9.2 Composition of Parenteral Nutrition: Type of lipids

Question: Does the type of lipids in parenteral nutrition affect outcomes in the critically ill adult patient?

Summary of evidence: There were 14 level 2 studies (Nijveldt 1998, Garnacho-Montero 2002, Iovinelli 2007, Wang 2009, Huschak 2005, Garcia de Lorenzo 2005, Guo 2008, Qu 2009, Zhao 2011, Pontes-Arruda 2012, Burkhart 2013, Gultekin 2014, Hall 2014 and Chen 2017) and 8 level 1 studies (Lindgren 2001, Grecu 2003, Friesecke 2008, Barbosa 2010, Gupta 2011, Khor 2011, Umperrez 2012 & Grau Carmona 2014) reviewed. For most of the studies, the focus of the investigation was on surrogate endpoints but the studies were still included because they did report on mortality or infections. Fourteen studies compared varying strategies of reducing omega-6 fatty acids to LCTs. Four of these studies compared LCTs plus medium chain triglycerides (MCT) to a LCT emulsion (Nijveldt 1998, Lindgren 2001, Garnacho-Montero 2002 and Iovinelli 2007); 1 study compared LCT + MCT + fish oil emulsion (Lipoplus) to a MCT + LCT emulsion (Barbosa 2010); 7 studies compared a fish oil containing emulsion mixed with LCT or LCT/MCT to a LCT or LCT+MCT mixture (Grecu 2003, Friesecke 2008, Guo 2008, Wang 2009, Grau Carmona 2014, Gultekin 2014 and Chen 2017) while 4 studies compared an olive oil containing emulsion (Clinoleic) to a LCT + MCT mixture (Garcia de-Lorenzo 2005, Huschak 2005, Umperezz 2012 & Pontes-Arruda 2012). One study that compared an outdated long chain triglyceride (LCT) emulsion to another form of LCT (Kari 1998) was removed in the 2013 CPGs as it did not involve a soybean oil reducing strategy. The Wang 2008 study was replaced by a later version of the study by the same authors that had more patients i.e. Wang 2009. All of the studies had a goal of reducing the amount of omega-6 fatty acids in the setting of PN use. PN with soy bean emulsions were used as the control solution with the exception of 6 studies that compared supplementation with intravenous fish oil emulsion to a control group that received no IV soybean oil (no lipids at all). Therefore a sensitivity analysis was completed with these studies being included and excluded (Qu 2009, Gupta 2011, Khor 2011, Zhao 2011, Burkhart 2013 and Hall 2014).

Mortality:
Overall omega-6 fatty acid reducing strategy: When all the studies that used an omega-6 fatty acid sparing strategy were aggregated, the use of a lower omega-6 fatty acid strategy had no effect on mortality (RR 0.92, 95% CI 0.73, 1.14, p = 0.43, heterogeneity I^2=0%; figure 1.1). When the studies in which the control group received no IV soybean oil were included, there was a trend towards a reduction in mortality in the fish oil group (RR 0.90, 95% CI 0.73, 1.06, p=0.17; figure 1.2).
LCT + MCT vs LCT: A meta-analysis of the studies of LCT+ MCT vs. LCT showed no difference in mortality between the groups (RR 0.84, 95 % CI 0.43, 1.61, p=0.59, heterogeneity I^2=0%; figure 1.1).
Fish Oils vs LCT or LCT + MCT: With respect to studies of fish oil containing emulsions vs. LCT or LCT+ MCT, there was no difference in mortality observed (RR 0.94, 95% CI 0.71, 1.24, p = 0.64, heterogeneity I^2=2%; figure 1.1). When the studies in which the control group received no IV soybean oil were included, this lack of an effect on mortality remained (p=0.24; figure 1.2).
Olive Oil vs LCT+MCT: No difference between the groups receiving the olive oil containing emulsions vs. LCT + MCT (RR 0.90, 95% CI 0.58, 1.39, p = 0.62, heterogeneity I^2=0%; figure 1.1) was observed.

Infections:
Overall omega-6 fatty acid reducing strategy: When all 6 studies that used a LCT (omega-6 fatty acid) sparing strategy were aggregated, the use of a lower LCT emulsion had no effect on infections (RR 0.95, 95% CI 0.69, 1.29, p = 0.73, heterogeneity I^2=39%; figure 1.3). As well, no effect was observed when including the study in which the control group received no IV soybean oil (p=0.63; figure 1.4).
LCT + MCT vs LCT: One study comparing LCT + MCT to MCT reported no differences in the incidences of new infections or positive blood cultures between the groups, however no data was reported (level 1 study Nijveldt 1998). In another study, a higher incidence of infections was observed in the intervention group (Lindgren 2001).
Fish Oils vs LCT or LCT + MCT: When the data from the 3 studies of fish oil emulsions vs. LCT or LCT+ MCT in PN fed patients were aggregated, there was a significant effect on reduction of infectious complications in the fish oil group (RR 0.65, 95% CI 0.44, 0.96, p = 0.03, heterogeneity I^2=0%; figure 1.3). When including the study in which the control group received no IV soybean oil, a similar effect was seen (p=0.02; figure 1.4).
Olive Oil vs LCT+MCT: When the data from the 3 studies of olive oil emulsions in PN fed patients were aggregated, there was a trend towards an increase in infections in the olive oil group (RR1.23, 95% CI 0.92, 1.63, p=0.16, heterogeneity I^2=0%, p=0.80; figure 1.3).

Hospital LOS:
Overall omega-6 fatty acid reducing strategy: When the 5 studies that used a LCT (omega-6 fatty acid) sparing strategy were aggregated, the use of a lower LCT emulsion was associated with a trend towards a reduction in hospital LOS when compared to LCT (WMD -5.99, 95% CI -13.68, 1.69, p = 0.13, heterogeneity I^2=89%; figure 1.5). The same trend was seen when including the studies in which the control group received no IV soybean oil (p=0.12; figure 1.6).
LCT + MCT vs LCT: No studies reported on hospital LOS.
Fish Oils vs LCT or LCT + MCT: When the data from the three studies of fish oil emulsions vs LCT+MCT or LCT that reported on this outcome were aggregated, no effect on hospital LOS was observed (WMD -5.87, 95% CI -15.27, 3.53, p =0.22, heterogeneity I^2= 94%; figure 1.5). A trend towards a reduction in hospital LOS was observed when including the studies in which the control group received no IV soybean oil (p=0.19; figure 1.6).
Olive Oil vs LCT+MCT: When the data from the two studies of olive oil emulsions were aggregated, olive oil emulsions had no effect on hospital length of stay (\WMD -6.79, 95% CI -13.68, 1.69, p = 0.13, heterogeneity I^2= 0%; figure 1.5).

ICU LOS
Overall omega-6 fatty acid reducing strategy: When all the studies that used a LCT (omega-6 fatty acid) sparing strategy were aggregated, the use of a lower LCT emulsion was associated with a significant reduction in ICU LOS (WMD -3.14, 95%CI -5.78, -0.50, p=0.02, heterogeneity I^2=77%; figure 1.7). The same significance was seen when including the studies in which the control group received no IV soybean oil (p=0.003; figure 1.8).
LCT + MCT vs LCT: When the data from the two studies comparing LCT+MCT to LCT were aggregated, there were no differences in ICU LOS between the two groups (WMD -1.46, 95 % CI -5.77, 2.85, p=0.51, heterogeneity I^2=78%; figure 1.7).

Fish Oils vs LCT or LCT + MCT: When the data from the five studies of fish oil emulsions vs LCT+MCT or LCT were aggregated, a significant reduction in ICU LOS was observed in the fish oil group (WMD -3.98, 95% CI -7.31, -0.64, p=0.02, heterogeneity I^2=72%; figure 1.7). A significant effect was also observed on ICU LOS when including the studies in which the control group received no IV soybean oil (p=0.01; figure 1.8).
Olive Oil vs LCT+MCT: When the data from the three studies of olive oil emulsions vs LCT+MCT to LCT were aggregated, olive oil emulsions had no effect on ICU length of stay (WMD -4.08, 95 % CI -10.97, 2.81, p=0.25, heterogeneity I^2=59%; figure 1.7).

Ventilator days:
Overall omega-6 fatty acid reducing strategy: LCT (omega-6 fatty acid) sparing strategies were associated with a trend towards a reduction in duration of ventilation, compared to LCT (WMD -2.57, 95% CI -5.51, 0.37, p =0.09, heterogeneity I^2=25%; figure 1.9). A trend was also observed when including the studies in which the control group received no IV soybean oil (p=0.10; figure 1.10).
LCT + MCT vs LCT: Only one study comparing LCT+MCT to LCT reported duration of ventilation and no significant differences were seen between the two groups (Iovinelli 2007).
Fish Oils vs LCT or LCT + MCT: When the data from the three studies of fish oils vs LCT+MCT or LCT were aggregated, there was a trend towards a reduction in the duration of mechanical ventilation (WMD -1.81, 95% CI -3.98, 0.36, p=0.10, heterogeneity I^2= 0%; figure 1.9.1). A trend was also observed when including the studies in which the control group received no IV soybean oil (p=0.17; figure 1.10.1).
Olive Oil vs LCT+MCT: The use of olive oil emulsions was associated with a significant reduction in the duration of mechanical ventilation (WMD -6.47, 95% CI -11.41, -1.53, p=0.01, heterogeneity I^2=0%; figure 1.9.2).

Other complications:
LCT + MCT vs LCT: A significant improvement in nutritional parameters (i.e. nitrogen balance, retinol binding protein, prealbumin) was observed in the groups receiving LCT + MCT in some of the studies (Garnacho-Montero, Lindgren) and a significant reduction in the time of weaning was seen in one study (Iovinellei 2007).
Fish Oils in PN fed patients vs LCT or LCT + MCT: The use of Omegaven was associated with a reduction in the need for surgery due to a subsequent septic episode when compared to LCT (p=0.010, Grecu 2003). Wang 2009 reported a reduction in the need for surgery for pancreatic necrosis in the group receiving fish oils but this was not statistically different. There was a trend towards a reduction in catheter related blood stream infections in the group receiving fish oils (p=0.10, Friesecke 2008) and better gas exchange (Barbosa 2010).
Olive Oil vs LCT+MCT: The use of olive oil emulsions was associated with better liver function (Garcia de Lorenzo 2005), lower blood sugars & carbon dioxide production (p =0.03 Huschak 2005).

Conclusions:
1) LCT reducing strategies, also known as soybean oil sparing strategies, have no effect on mortality or infections in critically ill adults.
2) LCT reducing strategies may be associated with a reduction in hospital LOS and duration of ventilation.
3) LCT reducing strategies are associated with a reduction in ICU LOS.
4) LCT + MCT emulsions, compared to LCT, have no effect on mortality or ICU length of stay in critically ill patients.
5) IV fish oils/fish oil containing emulsions vs LCT + MCT or LCT (or vs no IV soybean oil) have no effect on mortality or hospital LOS.

6) IV fish oils/fish oil containing emulsions vs LCT + MCT or LCT (or vs no IV soybean oil) are associated with a reduction in infections and ICU LOS.
7) IV fish oils/fish oil containing emulsions vs LCT + MCT or LCT (or vs no IV soybean oil) may be associated with a reduction in duration of ventilation.
8) Olive Oil containing emulsions, compared to LCT, have no effect on mortality or ICU/hospital LOS.
9) Olive Oil containing emulsions, compared to LCT, may be associated with increased infections.
10) Olive Oil containing emulsions, compared to LCT, are associated with a reduction in duration of ventilation.

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 is unfulfilled.

Table 1. Randomized studies evaluating type of lipids (PN) in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
Long Chain Triglyceride (LCT) plus Medium Chain Triglycerides (MCT) vs. LCT							
1) Nijveldt 1998	ICU, septic surgical patients, trauma N=20	C.Random: not sure ITT: yes Blinding: double (10)	PN + Lipofundin (50% LCT+ 50% MCT) vs. PN + Intralipid (100% LCT, soybean)	LCT + MCT ICU 2/12 (17)	LCT ICU 1/8 (13)	LCT + MCT NR	LCT NR
2) Lindgren 2001	ICU patients, sepsis, multi-trauma N=30	C.Random: yes ITT: yes Blinding: double (12)	PN + Structolipid (64% LCT + 36% MCT) vs. PN + Intralipid (100% LCT, soybean)	LCT + MCT 1/15 (7)	LCT 0/15 (0)	LCT + MCT 6/15 (40)	LCT 4/15 (27)
3) Garnacho-Montero 2002	Surgical ICU Patients with peritonitis and abdominal sepsis N=72	C.Random: not sure ITT: no Blinding: no (6)	PN + Lipofundin (50% LCT + 50% MCT) vs. PN with Intralipid (100% LCT, soybean) Both groups received PN with 45 % Branched chain amino acids	LCT + MCT ICU 8/35 (23) Hospital 11/35 (31)	LCT ICU 11/37 (30) Hospital 13/37 (35)	LCT + MCT NR	LCT NR
4) Iovinelli 2007	Patients with COPD requiring ventilation N=24	C.Random: yes ITT: yes Blinding: no (7)	PN + Lipofundin (50% LCT + 50% MCT) vs. 100% LCT (100% LCT, soybean). In both received 50% of non-protein calories given as lipids	LCT + MCT ICU 2/12 (17)	LCT ICU 3/12 (25)	LCT + MCT Catheter-related 1/12 (8)	LCT Catheter-related 2/12 (17)
Fish oil (ω 3) containing emulsions in PN fed patients vs. LCT or LCT+MCT							
5) Grecu 2003*	Patients with abdominal sepsis N=54 (15/54 in ICU)	C.Random: yes ITT: yes Blinding: double (12)	PN + Omegaven (10% fish oils) plus LCTs vs. PN with LCT	Omegaven + LCT ICU 2/28 (7)	LCT ICU 3/26 (12)	Omegaven VAP 0/8	LCT VAP 1/7 (14)
6) Friesecke 2008	Medical ICU patients N=166	C.Random: yes ITT: yes Blinding: double (10)	PN + Lipofundin MCT (50% LCT + 50% MCT) + Omegaven (10% fish oil) vs. Lipofundin MCT (50% LCT + 50% MCT)	LCT+MCT+Fish oil 28 day 18/83 (22)	LCT+MCT 28 day 22/82 (27)	LCT+MCT+Fish oil 10/83 (12)	LCT + MCT 11/82 (13)
7) Guo 2008	Septic ICU patients with APACHE II > 12 N=88	C.Random: no ITT: no Blinding: no (4)	PN with 20% lipid emulsion with an added 100 ml of Omega-3 PUFAs vs PN with 20% lipid emulsion	Omega 3 28 day 6/38	No omega-3 28 day 8/42	NR	NR

8) Wang 2009	Severe acute pancreatitis patients in ICU N=56	C.Random: no ITT: yes Blinding: double (11)	PN + Omegaven (10% fish oils) plus Lipovenos (LCTs, soybean oil) (ω3:ω6 ratio was 1:4) vs. PN with Lipovenos (LCTs, soybean oil). Both received same amounts of lipids (1 gm/kg/day)	Omegaven ICU 0/28 (0)	LCT ICU 2/28 (7)	Omegaven 6/28 (21)	LCT 9/28 (32)
10) Barbosa 2010	ICU patients with SIRS or sepsis requiring PN N=25	C.Random: yes ITT: yes Blinding: single (10)	PN + Lipolus (50% MCT, 40% LCTs soybean oil, 10% fish oil) vs. Nutriflex LipidSpecial (50% MCT, 50% LCT, soybean oil). Both received same amounts of lipids (~1 gm/kg/day)	MCT+LCT+Fish oil 5 day 2/13 (15) 28 day 4/13 (31)	MCT+LCT 5 day 1/10 (10) 28 day 4/10 (40)	MCT+LCT+Fish oil NR	MCT+LCT NR
11) Grau Carmona 2014	Medical and surgical pts requiring TPN N=175	C.Random: yes ITT: yes Blinding: double (10)	PN + Lipoplus (50% MCT, 40% LCTs soybean oil, 10% fish oil) vs PN + Lipofundin (50% LCT + 50% MCT)	MCT+LCT+Fish oil ICU 26/81 (32.5) Hospital 6/81 (11.1) 6-month 2/81 (4.3)	MCT+LCT ICU 16/78 (20.5) Hospital 6/78 (9.7) 6-month 2/78 (3.6)	MCT+LCT+Fish oil 17/81 (21)	MCT+LCT 29/78 (37.2)
12) Gultekin 2014	ICU pts needing TPN N=58	C.Random: unknown ITT: other Blinding: double (3)	PN + 100ml/day Omegavan (10% fish oils) plus Clinoleic (80% olive oil, 20% soybean oil) vs PN + Clinoleic. Both groups were prescribed IV lipids to provide 30-40% of total energy requirements.	Omegaven + olive Unspecified 8/16 (50)	Olive Unspecified 7/16 (44)	NR	NR
13) Chen 2017	ICU patients with SIRS N=78	C.Random: unknown ITT: yes Blinding: single (7)	PN containing 50g LCFA + 100 m/day containing 10g refined fish oil vs PN containing 50g LCFA. Both groups dosed at 20 kcal/kg for first 7 days, clowly increased to 30 kcal/kg afterwards	LCT+Fish oil 28 day 10/41 60 day 11/41	LCT 28 day 15/37 60 day 18/37	NR	NR
Fish oil (ω 3) containing IV lipid emulsions in PN, EN or orally fed patients vs. no IV soybean oil							
9) Qu 2009	Severe sepsis patients N=40	C.Random: no ITT: no Blinding: no (5)	Routine PN + omega 3 fish oil emulsion at 1-2 ml/kg/d vs routine PN.	Omega 3 28 day 4/20 (20)	No omega-3 28 day 2/20 (1)	NR	NR
14) Gupta 2011	ICU patients with suspected ARDS N=61	C.Random: yes ITT: yes Blinding: double (9)	EN (standard diet) + Omegaven 10% (ω3:ω6 ratio was 1:4) vs EN (standard diet)	Omegaven ICU 7/31 (23) Hospital 9/31 (29)	Standard EN ICU 13/30 (43) Hospital 14/30 (47)	NR	NR
15) Khor 2011	ICU patients with severe sepsis/septic shock N = 28	C.Random: yes ITT: No Blinding: double (8)	EN and/or oral diet supplementated with 100 ml 10% Omegavan (10g refined fish oil, EPA 12.5-28.2 g/L, DHA 14.4-30.9 g/L) vs. 100 ml 0.9% normal saline + EN and/or oral diet	NR	NR	NR	NR
16) Zhao 2011	ICU patients with sepsis N=116	C.Random: no ITT: no Blinding:no	Omega-3 fish oil lipid emulsion (Omegavan), 100 ml qd for 5-7 days vs standard treatment	Omegaven ICU 8/56 (14)	Standard EN ICU 11/60 (18)	NR	NR

		(5)					
17) Burkhart 2013	ICU Septic patients N=50	C.Random: unknown ITT: yes Blinding: single (assessor) (8)	2 ml.kg/d Omegavan vs no parenteral fish oils. Both groups received EN and/or PN without added fish oils at the discretion of the clinician.	Omegavan Hospital 13/25 (52)	No Omegavan Hospital 13/25 (52)	NR	NR
18) Hall 2014	ICU Septic patients N=60	C.Random: ? ITT: yes Blinding: no (9)	Omegavan at 0.2 g fish oils /kg/d given at a rate of 0.05 g FO/kg/d vs no fish oils. In both group nutrition was assessed, by those patients requiring it, by the intensivists and dietitians who commenced oral, nasogastric (enteral), or parenteral nutrition as directed by the underlying pathology.	Omegavan Hospital 4/30 (13.3) 28 day 4/30 (13.3)	No Omegavan Hospital 9/30 (30) 28 day 8/30 (26.7)	Omegavan 3/30 (10)	No Omegavan 5/30 (16.7)
Olive oil containing emulsions vs. LCT or LCT+MCT							
19) Garcia-de-Lorenzo 2005	Severe burn patients, burn severity index ≥ 7, TBSA > 30 % N=22	C.Random: not sure ITT: yes Blinding: double (10)	PN with ClinOleic 20% (80% olive oil, 20% soybean oil, (63% ω9, 37% ω6= restricted linoleic acid {ω6} content) vs. Lipofundin (50% LCT+ 50% MCT).	Clinoleic ICU 4/11 (36)	Lipofundin ICU 4/11 (36)	Clinoleic 6/11 (55)	Lipofundin 6/11 (55)
20) Huschak 2005**	ICU trauma patients N=33	CRandom: yes ITT: yes Blinding: None (7)	PN high fat (lipid:glucose 75:25) + Clinoleic (80% olive oil, 20% soybean oil) + EN Glucerrna (lipid:glucose 60:40) vs. PN high carbohydrate (lipid: glucose 37:63) + Lipofundin (50% LCT + 50% MCT) + EN Fresubin HP Energy (lipid:glucose 44:56)	High fat + Clinoleic ICU 4/18 (22)	Low fat + LCT + MCT ICU 1/15 (7)	High fat + Clinoleic Low fat +LCT+MCT Data not reported. Text indicates that infections were less frequent in high fat group (intervention group).	
21) Pontes-Arruda 2012	ICU pts requiring PN from 8 ICUs and 3 countries N=204	C.Random: yes ITT: yes Blinding: no (9)	PN with ClinOleic (n=103) vs PN with a MCT/LCT based IVLE (n=101)	ClinOleic ICU 19/103 (24) 28-day 24/103 (27)	MCT/LCT ICU 21/101 (21) 28-day 26/101 (26)	ClinOleic MCT/LCT All infections 39/103 (38) 35/101 (35) ICU acquired infections 28/103 (27) 23/101 (23) VAP/lower respiratory infections 9/103 (9) 11/101 (11)	
22) Umperrez 2012	Medical surgical ICU pts post op (88% emergency surgeries) N=100	C.Random: yes ITT: yes Blinding: double (14)	PN with ClinOleic 20% (80% olive oil, 20% soybean oil, ω6:ω3=9:1) vs Intralipid (100% soybean oil, ω6:ω3=7:1)	Clinoleic Hospital 5/51 (10)	Intralipid Hospital 8/49 (16)	Clinoleic Intralipid 29/51 (57) 21/49 (43) Pneumonia 7/51 (14) 5/49 (10)	

Table 1. continued Randomized studies evaluating type of lipids (PN) in critically ill patients (continued)

Study	LOS days		Ventilator days		Other
Long Chain Triglyceride (LCT) plus Medium Chain Triglycerides (MCT) vs. LCT					
1) Nijveldt 1998	LCT + MCT 13.8 ± 2.9 (12)	LCT 17.4 ± 3.0 (8)	LCT + MCT NR	LCT NR	NR
2) Lindgren 2001	LCT + MCT NR	LCT NR	LCT + MCT NR	LCT NR	LCT + MCT LCT Adverse effects 5/15 (33) 4/15 (27) Nitrogen balance at day 3 2.6 ± 5.6 gms -11.7 ± 4.8 gms
3) Garnacho-Montero 2002	LCT + MCT ICU 16.6 ± 6.1 (35)	LCT ICU 15.8 ± 7 (37)	LCT + MCT NR	LCT NR	LCT + MCT LCT Retinol binding protein 1.7 ± 1 0.8 ± 0.6 Nitrogen balance 14.2 ± 2.9 11.6 ± 4
4) Iovinelli 2007	LCT + MCT NR	LCT NR	LCT + MCT 10.6 ± 3.0 (12)	LCT 13.4 ± 3.5 (12)	LCT + MCT LCT Time before weaning 52 ± 36 hrs 127 ± 73 hrs
Fish oil (ω 3) containing emulsions in PN fed patients vs. LCT or LCT+MCT					
5) Grecu 2003*	Omegaven ICU 3.32 ± 1.48 (8) Hospital 11.68 ± 2.04 (28)	LCT ICU 9.28 ± 3.08 (7) Hospital 20.46 ± 3.27 (26)	Omegaven 2.83 ± 1.62 (8)	LCT 5.23 ± 2.80 (7)	Omegaven LCT Patients undergoing reoperation for septic episode 2/28 (7) 8/26 (31)
6) Friesecke 2008	Fish oil ICU 28 ± 25 (83)	LCT ICU 23 ± 20 (82)	LCT + MCT + Fish oil 22.8 ± 22.9 (83)	LCT + MCT 20.5 ± 19.0 (82)	LCT + MCT + Fish oils LCT+MCT Urinary Tract Infections 6/83 (7) 4/82 (5) Catheter-related infections 1/83 (1) 3/83 (4) Total EN Energy Intake (kcal/kg) 22.2 ± 5.5 21.6 ± 5.6
7) Guo 2008	Omega 3 ICU 21.1±2.9	No omega-3 ICU 28.4±4.2	NR	NR	NR

8) Wang 2009	NR	NR	NR	NR	Omegaven LCT Surgery of infected pancreatic necrosis 3/28 (11) 6/28 (21)
10) Barbosa 2010	MCT+LCT+Fish oil ICU 12 ± 14.4[a] (13) Hospital 22 ± 25.2[a] (13)	MCT+LCT ICU 13 ± 12.6 [a] (10) Hospital 55 ± 50.6 [a] (10)	MCT+LCT+Fish oil 10 ± 14.4 (13)	MCT+LCT 11 ± 12.64 (10)	MCT+LCT+ Fish oil MCT+LCT 2057± 418 kcals 1857 ± 255 kcals
11) Grau Carmona 2014	MCT+LCT+Fish oil ICU 18.9±15.5 (81) Hospital 41.1±41.0 (81)	MCT+LCT ICU 21.8±20.9 (78) Hospital 42.5±28.5 (78)	MCT+LCT+Fish oil 8.4±6.6 (67)	MCT+LCT 9.2±6.9 (64)	MCT+LCT+ Fish oil MCT+LCT Parenteral lipid intake [(g/kg BW)/d] 1.04 ± 0.12 1.05 ± 0.13 PN kcal 1,737 ± 353 1,782 ± 312
12) Gultekin 2014	Omegaven + olive Hospital 31.6 ± 4,3	Olive Hospital 30.6 ± 4,3	NR	NR	Omegavan + Olive oil Olive oil Kcal/kg/day 27.5±1.5 15.8±1.5 g protein/kg/d 1.3±0.2 1.1±0.1
13) Chen 2017	NR	NR	NR	NR	NR
Fish oil (ω 3) containing IV lipid emulsions in PN, EN or orally fed patients vs. no IV soybean oil					
9) Qu 2009	NR	NR	NR	NR	NR
14) Gupta 2011	Omegaven ICU 15.96 + 7.57 (31) Hospital 21.5+ 13.49 (31)	Standard EN ICU 15.88 + 6.47 (30) Hospital 26.63 + 18.22 (30)	Omegaven 11.78 + 10.63 (31)	Standard EN 10.71 + 14.55 (30)	
15) Khor 2011	Omegaven ICU 10.3 ± 8.4 (14) Hospital 19.6 ± 7.4 (14)	Saline ICU 8.4 ± 6.5 (13) Hospital 17.5 ± 6.0 (13)	Omegaven 13.0 ± 10.1 (9)	Saline 11.6 ± 9.5 (5)	NR
16) Zhao 2011	Omegaven ICU 8.0 ± 2.02 (56)	Control ICU 10.97 ± 2.02 (60)	NR	NR	NR
17) Burkhart 2013	Omegavan ICU 5 (3-22)	No Omegavan ICU 6 (2-33)	NR	NR	Omegavan no Omegavan Subsyndromal delirium 5 (25) 6(29) Sepsis associated delirium

					15 (75) 15 (71)
18) Hall 2014	Omegavan I CU 8.8±7.7 Hospital 26.7±18.2	No Omegavan I CU 12.3±12.4 Hospital 33.5±30.4	NR (reported as free ventilator days)	NR (reported as free ventilator days)	NR
Olive oil containing emulsions vs. LCT or LCT+MCT					
19) Garcia-de-Lorenzo 2005	Clinoleic ICU 32.9 ± 10.6[a] (11) Hospital 57 ± 15.3[a] (11)	Lipofundin ICU 41.8 ± 16.3[a] (11) Hospital 64.9 ± 27.2[a] (11)	Clinoleic 11.0 ± 11.93[a] (11)	Lipofundin 13.0 ± 16.25[a](11)	Clinoleic Lipofundin Multiple organ dysfunction score 11.0 ± 3.6 13.0 ± 4.9
20) Huschak 2005**	High fat + Clinoleic ICU 17.9 ± 11.2 (18)	Low fat + LCT + MCT ICU 25.1 ± 7.0 (15)	High fat + Clinoleic 13.0 ± 8.9 (18)	Low fat + LCT + MCT 20.4 ± 7.0 (15)	High fat + Clinoleic Low fat + LCT + MCT Total Energy Intake (kcal/kg) 17.9 ± 6.3 22.3 ± 4.2
21) Pontes-Arruda 2013	Clinoleic ICU 12 (7-17) Hospital 21 (15-25)	MCT/LCT ICU 11 (5-14) Hospital 18 (13-23)	NR	NR	Clinoleic MCT/LCT Nutritional Intake Lipids (g/day) 66 (61-73) 61 (54-67) Days on PN 12 (8-15) 11 (7-15) Dextrose (g/day) 288 (275-303) 281 (273-301) AAs (g/day) 87 (84-90) 87 (83-92)
22) Umperrez 2012	Clinoleic ICU 17 ± 18 (51) Hospital 40.8 ± 36 (51)	Intralipid ICU 15.2 ± 14 (49) Hospital 46.7 ± 48 (51)	Clinoleic NR	Intralipid NR	Clinoleic Intralipid Total Energy Intake (kcal/kg) 22 ± 6 22 ± 5

C.Random: concealed randomization
ITT: intent to treat
NR: not reported
MCT: medium chain triglycerides
LCT: long chain triglycerides
† hospital mortality unless specified
‡ number of patients with infections unless specified
* data obtained from author, 8 out of 28 in Omegaven and 7 out of 26 in LCT group were in ICU
**intervention includes high fat low CHO PN plus fish oil
[a] converted Standard Error Mean (SEM) to Standard deviation (SD)

Figure 1.1: Overall Mortality in studies using an omega-6 reducing strategy

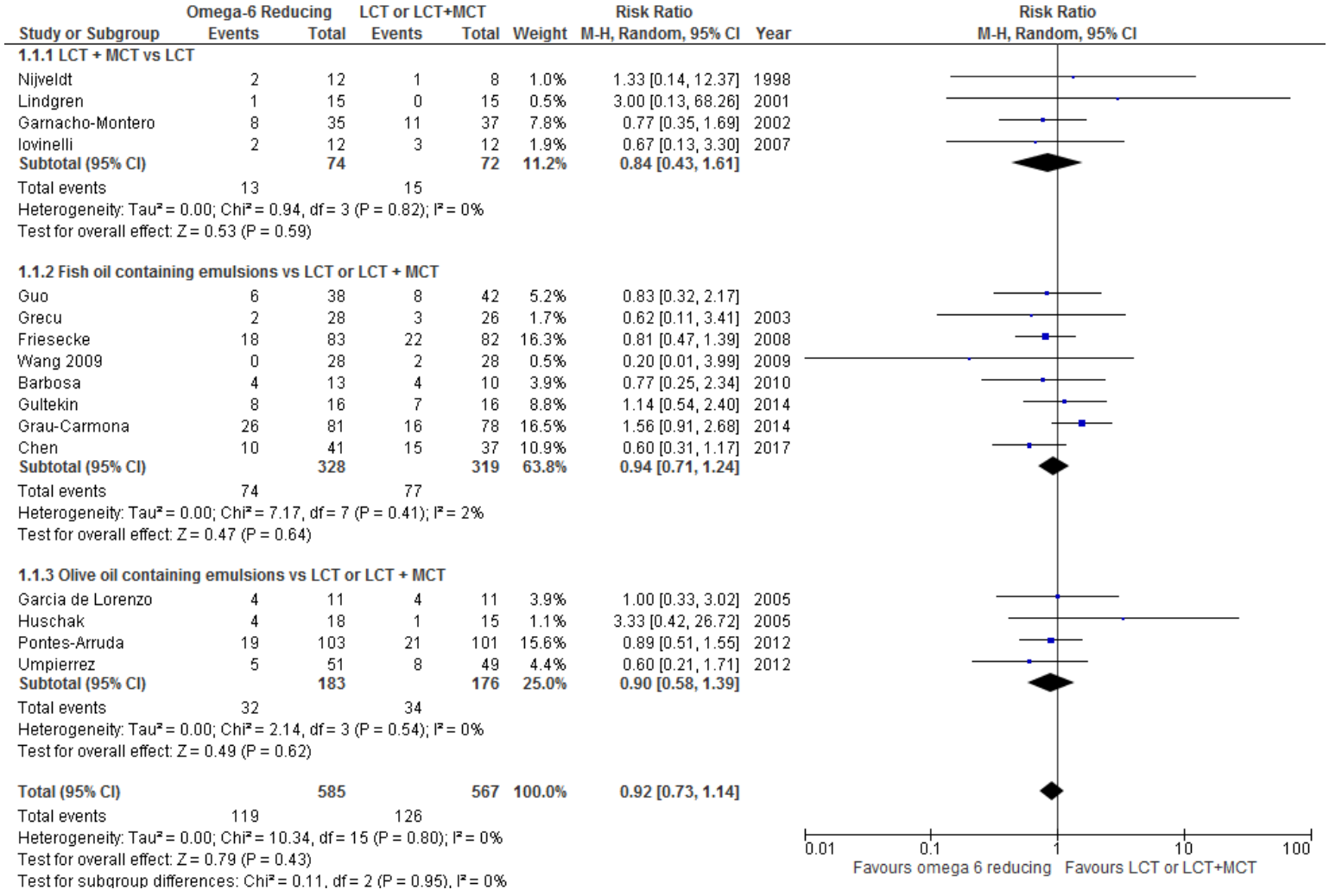

Figure 1.2 Overall Mortality in all studies (includes Qu, Gupta, Burkhart, Zhao & Hall)

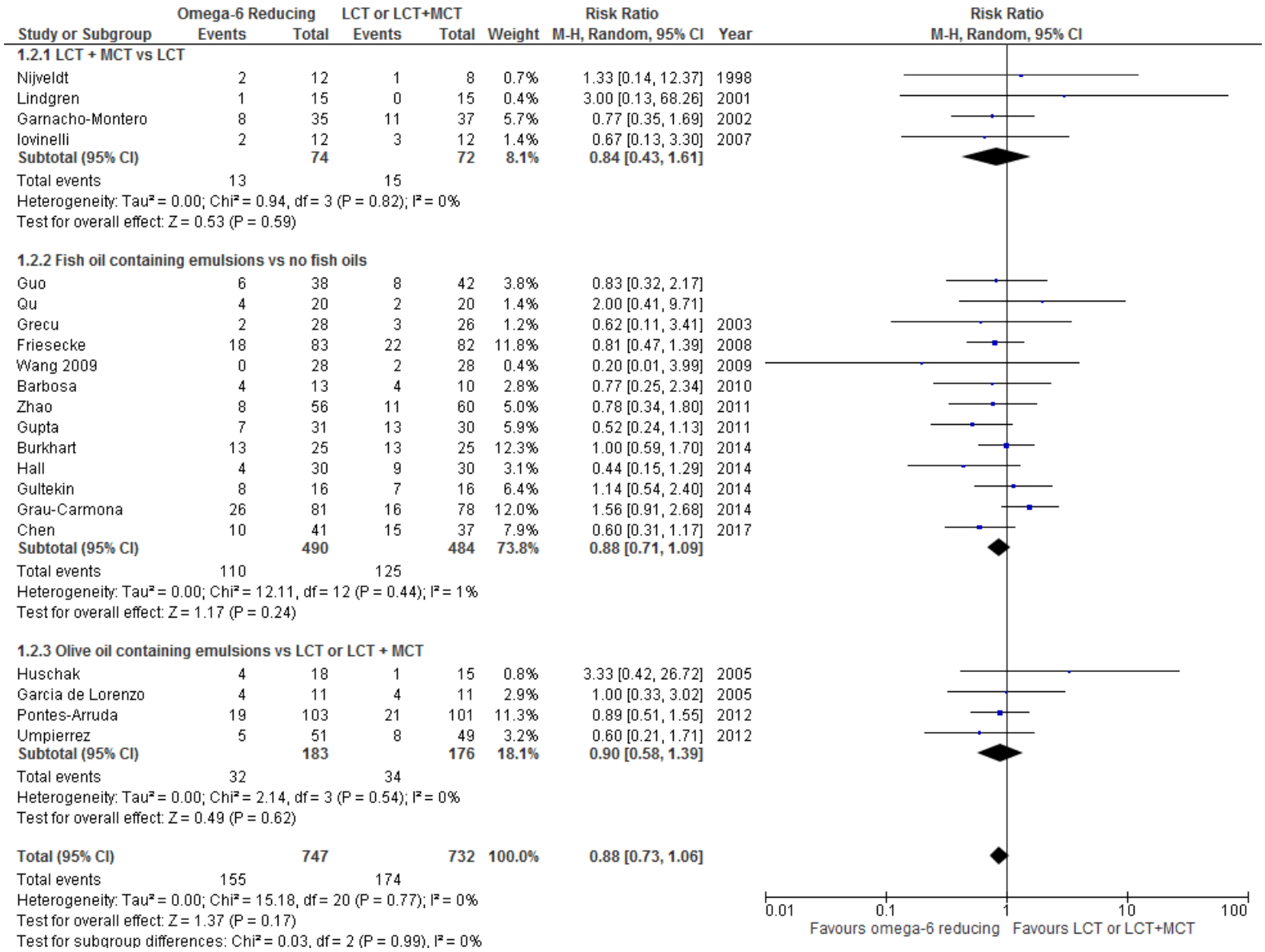

Figure 1.3 Infections in studies using an omega-6 reducing strategy

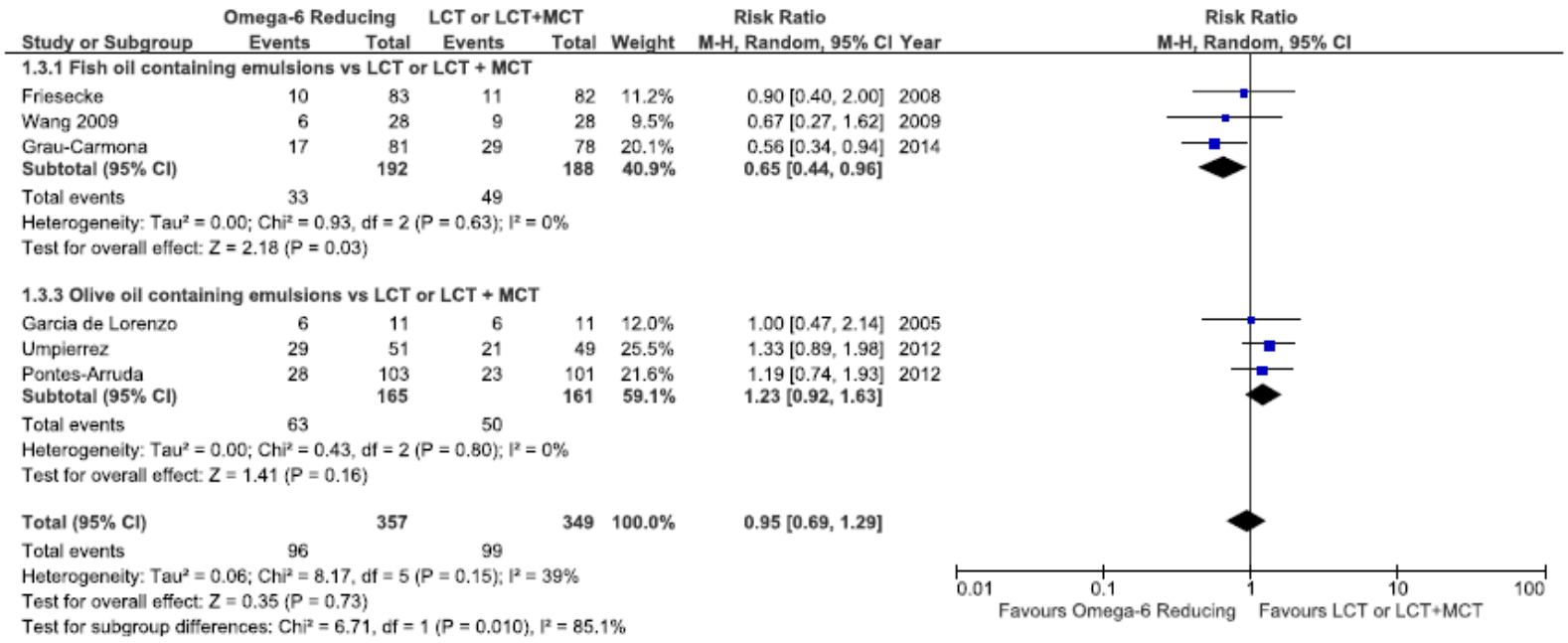

Figure 1.4 Infections in all studies (includes Hall)

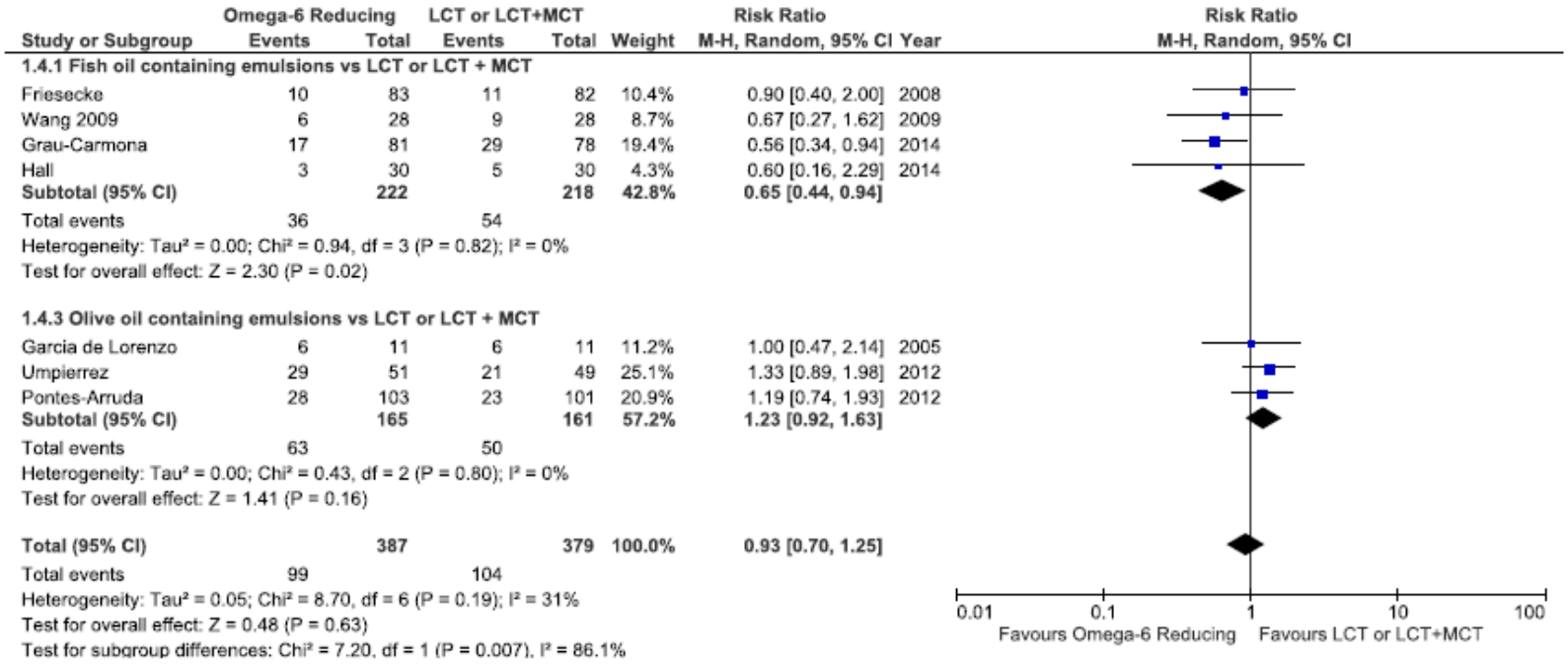

Figure 1.5 Hospital LOS in studies using an omega-6 reducing strategy

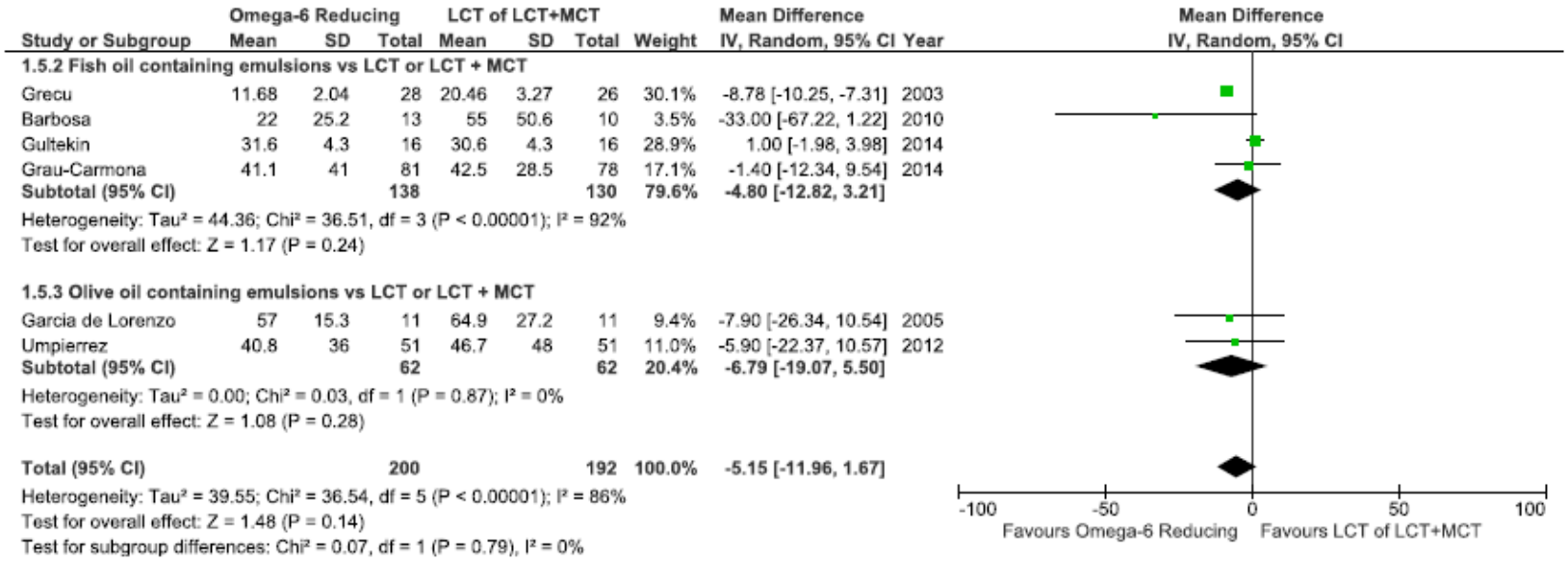

Figure 1.6 Hospital LOS in all studies (includes Khor, Gupta, Hall)

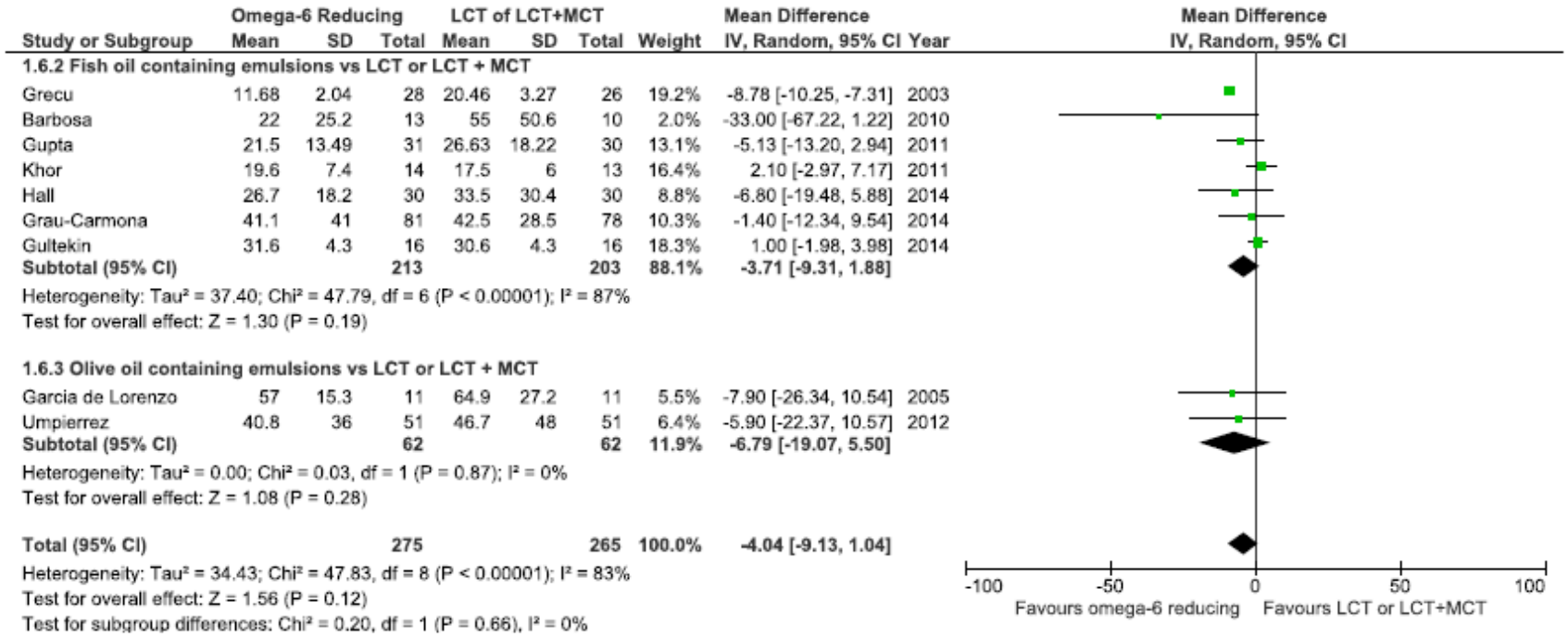

Figure 1.7 ICU LOS in studies using an omega-6 reducing strategy

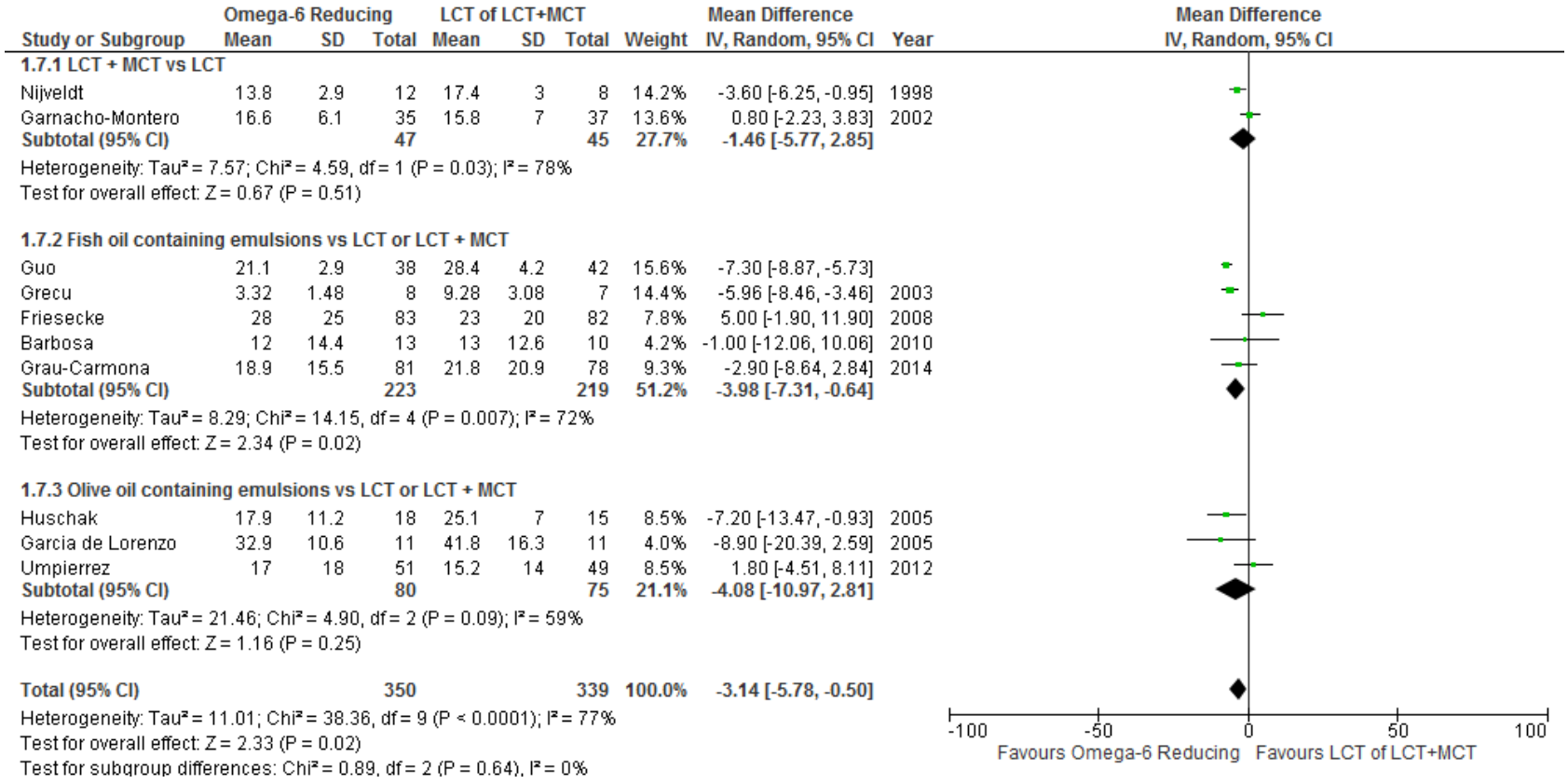

Figure 1.8 ICU LOS in all studies (includes Khor, Gupta, Zhao, Hall)

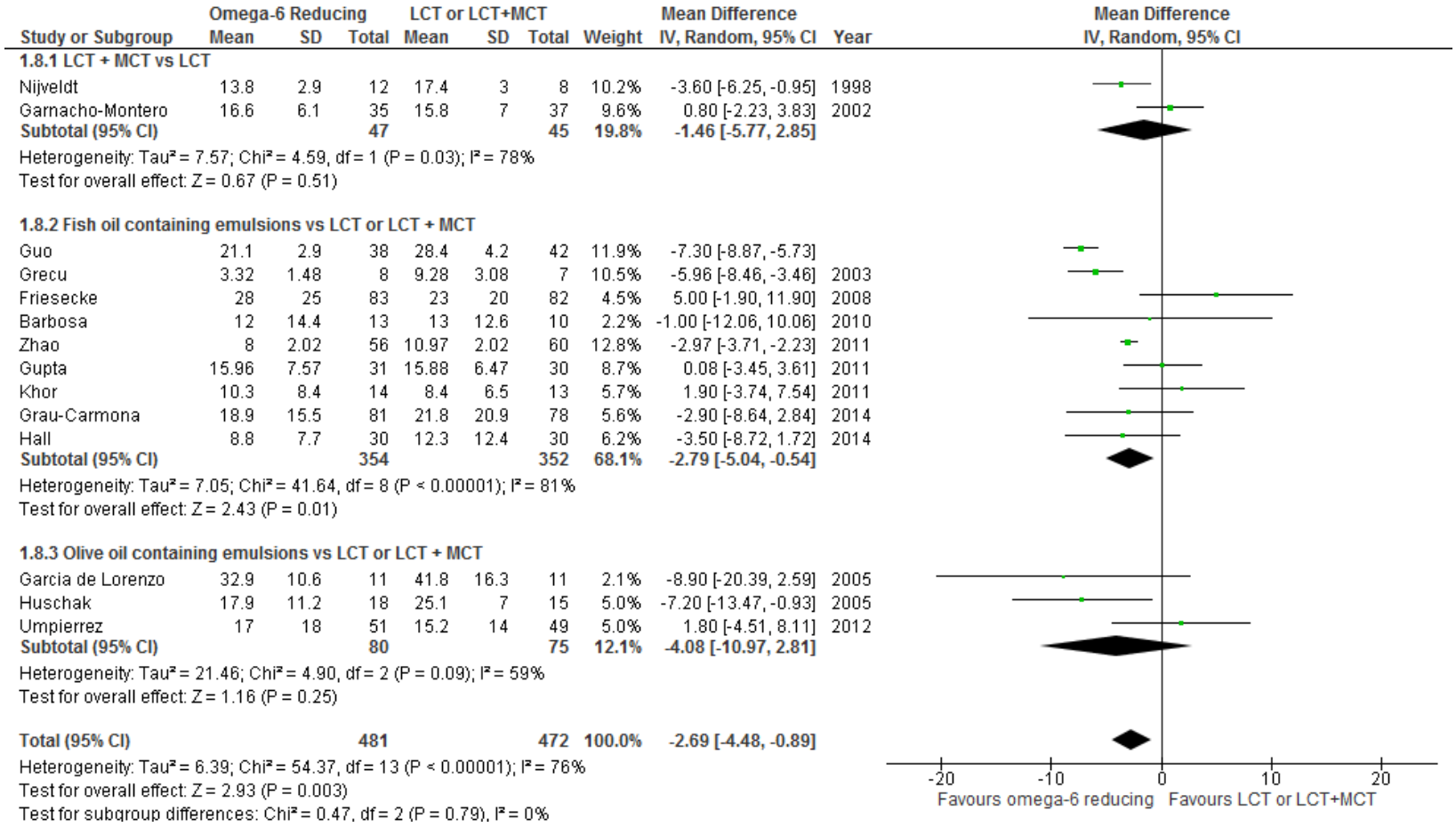

Figure 1.9 Ventilator Days in studies using an omega-6 reducing strategy

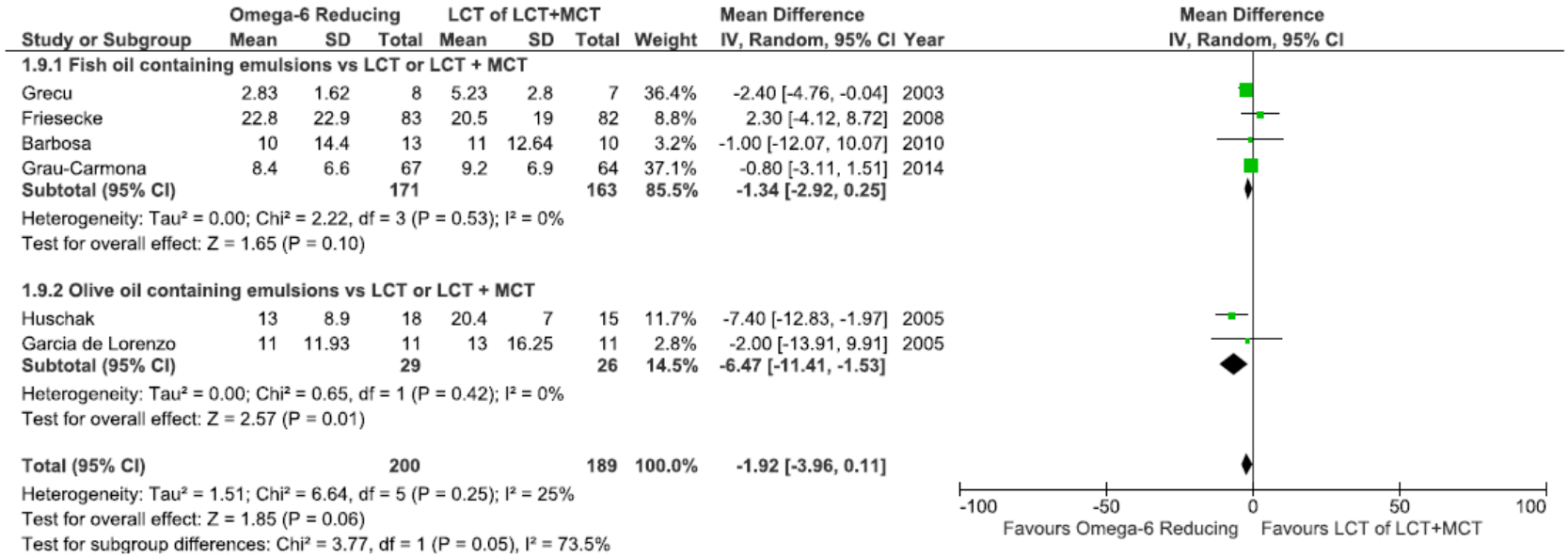

Figure 1.10 Ventilator Days in all studies (includes Khor, Gupta)

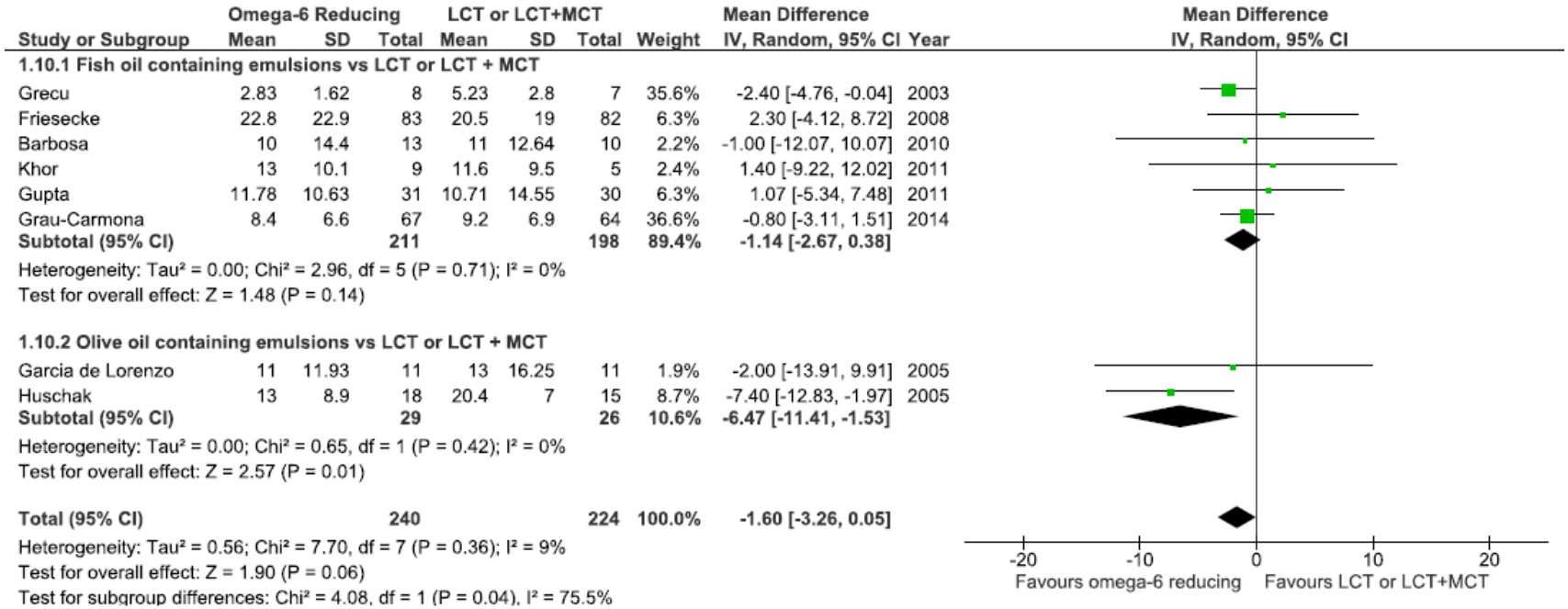

Table 2. Excluded Articles

#	Reason excluded	Citation
1	Cancer patients	Hutchison ML, Clemans G. Prospective trial of liposyn 20% in patients undergoing bone marrow transplantation. Clinical Nutrition. 1984 May;3:5-9
2	Unclear if randomized yet elective surgery pts	Gazzaniga AB, Day AT, Sankary H. The efficacy of a 20 per cent fat emulsion as a peripherally administered substrate. Surg Gynecol Obstet. 1985 May;160(5):387-92.
3	No clinical outcomes	Calon B, Pottecher T, Frey A, Ravanello J, Otteni JC, Bach AC. Long-chain versus medium and long-chain triglyceride-based fat emulsion in parental nutrition of severe head trauma patients. Infusionstherapie. 1990 Oct;17(5):246-8.
4	No clinical outcomes	Hwang TL, Huang SL, Chen MF. Effects of intravenous fat emulsion on respiratory failure. Chest 1990;97(4):934-8.
5	No clinical outcomes	Jarnberg P-O. Liposyn versus intralipid: A comparative study of two lipid emulsion in critically ill patients receiving total parenteral nutrition. 1991 50(1):38-44
6	No clinical outcomes	Diboune M, Ferard G, Ingenbleek Y, Tulasne PA, Calon B, Hasselmann M, Sauder P, Spielmann D, Metais P. Composition of phospholipid fatty acids in red blood cell membranes of patients in intensive care units: effects of different intakes of soybean oil, medium-chain triglycerides, and black-currant seed oil. JPEN J Parenter Enteral Nutr. 1992 Mar-Apr;16(2):136-41.
7	No clinical outcomes	Adams S, Yeh YY, Jensen GL. Changes in plasma and erythrocyte fatty acids in patients fed enteral formulas containing different fats. JPEN J Parenter Enteral Nutr. 1993 Jan-Feb;17(1):30-4.
8	No clinical outcomes	Ball MJ. Parenteral nutrition in the critically ill: use of a medium chain triglyceride emulsion. Intensive Care Med. 1993;19(2):89-95.
9	No clinical outcomes	Chassard D, Guiraud M, Gauthier J, Gelas P, Berrada KR, Bouletreau P. Effects of intravenous medium-chain triglycerides on pulmonary gas exchanges in mechanically ventilated patients. Crit Care Med. 1994 Feb;22(2):248-51.
10	No clinical outcomes	Jeevanandam M, Holaday NJ, Voss T, Buier R, Petersen SR. Efficacy of a mixture of medium-chain triglyceride (75%) and long-chain triglyceride (25%) fat emulsions in the nutritional management of multiple-trauma patients. Nutrition. 1995 May-Jun;11(3):275-84.
11	Elective surgery pts	Wachtler P, König W, Senkal M, Kemen M, Köller M. Influence of a total parenteral nutrition enriched with omega-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. J Trauma. 1997 Feb;42(2):191-8.
12	Elective surgery pts	Chambrier C, Guiraud M, Gibault JP, Labrosse H, Boulétreau P. Medium- and long-chain triacylglycerols in postoperative patients: structured lipids versus a physical mixture. Nutrition. 1999 Apr;15(4):274-7.
13	Cancer pts	Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. Cancer. 1998 Jan 15;82(2):395-402.
14	Elective surgery pts	Hailer S, Jauch KW, Wolfram G. Influence of different fat emulsions with 10 or 20% MCT/LCT or LCT on lipoproteins in plasma of patients after abdominal surgery. Ann Nutr Metab. 1998;42(3):170-80.
15	No clinical outcomes	Kalfarentzos F, Kokkinis K, Leukaditi K, Maroulis J, Onoufriou A, Alexopoulos K. Comparison between two fat emulsions: Intralipid 30 cent vs intralipid 10 cent in critically ill patients. Clin Nutr. 1998 Feb;17(1):31-4.
16	Not a omega-6 reducing strategy. Compares one LCT	Kari A, Hersio K, Takala J, Penttila I. Comparison of two long-chain triglyceride fat emulsions in parenteral nutrition of critically ill patients. Current Therapeutic Research. 1989 June;45(6):1077-87.

	to another	
17	No clinical outcomes	Masclans JR, Iglesia R, Bermejo B, Picó M, Rodriguez-Roisin R, Planas M. Gas exchange and pulmonary haemodynamic responses to fat emulsions in acute respiratory distress syndrome. Intensive Care Med. 1998 Sep;24(9):918-23.
18	No clinical outcomes	Smirniotis V, Kostopanagiotou G, Vassiliou J, Arkadopoulos N, Vassiliou P, Datsis A, et al. Long chain versus medium chain lipids in patients with ARDS: effects on pulmonary haemodynamics and gas exchange. Intensive care medicine 1998;24(10):1029-33.
19	Cancer pts	Furukawa K, Tashiro T, Yamamori H, Takagi K, Morishima Y, Sugiura T, Otsubo Y, Hayashi N, Itabashi T, Sano W, Toyoda Y, Nitta H, Nakajima N. Effects of soybean oil emulsion and eicosapentaenoic acid on stress response and immune function after a severely stressful operation. Ann Surg. 1999 Feb;229(2):255-61.
20	No clinical outcomes	Planas M, Porta I, Sagristá ML, Mora M, Padró JB, Picó M. Fatty acid composition of platelet membrane lipids after administration of two different fat emulsions in critically ill patients. Intensive Care Med. 1999 Apr;25(4):395-8.
21	Elective surgery pts	Linseisen J, Hoffmann J, Lienhard S, Jauch KW, Wolfram G. Antioxidant status of surgical patients receiving TPN with an omega-3-fatty acid-containing lipid emulsion supplemented with alpha-tocopherol. Clin Nutr. 2000 Jun;19(3):177-84.
22	Elective surgery pts	Heller AR, Fischer S, Rossel T, Geiger S, Siegert G, Ragaller M, et al. Impact of n-3 fatty acid supplemented parenteral nutrition on haemostasis patterns after major abdominal surgery. The British journal of nutrition. 2002;87 Suppl 1:S95-101.
23	Elective surgery patients	Kuse ER, Kotzerke J, Müller S, Nashan B, Lück R, Jaeger K. Hepatic reticuloendothelial function during parenteral nutrition including an MCT/LCT or LCT emulsion after liver transplantation - a double-blind study. Transpl Int. 2002 Jun;15(6):272-7. Epub 2002 Apr 30.
24	No clinical outcomes, not ICU patients	Manuel-y-Keenoy B, Nonneman L, De Bosscher H, Vertommen J, Schrans S, Klütsch K, De Leeuw I. Effects of intravenous supplementation with alpha-tocopherol in patients receiving total parenteral nutrition containing medium- and long-chain triglycerides. Eur J Clin Nutr. 2002 Feb;56(2):121-8.
25	No clinical outcomes	Schauder P, Rohn U, Schafer G, Korff G, Schenk HD. Impact of fish oil enriched total parenteral nutrition on DNA synthesis, cytokine release and receptor expression by lymphocytes in the postoperative period. The British journal of nutrition. 2002;87 Suppl 1:S103-10.
26	Elective surgery pts	Weiss G, Meyer F, Matthies B, Pross M, Koenig W, Lippert H. Immunomodulation by perioperative administration of n-3 fatty acids. The British journal of nutrition 2002;87 Suppl 1:S89-94.
27	No clinical outcomes	García-de-Lorenzo A, López-Martínez J, Planas M, Chacón P, Montejo JC, Bonet A, Ortiz-Leyba C, Sánchez-Segura JM, Ordóñez J, Acosta J, Grau T, Jiménez FJ. Safety and metabolic tolerance of a concentrated long-chain triglyceride lipid emulsion in critically ill septic and trauma patients. JPEN J Parenter Enteral Nutr. 2003 May-Jun;27(3):208-15.
28	Elective surgery or emergency surgery pts	Grau T, Ruiz de Adana JC, Zubillaga S, Fuerte S, Girón C. [Randomized study of two different fat emulsions in total parenteral nutrition of malnourished surgical patients;effect of infectious morbidity and mortality] [Article in Spanish]. Nutr Hosp. 2003 May-Jun;18(3):159-66.
29	No clinical outcomes	Koller M, Senkal M, Kemen M, Konig W, Zumtobel V, Muhr G. Impact of omega-3 fatty acid enriched TPN on leukotriene synthesis by leukocytes after major surgery. Clin Nutr. 2003;22(1):59-64.
30	No clinical outcomes	Mayer K, Meyer S, Reinholz-Muhly M, Maus U, Merfels M, Lohmeyer J, Grimminger F, Seeger W. Short-time infusion of fish oil-based lipid emulsions, approved for parenteral nutrition, reduces monocyte proinflammatory cytokine generation and adhesive interaction with endothelium in humans. J Immunol. 2003 Nov 1;171(9):4837-43.
31	No clinical outcomes	Mayer K, Fegbeutel C, Hattar K, Sibelius U, Krämer HJ, Heuer KU, Temmesfeld-Wollbrück B, Gokorsch S, Grimminger F, Seeger W. Omega-3 vs. omega-6 lipid emulsions exert differential influence on neutrophils in septic shock patients: impact on plasma fatty acids and lipid mediator generation. Intensive Care Med. 2003 Sep;29(9):1472-81.

32	No clinical outcomes	Mayer K, Gokorsch S, Fegbeutel C, Hattar K, Rosseau S, Walmrath D, Seeger W, Grimminger F. Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. Am J Respir Crit Care Med. 2003 May 15;167(10):1321-8. Epub 2003 Feb 25.
33	No clinical outcomes	Mayer K, Meyer S, Reinholz-Muhly M, Maus U, Merfels M, Lohmeyer J, et al. Short-time infusion of fish oil-based lipid emulsions, approved for parenteral nutrition, reduces monocyte proinflammatory cytokine generation and adhesive interaction with endothelium in humans. J Immunol. 2003;171(9):4837-43.
34	No clinical outcomes	Antébi H, Mansoor O, Ferrier C, Tétégan M, Morvan C, Rangaraj J, Alcindor LG. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. JPEN J Parenter Enteral Nutr. 2004 May-Jun;28(3):142-8.
35	Elective surgery & cancer pts	Heller AR, Rössel T, Gottschlich B, Tiebel O, Menschikowski M, Litz RJ, Zimmermann T, Koch T. Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. Int J Cancer. 2004 Sep 10;111(4):611-6.
36	Cancer pts	Chen FM, Wang JY, Sun LC, Juang RF, Huang TJ, Hsieh JS. Efficacy of medium-chain triglycerides compared with long-chain triglycerides in total parenteral nutrition in patients with digestive tract cancer undergoing surgery. Kaohsiung J Med Sci. 2005 Nov;21(11):487-94.
37	Surgical pts	Kłek S, Kulig J, Szczepanik AM, Jedrys J, Kołodziejczyk P. The clinical value of parenteral immunonutrition in surgical patients. Acta Chir Belg. 2005 Apr;105(2):175-9.
38	Not critically ill pts	Cano NJ, Saingra Y, Dupuy AM, Lorec-Penet AM, Portugal H, Lairon D, Cristol JP, Come A, Le Brun A, Atlan P, Leverve XM. Intradialytic parenteral nutrition: comparison of olive oil versus soybean oil-based lipid emulsions. Br J Nutr. 2006 Jan;95(1):152-9.
39	Surgical pts	Grimm H, Mertes N, Goeters C, Schlotzer E, Mayer K, Grimminger F, Fürst P. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. Eur J Nutr. 2006 Feb;45(1):55-60.
40	Surgical pts	Mertes N, Grimm H, Fürst P, Stehle P. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. Ann Nutr Metab. 2006;50(3):253-9.
41	No clinical outcomes	Tappy L, Berger MM, Schwarz JM, Schneiter P, Kim S, Revelly JP, Chioléro R. Metabolic effects of parenteral nutrition enriched with n-3 polyunsaturated fatty acids in critically ill patients. Clin Nutr. 2006 Aug;25(4):588-95.
42	Elective surgery pts	Senkal M, Geier B, Hannemann M, Deska T, Linseisen J, Wolfram G, Adolph M. Supplementation of omega-3 fatty acids in parenteral nutrition beneficially alters phospholipid fatty acid pattern. JPEN J Parenter Enteral Nutr. 2007 Jan-Feb;31(1):12-7.
43	Elective surgery pts; no clinical outcomes	Wendel M et al. Impact of total parenteral nutrition including omega-3 fatty acids on the regulation of plasma lipoproteins and glycemic control after major abdominal surgery. E-SPEN. 2007. 2:e103-e110
44	Elective surgery pts	Wichmann MW, Thul P, Czarnetzki HD, Morlion BJ, Kemen M, Jauch KW. Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicenter trial. Crit Care Med. 2007 Mar;35(3):700-6. Comment in: Crit Care Med. 2007 Mar;35(3):951.
45	Elective surgery pts	Berger MM, Tappy L, Revelly JP, Koletzko BV, Gepert J, Corpataux JM, Cayeux MC, Chiolero RL. Fish oil after abdominal aorta aneurysm surgery. Eur J Clin Nutr. 2008 Sep;62(9):1116-22. Epub 2007 May 30. Erratum in: Eur J Clin Nutr. 2009 Feb;63(2):302.
46	Cancer patients	Liang B, Wang S, Ye YJ, Yang XD, Wang YL, Qu J, Xie QW, Yin MJ. Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients. World J Gastroenterol. 2008 Apr 21;14(15):2434-9.
47	Lipid emulsion only infused for 12 hrs on one day, followed by standard PN	Sabater J, Masclans JR, Sacanell J, Chacon P, Sabin P, Planas M. Effects on hemodynamics and gas exchange of omega-3 fatty acid-enriched lipid emulsion in acute respiratory distress syndrome (ARDS): a prospective, randomized, double-blind, parallel group study. Lipids in health and disease. 2008;7:39.

48	Elective surgery pts	Shan Y-S et al. Evaluation of the stability and safety of Venolipid MCT/LCT 20% administered by an all-in-one system in patients after major gastrointestinal surgery. E-SPEN. 2008(3):e135-e141
49	Not ICU, no clinical outcomes	Wang X, Li W, Li N, Li J. Omega-3 fatty acids-supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: a randomized and controlled study. JPEN J Parenter Enteral Nutr. 2008 May-Jun;32(3):236-41.
50	no clinical ouctomes	Piper SN, Schade I, Beschmann RB, Maleck WH, Boldt J, Röhm KD. Hepatocellular integrity after parenteral nutrition: comparison of a fish-oil-containing lipid emulsion with an olive-soybean oil-based lipid emulsion. Eur J Anaesthesiol. 2009 Dec;26(12):1076-82.
51	Not ICU pts	Heidt MC, Vician M, Stracke SK, Stadlbauer T, Grebe MT, Boening A, Vogt PR, Erdogan A. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. Thorac Cardiovasc Surg. 2009 Aug;57(5):276-80.
52	Cancer patients	Piper SN, Schade I, Beschmann R,. Maleck W,. Boldt J, Rohm KD. Hepatocellular integrity after parenteral nutrition: comparison of a fish-oil-containing lipid emulsion with an olive-soybean oil-based lipid emulsion. European Journal of Anaesthesiology. 2009;26(12):1076-82.
53	Elective surgery pts	Puiggròs C, Sánchez J, Chacón P, Sabín P, Roselló J, Bou R, Planas M. Evolution of lipid profile, liver function, and pattern of plasma fatty acids according to the type of lipid emulsion administered in parenteral nutrition in the early postoperative period after digestive surgery. JPEN J Parenter Enteral Nutr. 2009 Sep-Oct;33(5):501-12.
54	No clinical outcomes	Xiong J, Zhu S, Zhou Y, Wu H, Wang C. Regulation of omega-3 fish oil emulsion on the SIRS during the initial stage of severe acute pancreatitis. J Huazhong Univ Sci Technolog Med Sci. 2009 Feb;29(1):35-8.
55	Elective surgery pts	Badía-Tahull MB, Llop-Talaverón JM, Leiva-Badosa E, Biondo S, Farran-Teixidó L, Ramón-Torrell JM, Jódar-Masanes R. A randomised study on the clinical progress of high-risk elective major gastrointestinal surgery patients treated with olive oil-based parenteral nutrition with or without a fish oil supplement. Br J Nutr. 2010;104(5):737-41.
56	Not ICU patients	Jiang ZM, Wilmore DW, Wang XR, Wei JM, Zhang ZT, Gu ZY, Wang S, Han SM, Jiang H, Yu K. Randomized clinical trial of intravenous soybean oil alone versus soybean oil plus fish oil emulsion after gastrointestinal cancer surgery. Br J Surg. 2010 Jun;97(6):804-9.
57	Control group did not receive soybean oil emulsion	Gupta A, Govil D, Bhatnagar S, Gupta S, Goyal J, Patel S, Baweja H. Efficacy and safety of parenteral omega 3 fatty acids in ventilated patients with acute lung injury. Indian J Crit Care Med. 2011 Apr;15(2):108-13.
58	Control group did not receive soybean oil emulsion	Khor BS, Liaw SJ, Shih HC, Wang LS. Randomized, double blind, placebo-controlled trial of fish-oil-based lipid emulsion infusion for treatment of critically ill patients with severe sepsis. Asian J Surg. 2011 Jan;34(1):1-10.
59	Cancer pts	Makay O, Kaya T, Firat O, Sozbilen M, Caliskan C, Gezer G, et al. omega-3 Fatty acids have no impact on serum lactate levels after major gastric cancer surgery. JPEN Journal of parenteral and enteral nutrition 2011;35(4):488-92.
60	No clinical outcomes	Sabater J, Masclans JR, Sacanell J, Chacon P, Sabin P, Planas M. Effects of an omega-3 fatty acid-enriched lipid emulsion on eicosanoid synthesis in acute respiratory distress syndrome (ARDS): A prospective, randomized, double-blind, parallel group study. Nutr Metab. 2011;8(1):22.
61	No clinical outcomes	Sungurtekin H, Değirmenci S, Sungurtekin U, Oguz BE, Sabir N, Kaptanoglu B. Comparison of the effects of different intravenous fat emulsions in patients with systemic inflammatory response syndrome and sepsis. Nutr Clin Pract. 2011 Dec;26(6):665-71.
62	Systematic Review individual ICU RCTs included	van der Meij BS, van Bokhorst-de van der Schueren MA, Langius JA, Brouwer IA, van Leeuwen PA. n-3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. Am J Clin Nutr. 2011 Nov;94(5):1248-65.

63	Not ICU patients, only 8-14% patients ventilated	Hajdú N, Belágyi T, Issekutz A, Bartek P, Gartner B, Oláh A. [Intravenous glutamine and early nasojejunal nutrition in severe acute pancreatitis – a prospective randomized clinical study]. Magy Seb. 2012 Apr;65(2):44-51. Hungarian.
64	Elective surgery pts	Han YY, Lai SL, Ko WJ, Chou CH, Lai HS. Effects of fish oil on inflammatory modulation in surgical intensive care unit patients. Nutr Clin Pract. 2012 Feb;27(1):91-8. Epub 2012 Jan 6.
65	patients with poisoning and not representative of ICU pts	Taftachi F, Sanaei-Zadeh H, Sepehrian B, Zamani N. Lipid emulsion improves Glasgow coma scale and decreases blood glucose level in the setting of acute non-local anesthetic drug poisoning--a randomized controlled trial. European review for medical and pharmacological sciences 2012;16 Suppl 1:38-42.
66	Cancer patients	Zhu MW, Tang DN, Hou J, Wei JM, Hua B, Sun JH, et al. Impact of fish oil enriched total parenteral nutrition on elderly patients after colorectal cancer surgery. Chinese medical journal. 2012;125(2):178-81.
67	Not randomized	Barros KV, Cassulino AP, Schalch L, Della Valle Munhoz E, Manetta JA, Noakes PS, Miles EA, Calder PC, Flor Silveira VL. Supplemental intravenous n-3 fatty acids and n-3 fatty acid status and outcome in critically ill elderly patients in the ICU receiving enteral nutrition. Clin Nutr. 2013 Aug;32(4):599-605.
68	Elective surgery pts	Berger MM, Delodder F, Liaudet L, Tozzi P, Schlaepfer J, Chiolero RL, Tappy L. Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial. Am J Clin Nutr. 2013 Feb;97(2):246-54. doi: 10.3945/ajcn.112.046573. Epub 2012 Dec 26. PubMed PMID: 23269816.
69	no true control group	Chen J, Yan J, Cai GL, Xu QH, Gong SJ, Dai HW, Yu YH, Li L. Structured lipid emulsion as nutritional therapy for the elderly patients with severe sepsis. Chin Med J (Engl). 2013 Jun;126(12):2329-32.
70	Systematic Review individual ICU RCTs included	Manzanares W, Dhaliwal R, Jurewitsch B, Stapleton RD, Jeejeebhoy KN, Heyland DK. Parenteral Fish Oil Lipid Emulsions in the Critically Ill : A Systematic Review and Meta-Analysis. 2013.
71	Meta Analysis	Manzanares W, Dhaliwal R, Jurewitsch B, Stapleton RD, Jeejeebhoy KN, Heyland DK. Parenteral Fish Oil Lipid Emulsions in the Critically Ill: A Systematic Review and Meta-Analysis. JPEN J Parenter Enteral Nutr. 2013 Apr 22.
72	Meta analysis	Manzanares W, Dhaliwal R, Jurewitsch B, Stapleton RD, Jeejeebhoy KN, Heyland DK. Alternative lipid emulsions in the critically ill: a systematic review of the evidence. Intensive Care Med. 2013 Jun 29.
73	Meta analysis	Palmer AJ, Ho CK, Ajibola O, Avenell A. The role of ω-3 fatty acid supplemented parenteral nutrition in critical illness in adults: a systematic review and meta-analysis. Crit Care Med. 2013 Jan;41(1):307-16.
74	Not randomized	Barros KV, Cassulino AP, Schalch L, Munhoz ED, Manetta JA, Calder PC, Silveira VL. Pharmaconutrition: acute Fatty Acid modulation of circulating cytokines in elderly patients in the ICU. JPEN J Parenter Enteral Nutr. 2014 May;38(4):467-74.
75	Meta analysis	Zhu D, Zhang Y, Li S, Gan L, Feng H, Nie W. Enteral omega-3 fatty acid supplementation in adult patients with acute respiratory distress syndrome: a systematic review of randomized controlled trials with meta-analysis and trial sequential analysis. Intensive Care Med. 2014 Apr;40(4):504-12.
76	Elective surgery pts	Metry AA, Abdelaal W, Ragaei M, Refaat M, Nakhla G. SMOFlipid versus Intralipid in Postoperative ICU Patients. Enliven Archive. 2014;1(6):1-8.

77	Not a relevant treatment paradigm	Najmi M, Vahdat Shariatpanahi Z, Tolouei M, Amiri Z. Effect of oral olive oil on healing of 10-20% total body surface area burn wounds in hospitalized patients. Burns. 2015 May;41(3):493-6.
78	meta analyses	Wan X, Gao X, Bi J, Tian F, Wang X. Use of n-3 PUFAs can decrease the mortality in patients with systemic inflammatory response syndrome: a systematic review and meta-analysis. Lipids Health Dis. 2015 Mar 31;14:23.
79	Meta analyses	Lu C, Sharma S, McIntyre L, Rhodes A, Evans L, Almenawer S, Leduc L, Angus DC, Alhazzani W. Omega-3 supplementation in patients with sepsis: a systematic review and meta-analysis of randomized trials. Ann Intensive Care. 2017 Dec;7(1):58.
80	Not critically ill pts	Jia Z.-Y., Yang J., Xia Y., Tong D.-N., Zaloga G.P., Qin H.-L., Qiu Z., Li W., Jiang X., Peng B., Xia J., Xiu D., Huang F., Zhang N., Pan H., Huang S., Zhou Y., Lin J., Ji J., Zhou Z., Li Z., Gao H., Zhang X., Du H. Safety and efficacy of an olive oil-based triple-chamber bag for parenteral nutrition: A prospective, randomized, multi-center clinical trial in China. Nutrition Journal. 2015; 14 (1).
81	Sub analysis of Hall 2014	Hall TC, Bilku DK, Neal CP, Cooke J, Fisk HL, Calder PC, Dennison AR. The impact of an omega-3 fatty acid rich lipid emulsion on fatty acid profiles in critically ill septic patients. Prostaglandins Leukot Essent Fatty Acids. 2016 Sep;112:1-11.