2.0 The Use of Enteral Nutrition vs. Parenteral Nutrition

Question: Does enteral nutrition compared to parenteral nutrition result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 20 level 2 studies and one level 1 study (Woodcock et al) that were reviewed and meta-analyzed. In the Woodcock study, data from ICU patients only were abstracted and there were 11/38 patients that crossed over between EN and PN group after randomization. There have been two more recent, large RCTs, Harvey 2014 and Reignier 2017, which enrolled 2400 and 2410 patients, respectively, across 33 and 44 sites. Other more recent smaller trials included patients fasting for at least 14 days (Xi 2014), patients with moderate traumatic brain injury (Meirelles 2011) and patients with severe acute pancreatitis (Wang 2013, Sun 2013). A priori, we considered that the harmful effect of PN may be associated with relative overfeeding and hyperglycemia. Accordingly, we conducted a subgroup analysis to determine the effect of excess calories (PN compared to EN) and higher glucose levels (across groups). The Moore 1992 study, which had been included in the 2009 summary, was reviewed again and excluded since it reports results of a meta-analysis and the individual studies have been included. Given concerns about population in the Mereilles 2011 and Wang 2013 studies not being critically ill as no mention of ventilation status and some missing data in the latter study, a sensitivity analysis was also done excluding these two studies.

Mortality: In the two largest studies (Harvey and Reignier), there were no significant differences between the PN group and the EN group in 30 or 28 day mortality (P = 0.57 and 0.33, respectively) or 90 day mortality (P = 0.4 and 0.28, respectively) or hospital mortality (P = 0.44 and 0.25, respectively). However, both studies showed a trend in the reduction in ICU mortality, favoring the PN group (P = 0.13 and 0.17, respectively). When these data were aggregated with the other 17 studies reporting on mortality, there was no difference in overall mortality between the groups receiving EN or PN (RR 1.04, 95% CI 0.97, 1.12, p=0.29, test for heterogeneity I^2 =2%, figure 1). When the trials in which the PN group were fed more calories than the EN group were aggregated, there was no effect seen (RR 1.19, 95% CI 0.86, 1.64, p = 0.30, heterogeneity I^2=31%; figure 1). Similarly, when the trials in which the PN and EN groups were fed isocalorically were aggregated, there was no effect on mortality (RR 1.02, 95% CI 0.92, 1.13, p =0.65, test for heterogeneity I^2=0%; figure 1). There was no difference in these subgroups (p=0.39; figure 1). In subgroup analysis comparing studies in which the PN group had higher blood sugars than the EN group to studies in which there was no difference in blood sugars, showed that increased mortality in the PN groups could not be explained by hyperglycemia (RR 0.93, 95% CI 0.30, 2.90, p=0.90, heterogeneity I^2=0%; figure 2). In a sensitivity analysis excluding Mereilles 2011, Wang 2013, there was still no difference in mortality between groups (RR 1.04, 95% CI 0.97, 1.12, p=0.21, test for heterogeneity I^2 =0%, figure not shown). When data from the 6 studies reporting on ICU mortality were aggregated, there was no effect seen (RR 1.04, 95% CI 0.97, 1.12, p = 0.28, heterogeneity I^2=0%, figure 3). There was also no effect seen when looking at subgroups where the PN group was fed more than the EN group and where the two groups were fed isocalorically (p = 0.38 and 0.71, respectively, figure 3).

Infections: When the 12 studies which reported on patients with infectious complications were statistically aggregated, the meta-analysis showed that EN compared to PN was associated with a significant reduction in the incidence of infectious complications (RR 0.74, 95% CI 0.59, 0.91, p=0.005, heterogeneity I^2=42%; figure 4). When the trials in which the PN group were fed more calories than the EN group were aggregated, EN compared to PN was also associated with a significant reduction in the incidence of infectious complications (RR 0.58, 95% CI 0.39, 0.88, p=0.009, heterogeneity I^2=53%; figure 4). When the trials in which the PN and EN groups were fed isocalorically were aggregated, EN compared to PN had no effect on infectious complications (RR 0.94, 95% CI 0.80, 1,10, p=0.44, heterogeneity I^2=0%; figure 4). There was a significant difference in these subgroups (p=0.03; figure 4). Another subgroup analysis showed that there was a trend between the increase in infections and hyperglycemia (RR 0.79, 95% CI 0.56, 1.11, p=0.17, heterogeneity I^2=0%; figure 5). In a sensitivity analysis excluding Mereilles 2011, EN compared to PN was associated with a significant reduction in infectious complications (RR 0.66, 95% CI 0.50, 0.86, p=0.003, heterogeneity I^2=38%, figure not shown.

LOS, Ventilator days: A total of 10 studies reported on hospital length of stay (in mean and standard deviation) and when the data were aggregated, enteral nutrition was associated with a trend towards a reduction in hospital LOS (WMD -3.12, 95% CI -7.43, 1.19, p=0.16, test for heterogeneity I^2 = 96%; figure 6). Only 6 studies reported on ICU LOS (in mean and standard deviation) and when the data were aggregated, the use of EN was associated with a reduction in ICU LOS (WMD -2.12, 95% CI -4.20, -0.04, p=0.05, heterogeneity I^2=94%; figure 7). A total of 5 studies reported on length of mechanical ventilation (in mean and standard deviation) and when the data were aggregated, there was a trend towards a reduction in ventilator days in the EN fed group (WMD -1.23, 95% CI -2.80, 0.34, p=0.13, heterogeneity I^2=87%, figure 8).

Nutritional complications: Of the 13 studies that reported on nutritional intake, 5 found that PN was associated with a higher calorie intake (Rapp, Young, Moore, Kudsk, Woodcock (Blood sugar values in the Woodcock pertain to the entire group, not the ICU population), the remaining 8 reported no significant difference in intakes between the groups (Adams, Hadley, Cerra, Dunham, Borzotta, Kalfarantzos, Wang, Harvey). A total of 7 studies reported on hyperglycemia and in 4 of these, EN was associated with lower incidences of hyperglycemia compared to PN (Adams p<0.001), (Borzotta p<0.05, Kalfarentzos) (Mereilles p<0.01). Three studies showed no difference in blood sugars between the groups receiving EN and PN (Moore 1989, Rapp, Harvey). Four studies showed that EN was associated with an increase in diarrhea (Cerra p<0.05, Young, Kudsk p<0.01, Harvey) while one showed an association with EN and a reduction in diarrhea (Borzotta p<0.05) and one study showed no difference (Adam). One study showed reported higher increases in total protein and albumin levels in the EN group vs. PN group level (p=0.032 and p=0.028 respectively, Chen 2019)

Other Complications: EN was also associated with an increase in vomiting (Cerra p<0.05), Harvey 2014 p <0.001). One study found less favourable neurological outcome at 3 months (p =0.05) in brain injured patients (Young, p=0.05), though this significance disappeared after 6 months and 1 year. More overall nutrition related complications were noted in EN vs PN (Dunham). Seven studies reported on diarrhea. There were significant reductions in the incidence of hypoglycemia (44 patients [3.7%] vs. 74 patients [6.2%]; P = 0.006) in the parenteral group in the largest study (Harvey 2014)

Cost: Four studies reported a cost savings with the use of EN vs PN (Adams, Cerra, Borzotta and Kalfarentzos).

Quality of Life (QOL) Outcomes: In a second publication (Harvey 2016), quality of life from the Harvey 2014 study was reported. In the trial, the EuroQol 5-dimension (5-level version) questionnaire (EQ-5D-5L) and a Health Services Questionnaire (to evaluate health and nutrition related quality of life (QOL)) were completed at 90 days post randomization and 1 year post-randomization with survivors. At 90 days and 1 year post randomization, Harvey et al found that health components from the EQ-5D-5L questionnaire were similar between groups. The results for nutrition related QOL were reported on a scale from 1 (worst possible satisfaction) to 7 (best possible satisfaction). At 90 days post-randomization, there was no difference in the mean response between the PN (mean (SD) of 5.2 (1.6, n=405)) and EN groups (5.1 (1.7, n=378)) (mean difference 0.10, 95% CI, -0.14, 0.33, p=0.43) (data not shown in table). At 1 year, there was also no significant difference (5.3 (1.6) in the PN group (n=338) vs 5.4 (1.6) in the EN group (n=322), mean difference -0.10, 95% CI,-0.35, 0.14, p=0.41) (data not shown in table).

Conclusions:

1) The use of EN compared to PN has no effect on mortality in critically ill patients.
2) The use of EN compared to PN is associated with a reduction in the number of infectious complications in the critically ill in trials where patients in the PN group received more calories than in the EN group.
3) The use of EN compared to PN may be associated with a reduction in ICU LOS and ventilator days and hospital LOS. Significant heterogeneity limits the inferences from these aggregated analyses.
4) The use of EN compared to PN may not be associated with an improvement in calories due to underfeeding in both groups
5) The use of EN may be associated with increased episodes of vomiting.
6) There is no difference between EN and PN in terms of patient reported outcomes

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 EN vs PN in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)† EN	Mortality # (%)† PN	Infections # (%)‡ EN	Infections # (%)‡ PN
1. Rapp 1983	Head Injured patients N=38 (<Ideal weight) Single-centre	C.Random: not sure ITT: no Blinding: no (4)	EN vs PN	9/18 (50)	3/20 (15)	NR	NR
2. Adams 1986	Trauma patients undergoing laporotomy N=46 36/46 ICU patients Single-centre	C.Random: not sure ITT: yes Blinding: no (8)	EN vs PN	1/23 (4)	3/23 (13)	15/23 (65)	17/23 (74)
3. Young 1987	Brain injured patients N=58 (N=51 analyzed) Single-centre	C.Random: not sure ITT: no Blinding: no (6)	EN vs PN	10/28 (36)	10/23 (43)	5/28 (18)	4/23 (17)
4. Peterson 1988	Critically ill patients with abdominal trauma N=59 Single-centre	C.Random: not sure ITT: no Blinding: no (5)	EN vs PN	NR	NR	2/21 (10)	8/25 (32)
5. Cerra 1988	ICU patients post sepsis N=70 (hypermetabolic patients) Single-centre	C.Random: not sure ITT: no Blinding: no (2)	EN vs PN	**ICU** 7/31 (22)	**ICU** 8/35 (23)	NR	NR
6. Moore 1989	Abdominal trauma patients N=75 Single-centre	C.Random: yes ITT: no Blinding: no (10)	EN vs PN	NR	NR	5/29 (17)	11/30 (37)

7. Kudsk 1992	Abdominal trauma N=98 Single-centre	C.Random: not sure ITT: no Blinding: single (10)	EN vs PN	**ICU** 1/51 (2)	**ICU** 1/45 (2)	9/51 (16)	18/45 (40)
8. Dunham 1994	Blunt trauma N=37 (TPN 15, EN 12, PN+EN 10) Single-centre	C.Random: not sure ITT: no Blinding: no (8)	EN vs PN	1/12 (7)	1/15 (8)	NR	NR
9. Borzotta 1994	Closed head injury N=59 Single-centre	C.Random: not sure ITT: no Blinding: no (6)	EN vs PN	5/28 (18)	1/21 (5)	51/28 per group	39/21 per group
10. Hadfield 1995	ICU patients, mainly cardiac bypass N=24 Single-centre	C.Random: not sure ITT: no Blinding: no (7)	EN vs PN	**ICU** 2/13 (15)	**ICU** 6/11 (55)	NR	NR
11. Kalfarentzos 1997	Severe acute pancreatitis N=38 Single-centre	C.Random: not sure ITT: no Blinding: single (9)	EN vs PN	**ICU** 1/18 (6)	**ICU** 2/20 (10)	5/18 (28)	10/20 (50)
12. Woodcock 2001	Patients needing nutrition support N=562 (randomized 64, of which ICU patients N=38 (TPN=21, EN=17) (all degrees of malnutirition) Single-centre	C.Random: yes ITT: yes Blinding: single (12)	EN vs PN	9/17 (53)	5/21 (24)	6/16 (38)	11/21 (52)

13. Casas 2007	Severe acute pancreatitis; ICU≥72 hrs N=22 Single-centre	C.Random: no/unsure ITT: Yes Blinding: No (8)	EN vs PN	**Hospital** 0/11 (0)	**Hospital** 2/11 (18)	1/11 (9)	3/11 (27)
14. Chen 2011	Elderly Patients in respiratory intensive care unit N=147 (EN=49, PN=49, EN+PN=49) Single-centre	C.Random: Yes ITT: Yes Blinding: No (7)	EN vs PN	**20-day** 11/49 (22)	**20-day** 10/49 (20)	5/49 (10)	18/49 (37)
15. Meirelles 2011	Adult patients with moderate traumatic brain injury N=22 Single-centre	C.Random: No ITT: No Blinding: No (5)	EN vs PN	**Unspecified** 1/12 (8.3)	**Unspecified** 1/10 (10)	**Total infectious complications** 2/12 (16.7) **Pneumonia (cases)** 2/12 (16.7) **Sepsis (cases)** 0	**Total infectious complications** 4/10 (40) **Pneumonia (cases)** 2/10 (20) **Sepsis (cases)** 2/10 (20)
16. Wang 2013	Patients 18-45 years with severe acute pancreatitis N=183 (PN=60, EN=61, EN+probiotics=62) Single-centre	C.Random: No ITT: No Blinding: Double (7)	EN vs PN	**Hospital** 3/61 (5)	**Hospital** 7/60 (12)	**Pancreatic sepsis** 13/61 (21) **MODS** 15/61 (24.6)	**Pancreatic sepsis** 24/60 (40) **MODS** 22/60 (36.7)
17. Sun 2013	Severe acute pancreatitis admitted to surgical ICU N=60 Single-centre	C.Random: No ITT: No Blinding: No (6)	EN vs PN	**Hospital** 2/30 (7)	**Hospital** 1/30 (3)	**Pancreatic** 3/30 (10) **MODS** 5/30 (17) **SIRS** 12/30 (40)	**Pancreatic** 10/30 (33) **MODS** 13/30 (43) **SIRS** 22/30 (73)

18. Harvey 2014	Adult patients admitted to a general ICU N=2400 Multi-centre	C.Random: Yes ITT: Yes Blinding: No (8)	EN vs PN	**ICU** 352/1197 (29.4) **Hospital** 450/1186 (37.9) **30-day** 409/1195 (34.2) **90-day** 464/1188 (39.1)	**ICU** 317/1190 (26.6) **Hospital** 431/1185 (36.4) **30-day** 393/1188 (33.1) **90-day** 442/1184 (37.3)	**Total infectious complications** 194/1197 (16.2)** **Infectious complications per pt** 0.21 +/- 0.5 **Pneumonia** 143/1197 (11.9) **Bloodstream inf** 21/1197 (1.8) **Surgical inf** 12/1197 (1.0)	**Total infectious complications** 194/1191 (16.3)** **Infectious complications per pt** 0.22 +/- 0.6 **Pneumonia** 135/1191 (11.3) **Bloodstream inf** 27/1191 (2.9) **Surgical inf** 10/1191 (0.8)
19. Xi 2014	ICU pts fasting at least 14 days, eligible for EN. Single Centre. N=45	C.Random: No ITT: Yes Blinding: No (7)	EN vs PN	**28-day** 0/22	**28-day** 0/23	**Positive blood cultures** 4/22 **Sepsis** 4/22 (17)	**Positive blood cultures** 0/23 **Sepsis** 5/23 (23)
20. Reignier 2017	Mechanically ventilated ICU pts receiving vasopressor support for shock. Multi-centre. N=2410	C.Random: Yes ITT: Yes Blinding: No (11)	EN vs PN	**ICU** 429/1202 (33) **Hospital** 498/1202 (36) **28-day** 443/1202 (37) **90-day** 530/1185 (45)	**ICU** 405/1208 (31) **Hospital** 479/1208 (34) **28-day** 422/1208 (35) **90-day** 507/1192 (43)	**ICU acquired** 173/1202 (14)	**ICU acquired** 194/1208 (16)
21. Chen 2019	Severe acute pancreatitis within 48 hrs admission Single centre N=140	C.Random: no ITT: yes Blinding: No (7)	EN vs PN EN via jejunostomy	**Not specified†** 10/70 (14.3%)	**Not specified †** 12/70 (17.1%)	NR	NR

C.Random: concealed randomization
* median/mean values, no standard deviation hence not included in meta-analysis
‡ refers to the # of patients with infections unless specified
** data on ICU patients/infections obtained directly from author

ITT: intent to treat
NR: not reported
† presumed hospital mortality unless otherwise specified

± ( ) : mean ± Standard deviation (number)
reported data pertaining to ICU patients only
NS = not statistically significant

Table 1. Randomized studies evaluating EN vs. PN in critically ill patients (continued)

Study	LOS days EN	LOS days PN	Ventilator days EN	Ventilator days PN	Cost EN	Cost PN	Other EN	Other PN
1. Rapp 1983	**Hospital** 49.4*	**Hospital** 52.6*	10.3*	10.4*	NR	NR	**Mean Calorie Intake (kcals) in study** 685 p=0.001 **Nitrogen Intake (gms)** 4.0 p=0.002 **N balance/24hrs, p=0.002** -17.6 **Hyperglycemia** no difference between groups	1750 10.2 -10.9
2) Adams 1986	**ICU** 13 ± 11 (19) **Hospital** 30 ± 21 (19)	**ICU** 10 ± 10 (17) **Hospital** 31 ± 29 (17)	12 ± 11 (17)	10 ± 10 (13)	$1346/day	$3729/day	**Calorie Intake (kcals) in study** 2088 p=NS **Caloric adequacy** 73% **N balance/24 hrs** -8.7+6.8 **Hyperglycemia (pt days)** 24/242 (10) **p<0.001** **Line Problems** 13/9 **Diarrhea (days/pt)** 3.5	2572 89% -4.1+4.6 49/220 (22) 9/7 3.8
3. Young 1987	NR	NR	NR	NR	NR	NR	**Calories ÷ BEE x 1.75** 59% $\pm$ 5.13% p=0.02 **Protein Intake (gm/kg/day)** 0.91 ± 0.09 p=0.004 **Favourable Neurological Outcome (3 months)** 17.9 % **Diarrhea** 23/28 (82)	75.6% $\pm$ 4.26% 1.35 ± 0.12 43.5 % 13/23 (57)

4. Peterson 1988	**ICU** 3.7 ± 0.8 (21) **Hospital** 13. 2 ± 1.6 (21)	**ICU** 4.6 ± 1.0 (25) **Hospital** 14.6 ± 1.9 (24)	NR	NR	NR	NR	**Day 5 Calorie Intake (kcals)** 2204 ± 173 2548 ± 85 P=0.04 **Day 5 Nitrogen Intake (gms)** 12.6 ± 1.0 14.8 ± 0.6
5. Cerra 1988	NR	NR	NR	NR	$228 ± 59 /day	$330 ± 61 /day	**NON PROTEIN Calorie Intake** 1684 ± 573 2000 ± 20 p=NS **Protein g/d** 80±26 88±20 **N-balance/d** -3.4±10 0.4±3.8 **MOSF** 7/31 (23) 7/35 (20) **Diarrhea** 25/31 (81) 9/35 (26) **Vomiting** 10/31 (32) 10/35 (6)
6. Moore 1989	NR	NR	NR	NR	NR	NR	**Non-protein Calorie Intake, day 5** 1847 ± 123 2261 ± 60 p=0.01 **Nitrogen intake, day 5, p=0.01** 12.4±0.8 15.4±0.4 **N balance, day 5, p=NS** -0.3±0.1 0.1±0.8 **Blood Sugars** no difference between the groups **Non-septic Complications** 6/29 (21) 7/30 (23)
7. Kudsk 1992	**Hospital** 20.5 ± 19.9 (51)	**Hospital** 19.6 ± 18.8 (45)	2.8 ± 4.9 (51)	3.2 ± 6.7 (45)	NR	NR	**NON PROTEIN Calorie Intake (kcal/kg/day)** 15.7 ± 4.2 19.1 ± 3.3 p<0.05 **Diarrhea** 11/51 (22) 7/45 (16)

8. Dunham 1994	NR	NR	NR	NR	NR	NR	**Calorie Intake** no difference between the groups **Protein Intake** no difference between the groups **Nutrition-related Complications** 3/12 (25) 2/15 (13)
9. Borzotta 1994	**Hospital (assumed)** 39 ± 23.1	**Hospital (assumed)** 36.9 ± 14	NR	NR	$121,941	$112,450	**Calorie Intake** no difference between the groups **Placement Complications** 3/28 (11) 0/21 (0) **Aspiration** 3/28 (11) 0/21 (0) **Hyperglycemia** 12/28 (44) 16/21 (76) P=<0.05 **Diarrhea** 30% 62%
10. Hadfield 1995	NR	NR	NR	NR	NR	NR	NR
11. Kalfarentzos 1997	**ICU** 11 (5-21) * **Hospital** 40 (25-83) *	**ICU** 12 (5-24) * **Hospital** 39 (22-73) *	15 (6-16) *	11 (7-31) *	£70/day savings	NR	**Non-protein Calorie Intake (kcal/kg/day)** 24.1 24.5 p=NS **Protein Intake (gm/kg/day)** 1.43 1.45 p=NS **Hyperglycemia** 4/18 (22) 9/20 (45) p=NR
12. Woodcock 2001	33.2 ± 43 (16)	27.3 ± 18.7 (18)	NR	NR	NR	NR	**% Target Intake Achieved** 54.1% 96.7% p<0.001 **< 80% Target Intake** 62.5% 6.3% p<0.001
13. Casas 2007	**Hospital** 30.2 (average)	**Hospital** 30.7 (average)	NR	NR	NR	NR	**Kcal/kg/d, p=ns, n=11 in both groups** 20.09±1.83 20.8±1.68 P=NS **Nitrogen g/kg/d, p<0.005** 0.148±0.016 0.186±0.009

14. Chen 2011	**ICU** 9.09 ± 2.75 **Hospital** 23.32 ± 5.6	**ICU** 9.60 ± 3.06 **Hospital** 22.24 ± 3.27	7.95 ± 2.11	8.23 ± 2.42	NR	NR	**Non-infectious Complications** 10/49 (20) 21/49 (43) **Gastric Residuals** 6/49 (12) 0/49 (0) **Diarrhea** 6/49 (12) 8/49 (16)
15. Meirelles 2011	**ICU** 14 (5-26)	**ICU** 14 (6-24)	NR	NR	NR	NR	**Kcal over 5 days** 5958 +/- 3619 6586 +/- 1052 P=0.34 **Mean daily N-balance, p=0.34** -4.6g/day -5.9g/day **Blood Glucose (mg/dl)** 102.4 (91.6 – 113.2) 134.4 (122.6-146.2) p < 0.0111
16. Wang 2013	NR	NR	NR	NR	NR	NR	NR
17. Sun 2013	**ICU** 9 (5-14)	**ICU** 12 (8-21)	NR	NR	NR	NR	NR

18. Harvey 2014	**ICU** 11.3 + 12,5 (1197) **Hospital** 26.8 + 33.2 (1186)	**ICU** 12 + 13.5 (1190) **Hospital** 27.5 + 33.9 (1185)	8.2 + 9.3 (1197)	8.7 + 11,5 (1189)	Cost effectiveness at 1 year 26775± 26273 £ (1197)	Cost-effectiveness at 1 year 28354± 32144 £ (1191)	**Vomiting** 1/1197 (0.1) 1/1197 (0.1) **Aspiration/Regurgitation** 4/1197 (0.3) 2/1191 (0.2) **Diarrhea** 250/1197 (21) 192/1191 (16.2) **Total kcal received during intervention period (kcal/kg)** 74 + 44 89 + 44 P=NR **Total protein received during intervention period (g/kg)** 3 + 2 3 + 2 EQ-5D-5L Mobility among survivors (no problems) 172/473 (37) 166/467 (36) EQ-5D-5L Self-care among survivors (no problems) 287/473 (61) 280/467 (61) EQ-5D-5L Usual Activities among survivors (no problems) 163/473 (34) 151/467 (32) EQ-5D-5L Pain/Discomfort among survivors (no problems) 159/473 (34) 145/467 (31) EQ-5D-5L Anxiety/Depression among survivors (no problems) 235/473 (50) 218/467 (47) EQ-5D-5L utility score (survivors) (imputated) 0.683±0.292 (1197) 0.684±0.285 (1191) Quality adjusted life years at 1 year (imputated) 0.335±0.332 (1197) 0.348±0.333 (1191)

19. Xi 2014	**ICU** 8.52 + 3.6 (22) **Hospital** 20.43 + 10.49 (22)	**ICU** 20.33 + 4.47 (23) **Hospital** 38.76 + 15.04 (23)	2.96 + 1.74 (22)	8.62 + 3.6 (23)	**Hospital cost x 10^4** 1.45 + 0.25	**Hospital cost x 10^4** 3.47 + 0.69	NR
20. Reignier 2017	**ICU** 9.0 (5.0-16.0) 13.7+16.1** N=1201 **Hospital** 17.0 (8.0-32.0) 25.1+28.4** N=1202	**ICU** 10.0 (5.0-17.0) 13.7+13.9** N=1207 **Hospital** 18.0 (9.0-33.0) 25.9+27.0** N=1208	10.7+14.4** N=1201	10.9+12.6** N=1207	NR	NR	**Diarrhea** 432/1202 (36) 393/1208 (33) **Kcal/kg/d** 17.8 + 5.5 19.6 + 5.3 P<0.0001 **Protein g/kg/d** 0.7 + 0.2 0.8 + 0.2 P<0.0001
21) Chen 2019	**Hospital** 16.09 ± 1.64	**Hospital** 27.16 ± 4.25	NR	NR	NR	NR	**Total Protein level** significantly higher increases in EN vs PN p=0.032 **Albumin levels** significantly higher increases in EN vs PN p=0.028

C.Random: concealed randomization; ITT: intent to treat
± ( ) : mean ± Standard deviation (number)
* median/mean values, no standard deviation hence not included in meta-analysis
NR: not reported reported data pertaining to ICU patients only
‡ refers to the # of patients with infections unless specified
† presumed hospital mortality unless otherwise specified
NS = not statistically significant
** data obtained directly from authors

Figure 1. Studies comparing EN vs PN: Overall Mortality

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 Mortality (PN>EN kcal)							
Rapp 1983	9	18	3	20	0.4%	3.33 [1.07, 10.43]	1983
Young 1987	10	28	10	23	1.2%	0.82 [0.42, 1.62]	1987
Kudsk 1992	1	51	1	45	0.1%	0.88 [0.06, 13.70]	1992
Woodcock 2001	9	17	5	21	0.7%	2.22 [0.92, 5.40]	2001
Chen 2011	11	49	10	49	1.0%	1.10 [0.51, 2.35]	2011
Reignier 2017	498	1202	479	1208	49.7%	1.04 [0.95, 1.15]	2017
Subtotal (95% CI)		**1365**		**1366**	**53.2%**	**1.19 [0.86, 1.64]**	
Total events	538		508				
Heterogeneity: Tau² = 0.05; Chi² = 7.22, df = 5 (P = 0.20); I² = 31%							
Test for overall effect: Z = 1.04 (P = 0.30)							
1.2.2 Mortality (PN~EN kcal)							
Adams 1986	1	23	3	23	0.1%	0.33 [0.04, 2.97]	1986
Borzotta 1994	5	28	1	21	0.1%	3.75 [0.47, 29.75]	1994
Dunham 1994	1	12	1	15	0.1%	1.25 [0.09, 17.98]	1994
Hadfield 1995	2	13	6	11	0.3%	0.28 [0.07, 1.13]	1995
Kalfarentzos 1997	1	18	2	20	0.1%	0.56 [0.05, 5.62]	1997
Cerra 1988	7	31	8	35	0.7%	0.99 [0.40, 2.41]	1998
Casas 2007	0	11	2	11	0.1%	0.20 [0.01, 3.74]	2007
Meirelles 2011	1	12	1	10	0.1%	0.83 [0.06, 11.70]	2011
Sun 2013	2	30	1	30	0.1%	2.00 [0.19, 20.90]	2013
Wang 2013	3	61	7	60	0.3%	0.42 [0.11, 1.55]	2013
Harvey 2014	450	1186	431	1185	43.7%	1.04 [0.94, 1.16]	2014
Xi 2014	0	22	0	23		Not estimable	2014
Chen 2019	10	70	12	70	1.0%	0.83 [0.39, 1.80]	2019
Subtotal (95% CI)		**1517**		**1514**	**46.8%**	**1.02 [0.92, 1.13]**	
Total events	483		475				
Heterogeneity: Tau² = 0.00; Chi² = 9.88, df = 11 (P = 0.54); I² = 0%							
Test for overall effect: Z = 0.45 (P = 0.65)							
Total (95% CI)		**2882**		**2880**	**100.0%**	**1.04 [0.97, 1.12]**	
Total events	1021		983				
Heterogeneity: Tau² = 0.00; Chi² = 17.27, df = 17 (P = 0.44); I² = 2%							
Test for overall effect: Z = 1.05 (P = 0.29)							
Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%							

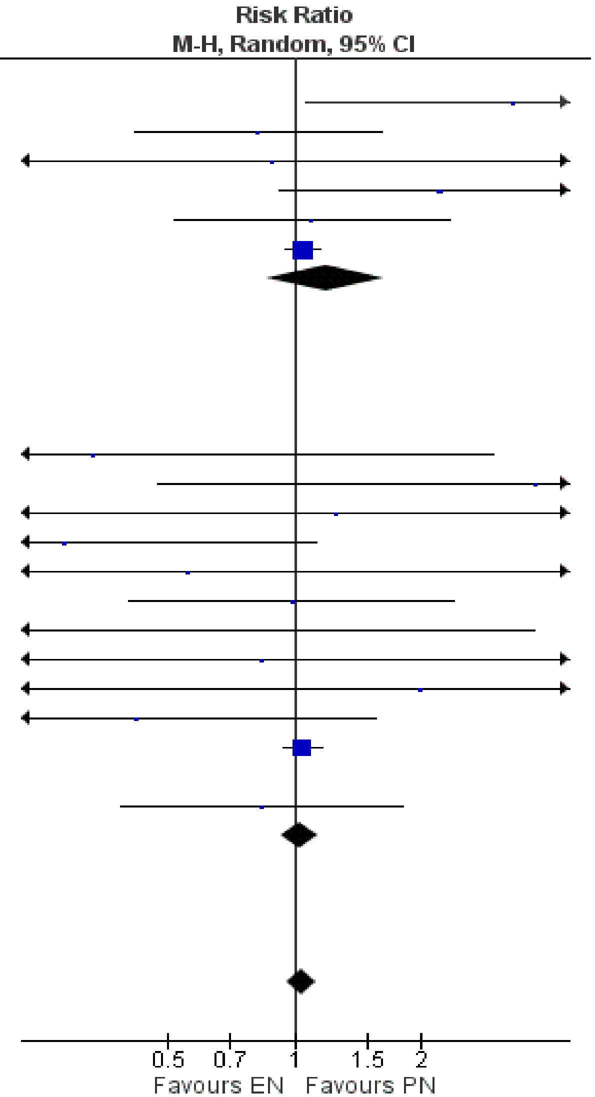


Figure 2. Overall mortality in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Adams	1	23	3	23	27.1%	0.33 [0.04, 2.97]	1986
Borzotta	5	28	1	21	30.2%	3.75 [0.47, 29.75]	1994
Kalfarentzos	1	18	2	20	24.2%	0.56 [0.05, 5.62]	1997
Meirelles	1	12	1	10	18.6%	0.83 [0.06, 11.70]	2011
Total (95% CI)		**81**		**74**	**100.0%**	**0.93 [0.30, 2.90]**	
Total events	8		7				

Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

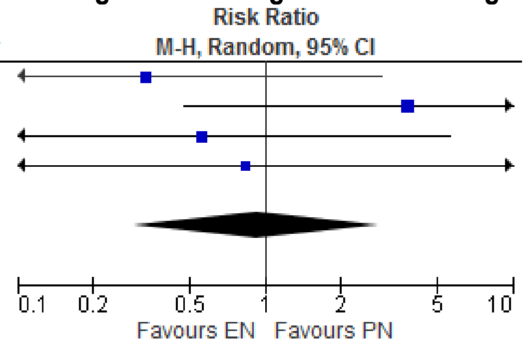


Figure 3. ICU Mortality

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.19.1 Mortality (PN>EN kcal)							
Kudsk	1	51	1	45	0.1%	0.88 [0.06, 13.70]	1992
Reignier	498	1202	479	1208	53.4%	1.04 [0.95, 1.15]	2017
Subtotal (95% CI)		**1253**		**1253**	**53.5%**	**1.04 [0.95, 1.15]**	
Total events	499		480				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%							
Test for overall effect: Z = 0.89 (P = 0.38)							
1.19.2 Mortality (PN~EN kcal)							
Hadfield	2	13	6	11	0.3%	0.28 [0.07, 1.13]	1995
Kalfarentzos	1	18	2	20	0.1%	0.56 [0.05, 5.62]	1997
Cerra	7	31	8	35	0.6%	0.99 [0.40, 2.41]	1998
Harvey	450	1186	431	1185	45.6%	1.04 [0.94, 1.16]	2014
Subtotal (95% CI)		**1248**		**1251**	**46.5%**	**0.93 [0.63, 1.36]**	
Total events	460		447				
Heterogeneity: Tau² = 0.05; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%							
Test for overall effect: Z = 0.38 (P = 0.71)							
Total (95% CI)		**2501**		**2504**	**100.0%**	**1.04 [0.97, 1.12]**	
Total events	959		927				

Heterogeneity: Tau² = 0.00; Chi² = 3.74, df = 5 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%

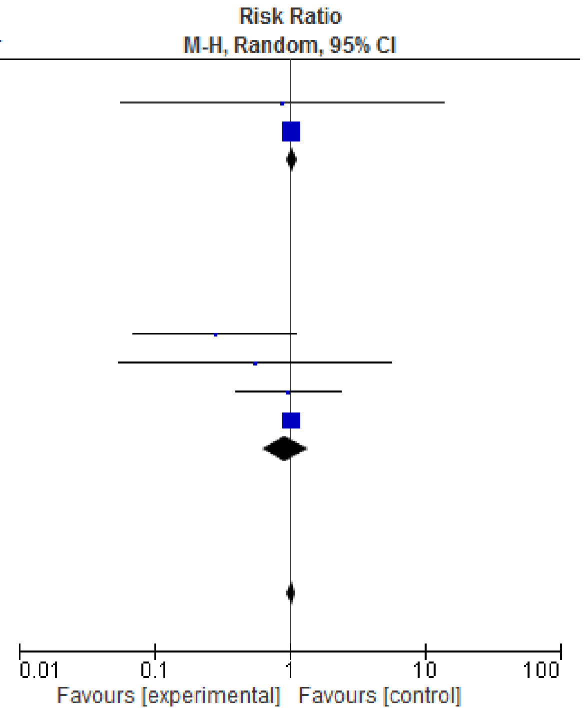


Figure 4. Studies comparing EN vs PN: Infectious complications

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Infections (PN>EN kcal)							
Young	5	28	4	23	2.9%	1.03 [0.31, 3.39]	1987
Peterson	2	21	8	25	2.1%	0.30 [0.07, 1.25]	1988
Moore	5	29	11	30	4.6%	0.47 [0.19, 1.19]	1989
Kudsk	9	51	18	45	7.3%	0.44 [0.22, 0.88]	1992
Woodcock	6	16	11	21	6.4%	0.72 [0.34, 1.52]	2001
Chen	5	49	18	49	4.7%	0.28 [0.11, 0.69]	2011
Reignier	173	1202	194	1208	24.2%	0.90 [0.74, 1.08]	2017
Subtotal (95% CI)		**1396**		**1401**	**52.2%**	**0.58 [0.39, 0.88]**	
Total events	205		264				
Heterogeneity: Tau² = 0.14; Chi² = 12.77, df = 6 (P = 0.05); I² = 53%							
Test for overall effect: Z = 2.60 (P = 0.009)							
1.1.2 Infections (PN~EN kcal)							
Adams	15	23	17	23	15.2%	0.88 [0.60, 1.30]	1986
Kalfarentzos	5	18	10	20	5.1%	0.56 [0.23, 1.32]	1997
Casas	1	11	3	11	1.0%	0.33 [0.04, 2.73]	2007
Justo Meirelles	2	12	4	10	2.0%	0.42 [0.10, 1.82]	2011
Harvey	194	1197	194	1191	24.5%	0.99 [0.83, 1.19]	2014
Subtotal (95% CI)		**1261**		**1255**	**47.8%**	**0.94 [0.80, 1.10]**	
Total events	217		228				
Heterogeneity: Tau² = 0.00; Chi² = 4.02, df = 4 (P = 0.40); I² = 0%							
Test for overall effect: Z = 0.77 (P = 0.44)							
Total (95% CI)		**2657**		**2656**	**100.0%**	**0.74 [0.59, 0.91]**	
Total events	422		492				
Heterogeneity: Tau² = 0.04; Chi² = 18.91, df = 11 (P = 0.06); I² = 42%							
Test for overall effect: Z = 2.79 (P = 0.005)							
Test for subgroup differences: Chi² = 4.53, df = 1 (P = 0.03), I² = 77.9%							

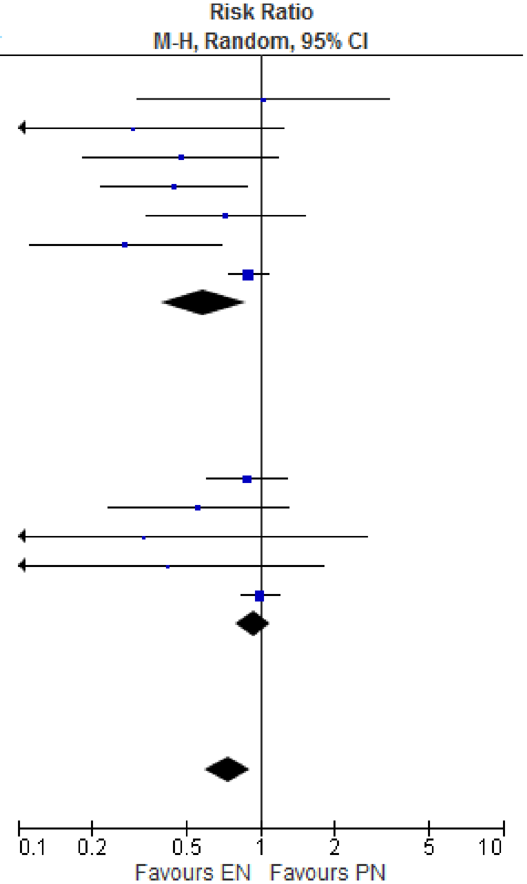


Figure 5. Infections in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Adams	15	23	17	23	79.0%	0.88 [0.60, 1.30]	1986
Kalfarentzos	5	18	10	20	15.7%	0.56 [0.23, 1.32]	1997
Meirelles	2	12	4	10	5.4%	0.42 [0.10, 1.82]	2011
Total (95% CI)		**53**		**53**	**100.0%**	**0.79 [0.56, 1.11]**	
Total events	22		31				

Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.17)

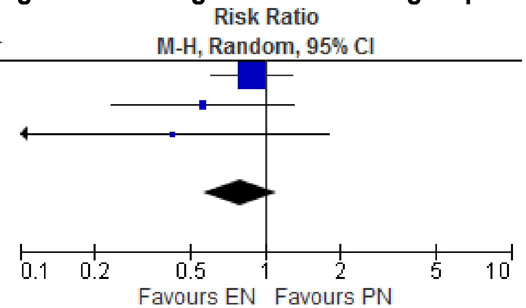


Figure 6. Hospital LOS

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.3.1 Hospital LOS (PN>EN kcal)									
Peterson 1988	13.2	1.6	21	14.6	1.9	21	13.5%	-1.40 [-2.46, -0.34]	1988
Kudsk 1992	20.5	19.9	51	19.6	18.8	45	9.4%	0.90 [-6.85, 8.65]	1992
Woodcock 2001	33.2	43	16	27.3	18.7	18	2.8%	5.90 [-16.87, 28.67]	2001
Chen 2011	23.32	5.6	49	22.24	3.27	49	13.2%	1.08 [-0.74, 2.90]	2011
Reignier 2017	25.1	28.4	1202	25.9	27	1208	13.1%	-0.80 [-3.01, 1.41]	2017
Subtotal (95% CI)			**1339**			**1341**	**52.1%**	**-0.47 [-1.75, 0.81]**	
Heterogeneity: Tau² = 0.63; Chi² = 5.84, df = 4 (P = 0.21); I² = 32%									
Test for overall effect: Z = 0.72 (P = 0.47)									
1.3.2 Hospital LOS (PN~EN kcal)									
Adams 1986	30	21	19	31	29	17	4.5%	-1.00 [-17.71, 15.71]	1986
Borzotta 1994	39	23.1	28	36.9	14	21	7.6%	2.10 [-8.34, 12.54]	1994
Harvey 2014	26.8	33.2	1186	27.5	33.9	1185	12.9%	-0.70 [-3.40, 2.00]	2014
Xi 2014	20.43	10.49	22	38.76	15.04	23	9.6%	-18.33 [-25.88, -10.78]	2014
Chen 2019	16.09	1.64	70	27.16	4.25	70	13.5%	-11.07 [-12.14, -10.00]	2019
Subtotal (95% CI)			**1325**			**1316**	**47.9%**	**-6.59 [-13.74, 0.56]**	
Heterogeneity: Tau² = 50.29; Chi² = 59.95, df = 4 (P < 0.00001); I² = 93%									
Test for overall effect: Z = 1.81 (P = 0.07)									
Total (95% CI)			**2664**			**2657**	**100.0%**	**-3.12 [-7.43, 1.19]**	

Heterogeneity: Tau² = 35.63; Chi² = 250.18, df = 9 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Chi² = 2.72, df = 1 (P = 0.10), I² = 63.3%

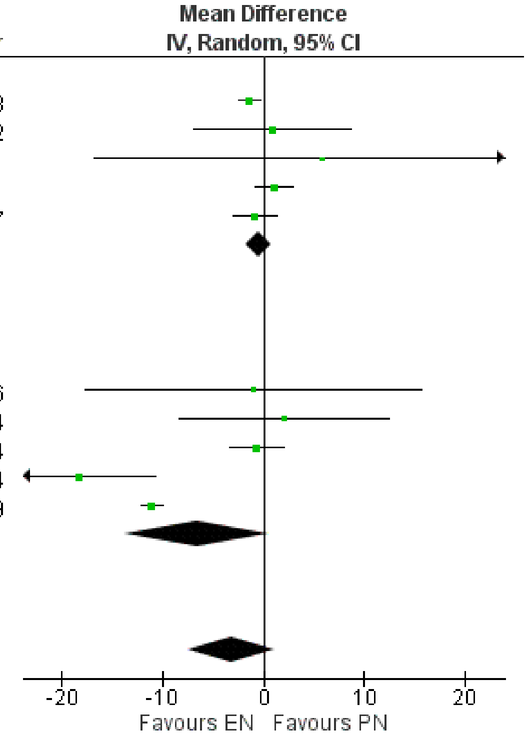


Figure 7. ICU LOS

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.6.1 ICU LOS (PN>EN)									
Peterson	3.7	0.8	21	4.6	1	25	20.1%	-0.90 [-1.42, -0.38]	1988
Chen	9.09	2.75	49	9.6	3.06	49	19.1%	-0.51 [-1.66, 0.64]	2011
Reignier	13.7	16.1	1201	13.7	13.9	1207	19.0%	0.00 [-1.20, 1.20]	2017
Subtotal (95% CI)			**1271**			**1281**	**58.2%**	**-0.72 [-1.16, -0.28]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 2 (P = 0.37); I² = 0%									
Test for overall effect: Z = 3.21 (P = 0.001)									
1.6.2 ICU LOS (PN~EN kcal)									
Adams	13	11	19	10	10	17	6.3%	3.00 [-3.86, 9.86]	1986
Xi	8.52	3.6	22	20.33	4.47	23	16.1%	-11.81 [-14.18, -9.44]	2014
Harvey	11.3	12.5	1197	12	13.5	1190	19.3%	-0.70 [-1.74, 0.34]	2014
Subtotal (95% CI)			**1238**			**1230**	**41.8%**	**-3.50 [-12.23, 5.24]**	
Heterogeneity: Tau² = 55.42; Chi² = 73.31, df = 2 (P < 0.00001); I² = 97%									
Test for overall effect: Z = 0.78 (P = 0.43)									
Total (95% CI)			**2509**			**2511**	**100.0%**	**-2.12 [-4.20, -0.04]**	
Heterogeneity: Tau² = 5.54; Chi² = 85.27, df = 5 (P < 0.00001); I² = 94%									
Test for overall effect: Z = 2.00 (P = 0.05)									
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%									

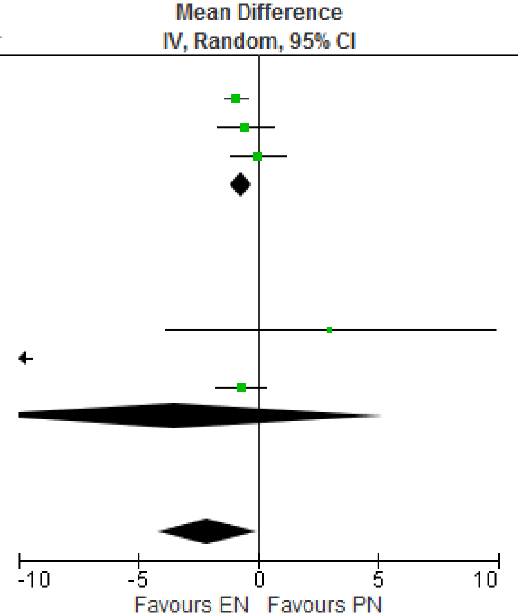
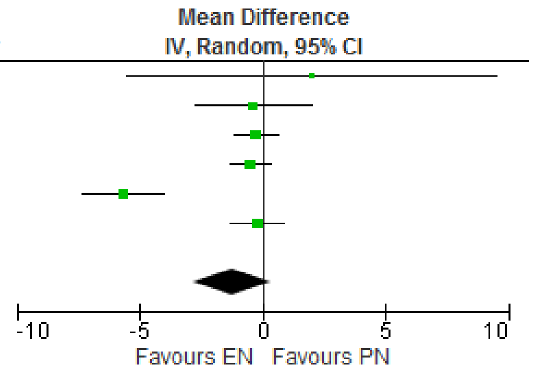


Figure 8. Mechanical Ventilation

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Adams	12	11	17	10	10	13	3.6%	2.00 [-5.54, 9.54]	1986
Kudsk	2.8	4.9	51	3.2	6.7	45	15.0%	-0.40 [-2.77, 1.97]	1992
Chen	7.95	2.11	49	8.23	2.42	49	21.2%	-0.28 [-1.18, 0.62]	2011
Harvey	8.2	9.3	1197	8.7	11.5	1189	21.4%	-0.50 [-1.34, 0.34]	2014
Xi	2.96	1.74	22	8.62	3.6	23	18.2%	-5.66 [-7.30, -4.02]	2014
Reignier	10.7	14.4	1201	10.9	12.6	1207	20.6%	-0.20 [-1.28, 0.88]	2017
Total (95% CI)			**2537**			**2526**	**100.0%**	**-1.23 [-2.80, 0.34]**	
Heterogeneity: Tau² = 2.81; Chi² = 37.28, df = 5 (P < 0.00001); I² = 87%									
Test for overall effect: Z = 1.53 (P = 0.13)									



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