Jul;222(1):73-7.
14	Elective surgery pts	Seenu V, Goel AK. Early oral feeding after elective colorectal surgery: is it safe. <i>Trop Gastroenterol.</i> 1995 Oct-Dec;16(4):72-3.
15	Not ICU pts	Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. <i>Gut</i> 1996;39(6):833-5.
16	Elective surgery pts	Carr CS, Ling KD, Boulos P, Singer M. Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. <i>BMJ.</i> 1996 Apr 6;312(7035):869-71.
17	Elective surgery pts	Choudhry U, Barde CJ, Markert R, Gopalswamy N. Percutaneous endoscopic gastrostomy: a randomized prospective comparison of early and delayed feeding. <i>Gastrointest Endosc.</i> 1996 Aug;44(2):164-7. PubMed PMID: 8858322.
18	Elective surgery pts	Ortiz H, Armendariz P, Yarnoz C. Is early postoperative feeding feasible in elective colon and rectal surgery? <i>Int J Colorectal Dis.</i> 1996;11(3):119-21.
19	Elective surgery pts	Hartsell PA, Frazee RC, Harrison JB, Smith RW. Early postoperative feeding after elective colorectal surgery. <i>Arch Surg.</i> 1997 May;132(5):518-20; discussion 520-1.
20	Cancer pts	Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW, Shike M, Brennan MF. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. <i>Ann Surg.</i> 1997 Oct;226(4):567-77.
21	Elective surgery pts	Schilder JM, Hurteau JA, Look KY, Moore DH, Raff G, Stehman FB, Sutton GP. A prospective controlled trial of early postoperative oral intake following major abdominal gynecologic surgery. <i>Gynecol Oncol.</i> 1997 Dec;67(3):235-40.
22	Unclear if ICU pts, no clinical outcomes	Wang S, Wang S, Li A. [A clinical study of early enteral feeding to protect the gut function in burned patients] [Article in Chinese]. <i>Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi.</i> 1997 Jul;13(4):267-71.
23	Elective surgery pts	Watters JM, Kirkpatrick SM, Norris SB, Shamji FM, Wells GA. Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. <i>Ann Surg.</i> 1997 Sep;226(3):369-77
24	Not ICU pts	McCarter TL, Condon SC, Aguilar RC, Gibson DJ, Chen YK. Randomized prospective trial of early versus delayed feeding after percutaneous endoscopic gastrostomy placement. <i>Am J Gastroenterol.</i> 1998 Mar;93(3):419-21.
25	Not ICU pts	Schulte-Bockholt A et al. Immediate versus next day PEG feeding: a randomized prospective study in ICU/intermediate care patients. <i>Gastroenterology. Abstracts 1998: Growth Development & Nutrition.</i> A907. Abstract number G3719
26	Elective surgery pts	Schwenk W, Böhm B, Haase O, Junghans T, Müller JM. Laparoscopic versus conventional colorectal resection: a prospective randomized study of postoperative ileus and early postoperative feeding. <i>Arch Surg.</i> 1998 Mar;383(1):49-55.
27	Elective surgery pts	Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: a prospective randomized trial. <i>Aust N Z J Surg.</i> 1998 Feb;68(2):125-8.
28	Elective surgery pts	Beier-Holgersen R, Brandstrup B. Influence of early postoperative enteral nutrition versus placebo on cell-mediated immunity, as measured with the Multitest CMI. <i>Scand J Gastroenterol.</i> 1999 Jan;34(1):98-102. PubMed PMID: 10048740.
29	Not a RCT	Zaloga GP. Early enteral nutritional support improves outcome: hypothesis or fact? <i>Crit Care Med</i> 1999 Feb;27(2):259-61.
30	Elective surgery pts	Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomized controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. <i>Gut.</i> 2000 Jun;46(6):813-8.
31	EN vs. no nutrition	Powell JJ, Murchison JT, Fearon KC, Ross JA, Siriwardena AK. Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. <i>Br J Surg.</i> 2000 Oct;87(10):1375-81.

32	Systematic review	Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. <i>BMJ</i> . 2001 Oct 6;323(7316):773-6.
33	Meta-analysis	Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. <i>Crit Care Med</i> 2001 Dec;29(12):2264-70.
34	No clinical outcomes	Peng YZ, Yuan ZQ, Xiao GX. Burns. Effects of early enteral feeding on the prevention of enterogenic infection in severely burned patients. 2001 Mar;27(2):145-9.
35	Elective surgery/cancer pts	Soliani P, Dell'Abate P, Del Rio P, Arcuri MF, Salsi P, Cortellini P, Sianesi M. [Early enteral nutrition in patients treated with major surgery of the abdomen and the pelvis] [Article in Italian] <i>Chir Ital</i> . 2001 Sep-Oct;53(5):619-32.
36	Elective surgery	de Aguilar-Nascimento JE, Göelzer J. [Early feeding after intestinal anastomoses: risks or benefits?] [Article in Portuguese] <i>Rev Assoc Med Bras</i> . 2002 Oct-Dec;48(4):348-52.
37	Pseudo-randomized	Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, Fraser V, Kollef MH. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. <i>JPEN J Parenter Enteral Nutr</i> . 2002 May-Jun;26(3):174-81.
38	Not ICU pts	Page RD, Oo AY, Russell GN, Pennefather SH. Intravenous hydration versus naso-jejunal enteral feeding after esophagectomy: a randomised study. <i>Eur J Cardiothorac Surg</i> . 2002 Nov;22(5):666-72. PubMed PMID: 12414028.
39	Not delayed nutrient intake	Zhao G, Wang CY, Wang F, Xiong JX. Clinical study on nutrition support in patients with severe acute pancreatitis. <i>World J Gastroenterol</i> . 2003 Sep;9(9):2105-8.
40	Elective surgery pts	Feo CV, Romanini B, Sortini D, Ragazzi R, Zamboni P, Pansini GC, Liboni A. Early oral feeding after colorectal resection: a randomized controlled study. <i>ANZ J Surg</i> . 2004 May;74(5):298-301.
41	Not ventilated patients as confirmed by authors	Kaur N, Gupta MK, Minocha VR. Early enteral feeding by nasoenteric tubes in patients with perforation peritonitis. <i>World J Surg</i> 2005 Aug;29(8):1023-7.
42	Systematic review	Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. <i>Cochrane Database Syst Rev</i> . 2006 Oct 18;(4):CD004080.
43	No clinical outcomes	Cheng G, Han C. Economic evaluation of early enteral nutrition in severely burned patients. <i>Chinese Journal of Clinical Nutrition</i> . 2006;1:003.
44	Elective surgery pts	Dong GH, Cai JF, Hao J, Zhong QG, Li YJ. [Effect of early enteral nutrition on immune function of the patients after operation for severe abdominal trauma]. <i>Zhonghua Wei Chang Wai Ke Za Zhi</i> . 2006 Mar;9(2):145-7. Chinese. PubMed PMID: 16555157.
45	Systematic review	Wasiak J, Cleland H, Jeffery R. Early versus delayed enteral nutrition support for burn injuries. <i>Cochrane Database Syst Rev</i> . 2006 Jul 19;3:CD005489.
46	Systematic review	Wasiak J, Cleland H, Jeffery R. Early versus late enteral nutritional support in adults with burn injury: a systematic review. <i>J Hum Nutr Diet</i> . 2007 Apr;20(2):75-83.
47	Meta-analysis	Bechtold ML, Matteson ML, Choudhary A, Puli SR, Jiang PP, Roy PK. Early versus delayed feeding after placement of a percutaneous endoscopic gastrostomy: a meta-analysis. <i>Am J Gastroenterol</i> . 2008 Nov;103(11):2919-24. Epub 2008 Aug 21. PubMed PMID: 18721239.
48	Meta-analysis	Petrov MS, Pylypchuk RD, Emelyanov NV. Systematic review: nutritional support in acute pancreatitis. <i>Aliment Pharmacol Ther</i> . 2008 Sep 15;28(6):704-12. Review. PubMed PMID: 19145726.
49	Meta-analysis	Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. <i>Intensive Care Med</i> . 2009 Dec;35(12):2018-27. Epub 2009 Sep 24. PubMed PMID: 19777207.
50	Meta-analysis	Lidder PG, Lewis S, Duxbury M, Thomas S. Systematic review of postdischarge oral nutritional supplementation in patients undergoing GI surgery. <i>Nutr Clin Pract</i> . 2009 Jun-Jul;24(3):388-94. Review. PubMed PMID: 19483068.

51	Elective surgery pts	Minig L, Biffi R, Zanagnolo V, Attanasio A, Beltrami C, Bocciolone L, Botteri E, Colombo N, Iodice S, Landoni F, Peiretti M, Roviglione G, Maggioni A. Reduction of postoperative complication rate with the use of early oral feeding in gynecologic oncologic patients undergoing a major surgery: a randomized controlled trial. <i>Ann Surg Oncol.</i> 2009 Nov;16(11):3101-10.
52	Elective surgery pts	Minig L, Biffi R, Zanagnolo V, Attanasio A, Beltrami C, Bocciolone L, Botteri E, Colombo N, Iodice S, Landoni F, Peiretti M, Roviglione G, Maggioni A. Early oral versus "traditional" postoperative feeding in gynecologic oncology patients undergoing intestinal resection: a randomized controlled trial. <i>Ann Surg Oncol.</i> 2009 Jun;16(6):1660-8. Epub 2009 Mar 28. PubMed PMID: 19330379.
53	Preliminary report	Bakker OJ, van Santvoort HC, van Brunschot S, Ahmed Ali U, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Brink MA, Dejong CH, van Geenen EJ, van Goor H, Heisterkamp J, Houdijk AP, Jansen JM, Karsten TM, Manusama ER, Nieuwenhuijs VB, van Ramshorst B, Schaapherder AF, van der Schelling GP, Spanier MB, Tan A, Vecht J, Weusten BL, Witterman BJ, Akkermans LM, Gooszen HG; Dutch Pancreatitis Study Group. Pancreatitis, very early compared with normal start of enteral feeding (PYTHON trial): design and rationale of a randomised controlled multicenter trial. <i>Trials.</i> 2011 Mar 10;12:73. PubMed PMID: 21392395; PubMedCentral PMCID: PMC3068962.
54	Elective surgery pts	Barlow R, Price P, Reid TD, Hunt S, Clark GW, Havard TJ, Puntis MC, Lewis WG. Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. <i>Clin Nutr.</i> 2011 Oct;30(5):560-6. Epub 2011 May 20. PubMed PMID: 21601319.
55	Same data reported in Nguyen 2008	Nguyen NQ, Besanko LK, Burgstad C, Bellon M, Holloway RH, Chapman M, Horowitz M, Fraser RJ. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. <i>Crit Care Med.</i> 2012 Jan;40(1):50-4. PubMed PMID:21926614.
56	Not a RCT: historical control group	Kesey J, Dissanaika S. A protocol of early aggressive acceleration of tube feeding increases ileus without perceptible benefit in severely burned patients. <i>J Burn Care Res.</i> 2013 Sep-Oct;34(5):515-20.
57	Meta-analyses	Wang X, Dong Y, Han X, Qi X-Q, Huang C-G, Hou L. (2013) Nutritional Support for Patients Sustaining Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Prospective Studies. <i>PLoS ONE.</i> 8(3): e58838.
58	Use of PN doesn't allow us to attribute any difference observed to early vs late EN.	Bakiner O, Bozkirli E, Giray S, Alier Z, Kozanoglu I, Sezgin N, Sariturk C, Ertorer E. Impact of early versus late enteral nutrition on cell mediated immunity and its relationship with glucagon like peptide-1 in intensive care unit patients: a prospective study. <i>Crit Care.</i> 2013 Jun 20;17(3):R123.
59	Not critically ill pts	Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, Dejong CH, van Goor H, Bosscha K, Ahmed Ali U, et al.; Dutch Pancreatitis Study Group. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. <i>N Engl J Med</i> 2014;371:1983–1993.
60	Unclear if critically ill pts	Li CH, Chen DP, Yang J. Enteral Nutritional Support in Patients with Head Injuries After Craniocerebral Surgery. <i>Turk Neurosurg.</i> 2015;25(6):873-6. doi: 10.5137/1019-5149.JTN.9503-13.1. PubMed PMID: 26617135.
61	Not critically ill pts	Stimac D, Poropat G, Hauser G, Licul V, Franjic N, Valkovic Zujic P, Milic S. Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: A randomized clinical trial. <i>Pancreatology.</i> 2016 Jul-Aug;16(4):523-8.