

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, Umperrez 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 One study that compared an outdated long chain triglyceride (LCT) emulsion to another form of LCT (Kari 1998) was removed in the 2013 CPGs as it did not involve a soybean oil reducing strategy.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 (Iovinelli 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) (ω 3: ω 6 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 Omegaven (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, slowly 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% (ω 3: ω 6 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 supplemented with 100 ml 10% Omegaven (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 (Omegaven), 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% $\omega 9$, 37% $\omega 6$ = restricted linoleic acid { $\omega 6$ 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 Glucerna (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 39/103 (38) 28/103 (27) VAP/lower respiratory infections 9/103 (9)	MCT/LCT 35/101 (35) 23/101 (23) 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, $\omega 6:\omega 3=9:1$) vs Intralipid (100% soybean oil, $\omega 6:\omega 3=7:1$)	Clinoleic Hospital 5/51 (10)	Intralipid Hospital 8/49 (16)	Clinoleic 29/51 (57) 7/51 (14)	Intralipid 21/49 (43) Pneumonia 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 Adverse effects 5/15 (33) Nitrogen balance at day 3 2.6 ± 5.6 gms	LCT 4/15 (27) -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 Retinol binding protein 1.7 ± 1 Nitrogen balance 14.2 ± 2.9	LCT 0.8 ± 0.6 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 Time before weaning 52 ± 36 hrs	LCT 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 Patients undergoing reoperation for septic episode 2/28 (7)	LCT 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 Urinary Tract Infections 6/83 (7) Catheter-related infections 1/83 (1) Total EN Energy Intake (kcal/kg) 22.2 ± 5.5	LCT+MCT 4/82 (5) 3/83 (4) 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 Surgery of infected pancreatic necrosis 3/28 (11)	LCT 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 2057 ± 418 kcals	MCT+LCT 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 Parenteral lipid intake [(g/kg BW)/d] 1.04 ± 0.12 PN kcal 1,737 ± 353	MCT+LCT 1.05 ± 0.13 1,782 ± 312
12) Gultekin 2014	Omegaven + olive Hospital 31.6 ± 4,3	Olive Hospital 30.6 ± 4,3	NR	NR	Omegavan + Olive oil Kcal/kg/day 27.5±1.5 g protein/kg/d 1.3±0.2	Olive oil 15.8±1.5 1.1±0.1
13) Chen 2017	NR	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	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 Subsyndromal delirium 5 (25) Sepsis associated delirium	no Omegavan 6(29)

					15 (75)	15 (71)
18) Hall 2014	Omegavan ICU 8.8±7.7 Hospital 26.7±18.2	No Omegavan ICU 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 Multiple organ dysfunction score 11.0 ± 3.6	Lipofundin 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 Total Energy Intake (kcal/kg) 17.9 ± 6.3	Low fat + LCT + MCT 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 Nutritional Intake Lipids (g/day) 66 (61-73) Days on PN 12 (8-15) Dextrose (g/day) 288 (275-303) AAs (g/day) 87 (84-90)	MCT/LCT 61 (54-67) 11 (7-15) 281 (273-301) 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 Total Energy Intake (kcal/kg) 22 ± 6	Intralipid 22 ± 5

C.Random: concealed randomization

ITT: intent to treat

NR: not reported

* data obtained from author, 8 out of 28 in Omegaven and 7 out of 26 in LCT group were in ICU

^a converted Standard Error Mean (SEM) to Standard deviation (SD)

MCT: medium chain triglycerides

LCT: long chain triglycerides

† hospital mortality unless specified

‡ number of patients with infections unless specified

**intervention includes high fat low CHO PN plus fish oil

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

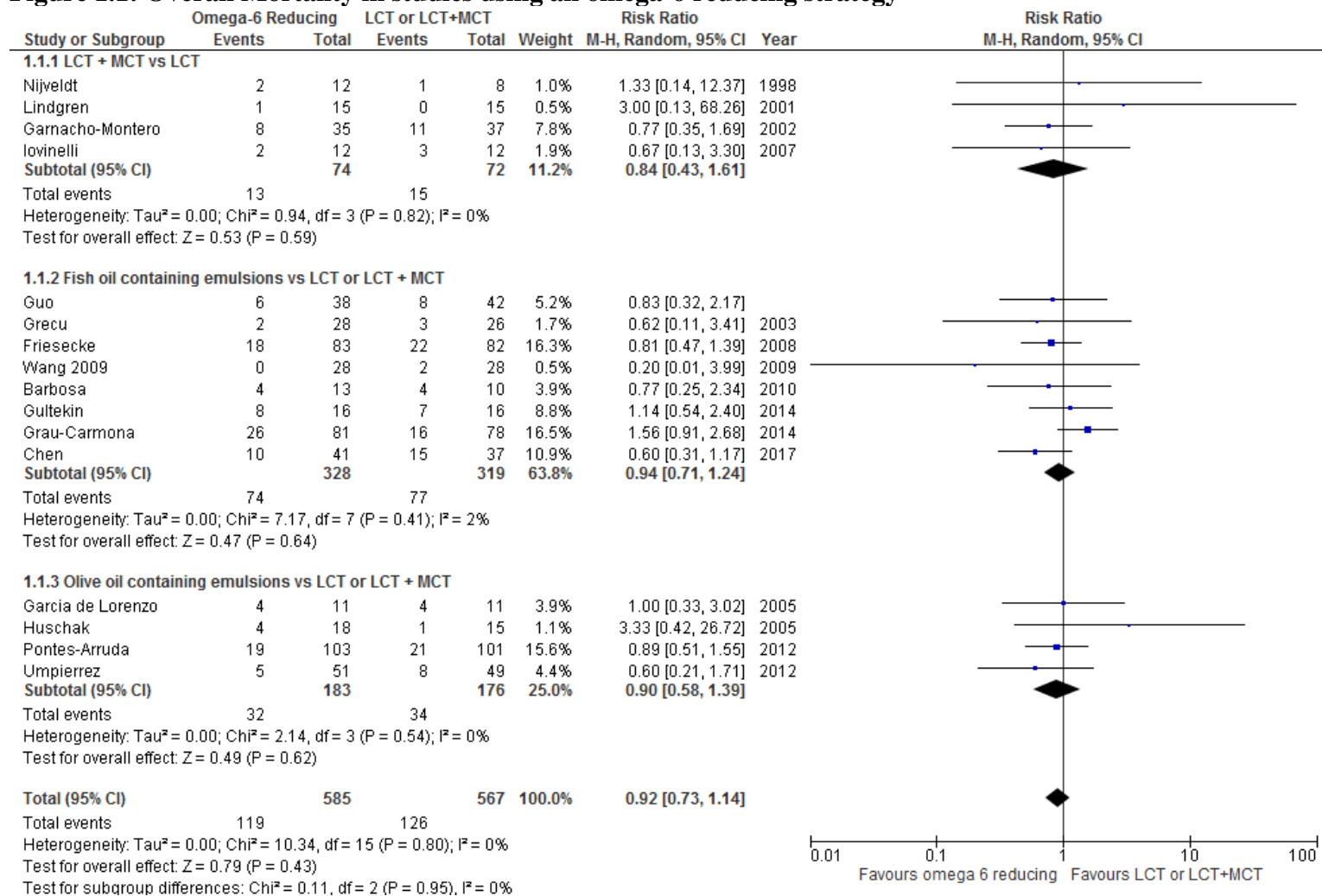


Figure 1.2 Overall Mortality in all studies (includes Qu, Gupta, Burkhart, Zhao & Hall)

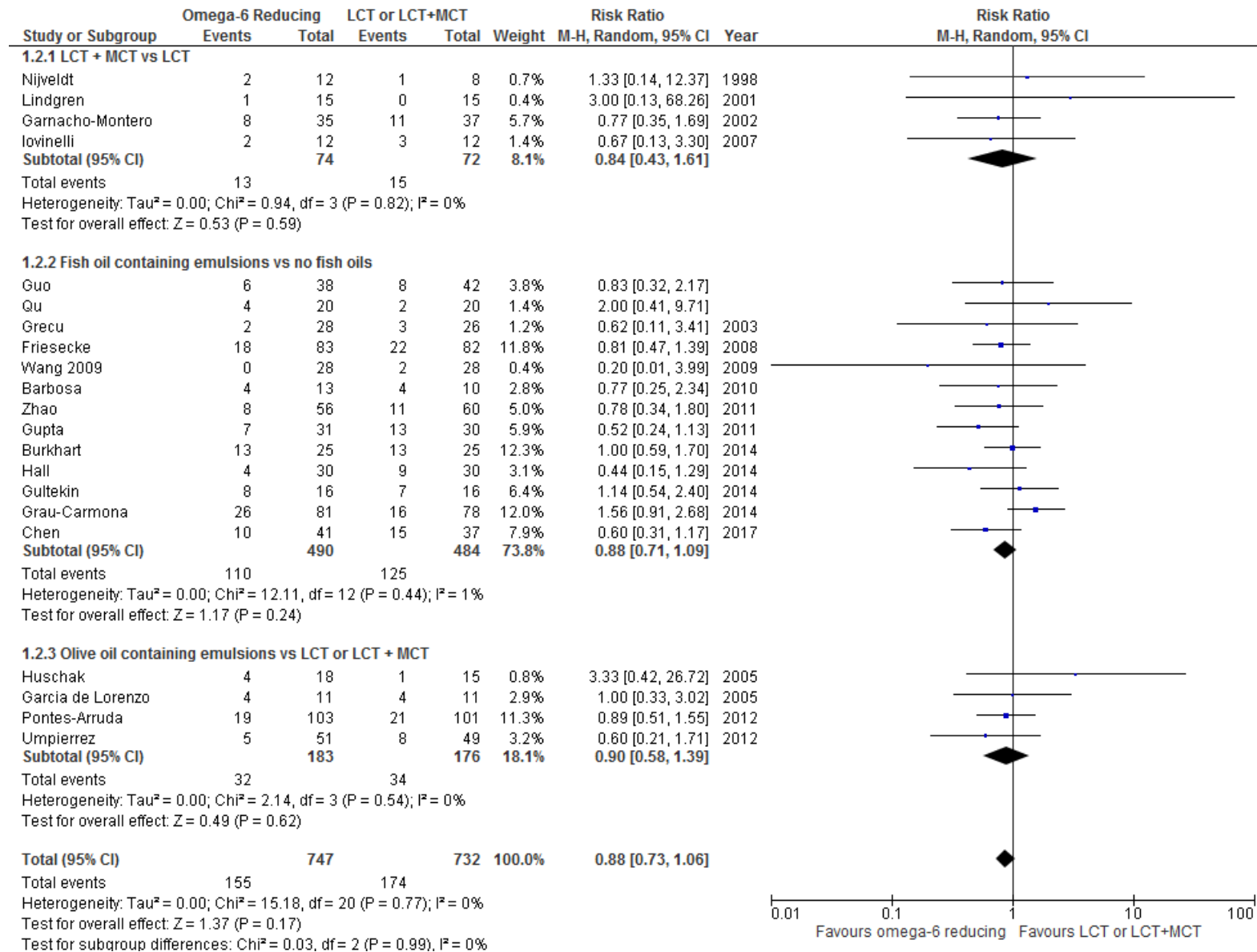


Figure 1.3 Infections in studies using an omega-6 reducing strategy

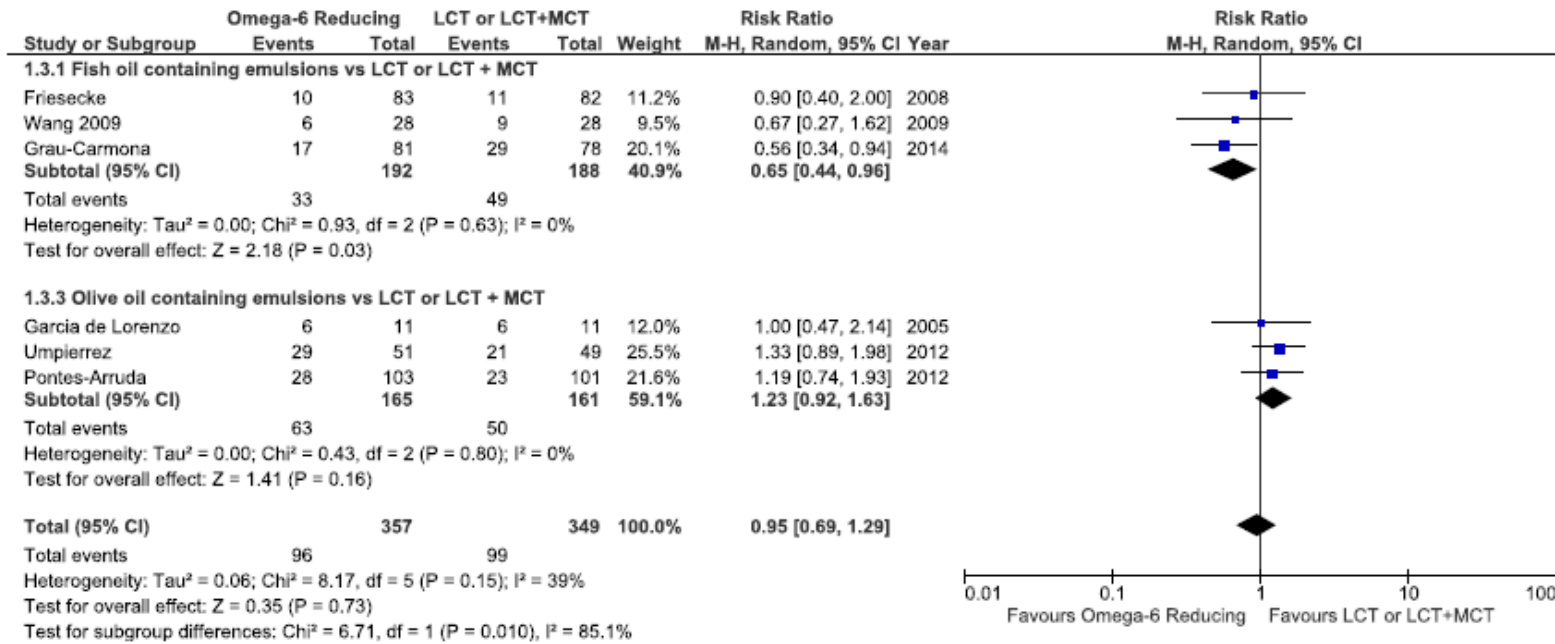


Figure 1.4 Infections in all studies (includes Hall)

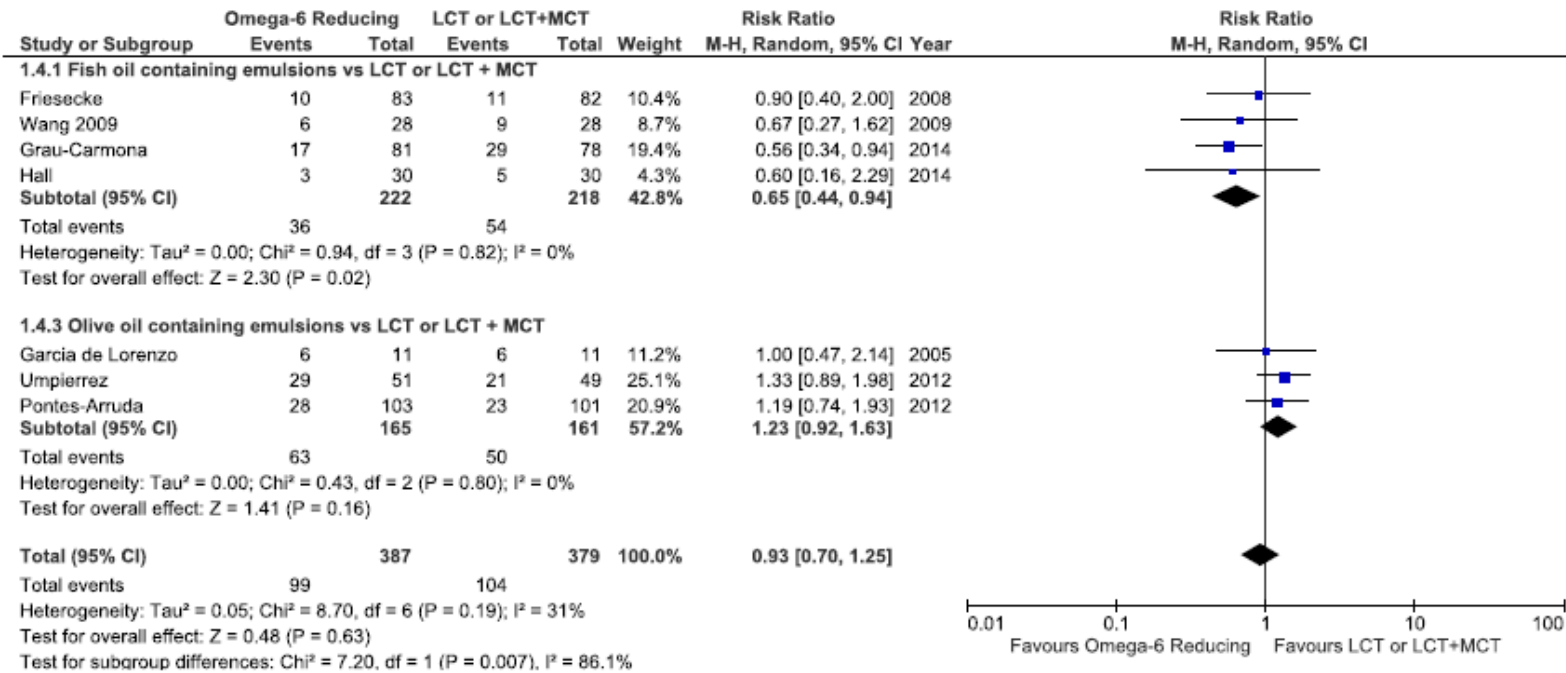


Figure 1.5 Hospital LOS in studies using an omega-6 reducing strategy

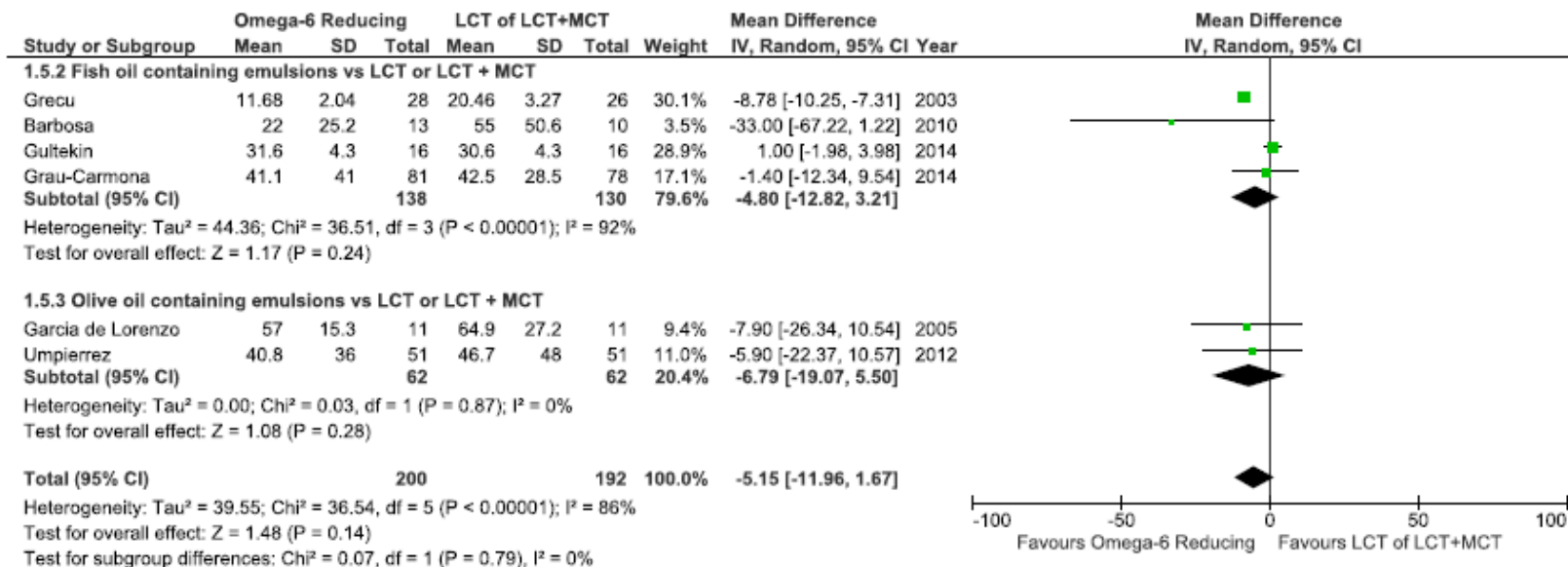


Figure 1.6 Hospital LOS in all studies (includes Khor, Gupta, Hall)

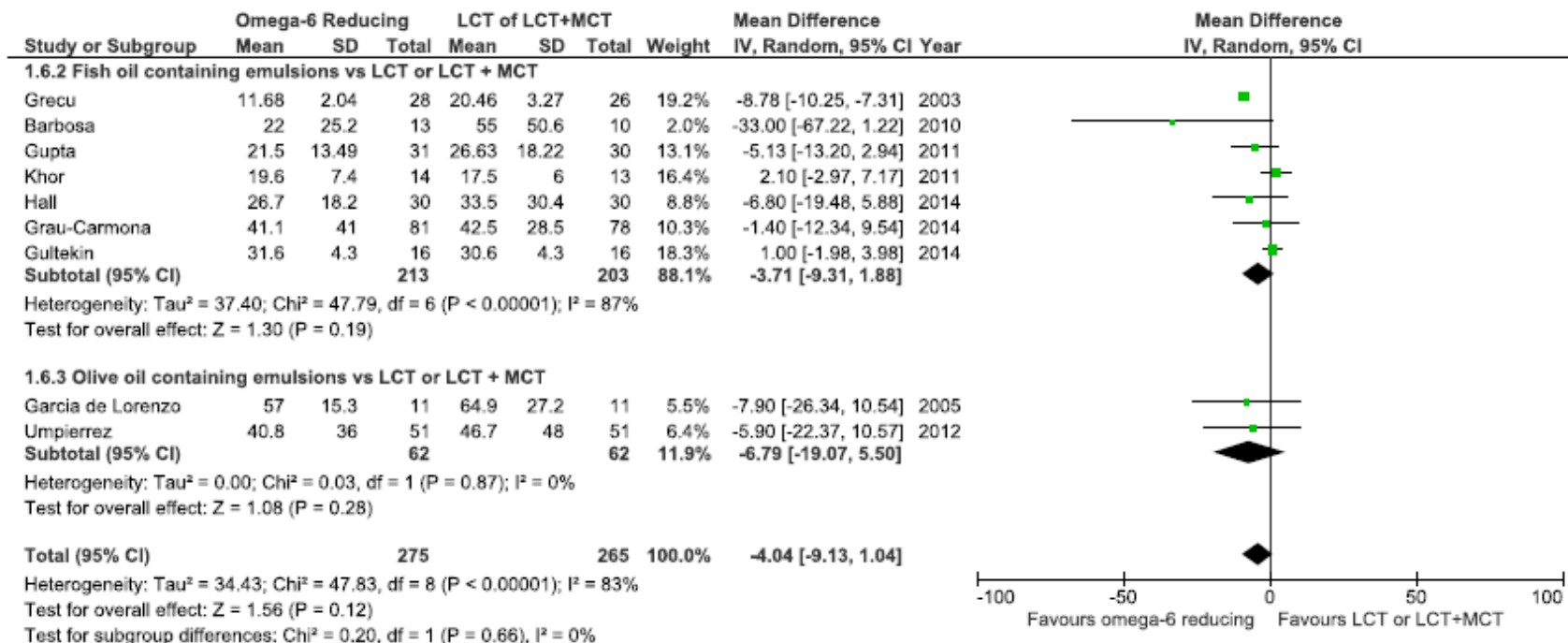


Figure 1.7 ICU LOS in studies using an omega-6 reducing strategy

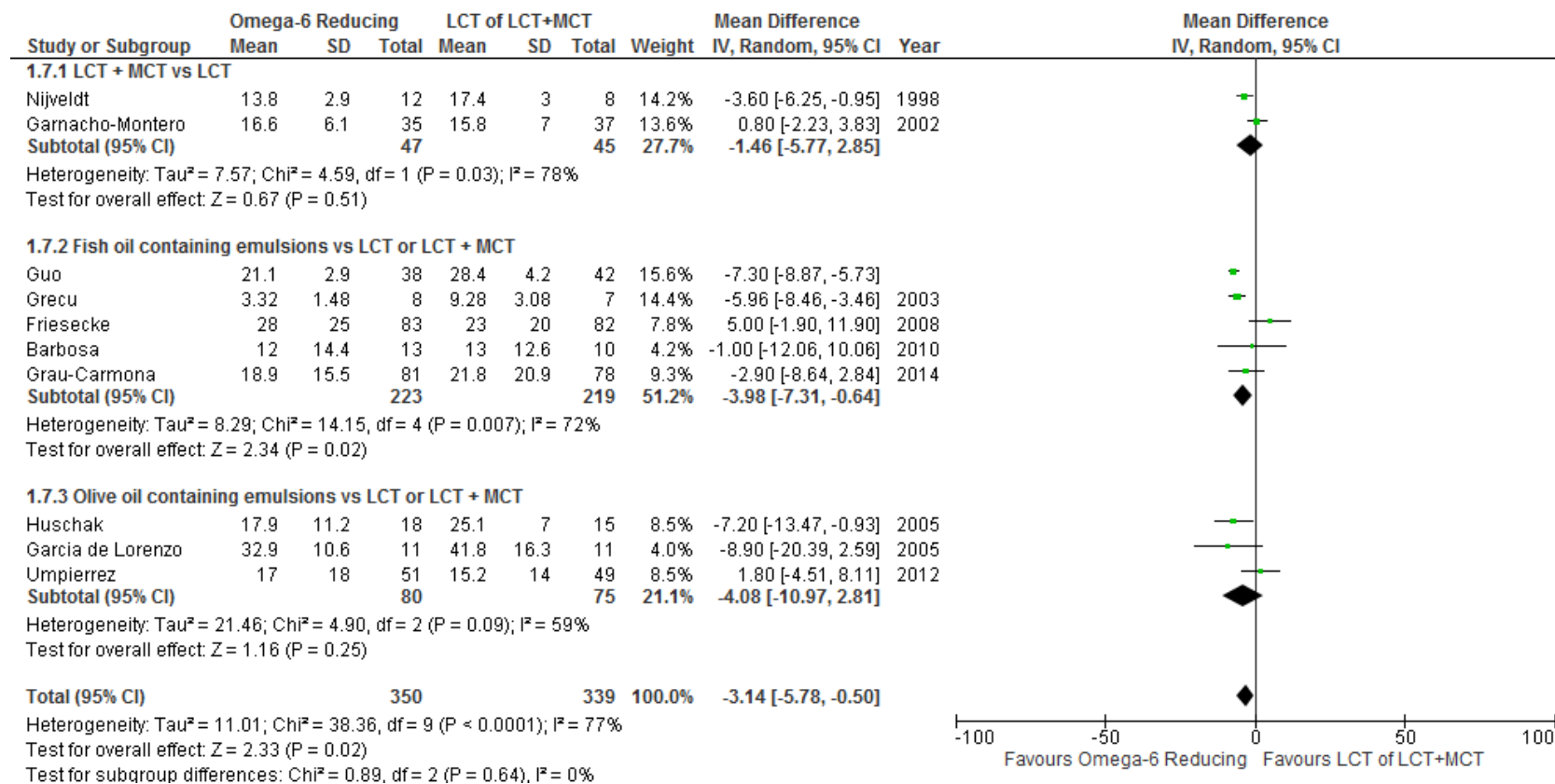


Figure 1.8 ICU LOS in all studies (includes Khor, Gupta, Zhao, Hall)

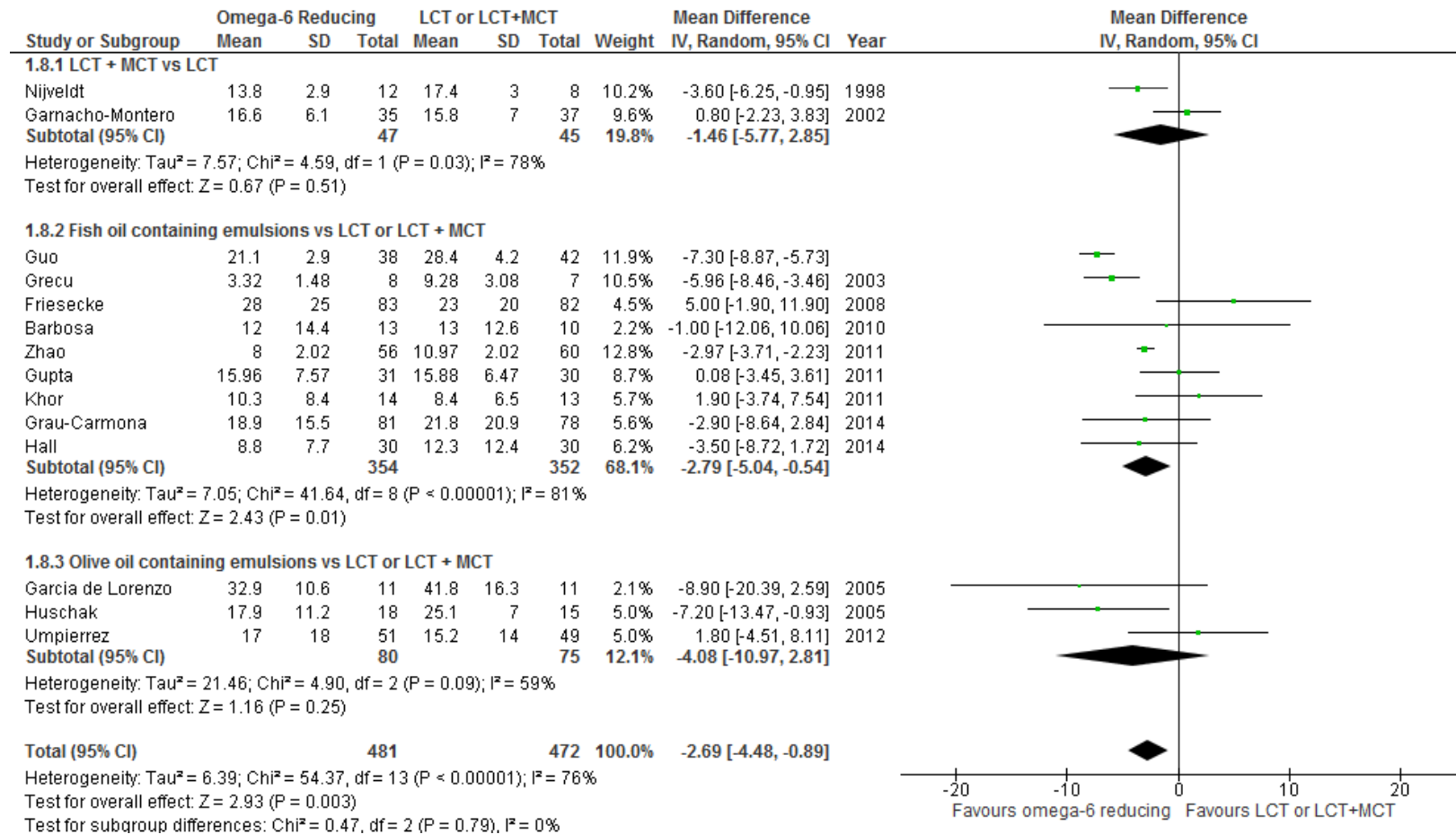


Figure 1.9 Ventilator Days in studies using an omega-6 reducing strategy

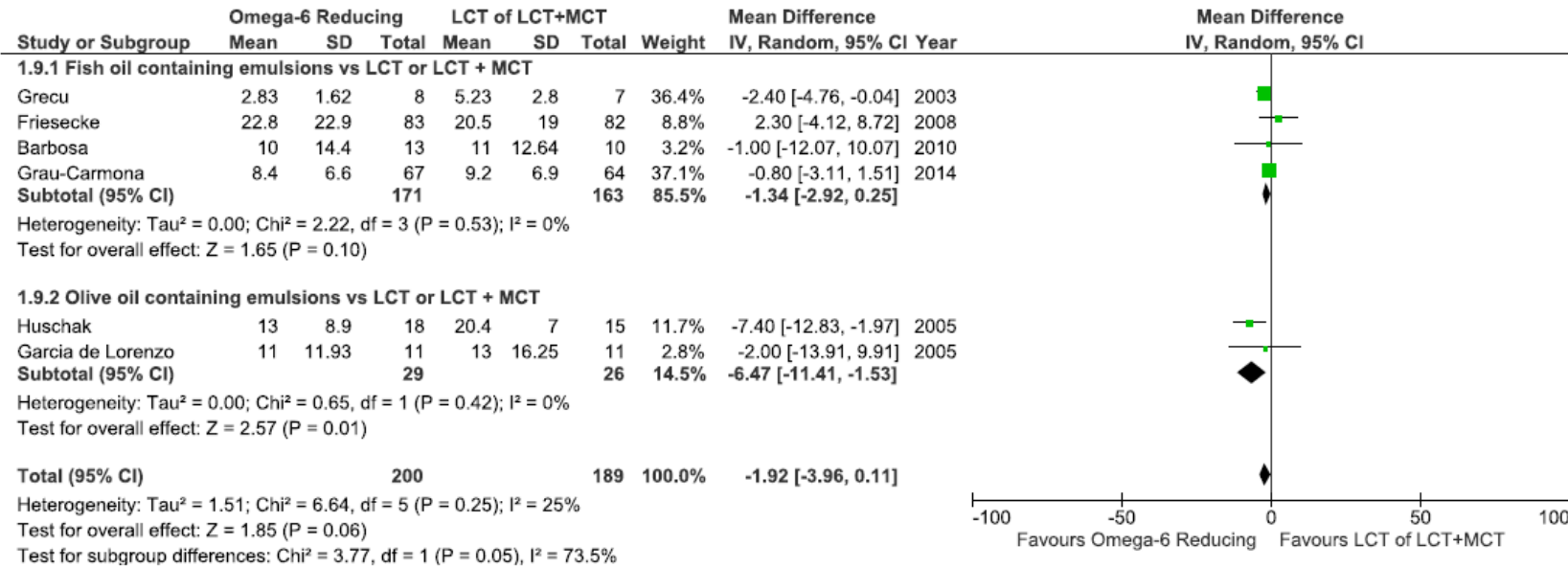


Figure 1.10 Ventilator Days in all studies (includes Khor, Gupta)

