9.3 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: A total of 21 level 2 studies (Nijveldt 1998, Lindgren 2001, Garnacho-Montero 2002, Garcia de Lorenzo 2005, Iovinelli 2007, Guo 2008, Wang 2009, Qu 2009, Barbosa 2010, Sabater 2011, Khor 2011, Zhao 2011, Pontes-Arruda 2012, Burkhart 2013, Gultekin 2014, Hall 2014, Wang 2014, Chen 2017a, Chen 2017b, Donaghue 2019 and Singer 2021) and 5 level 1 studies (Grecu 2003, Friesecke 2008, Gupta 2011, Umperrez 2012 & Grau Carmona 2014) were 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 clinical outcomes such as mortality or infections.
Twenty-one trials using parenteral nutrition compared varying strategies of reducing omega-6 fatty acids from soybean oil (SO), and 5 trials used FO as a stand-alone supplement (Gupta 2011, Khor 2011, Zhao 2011, Burkhart 2014 and Hall 2015)

Omega-6 reducing lipid emulsions: SO/MCT or SO/OO
Four trials compared mixtures of SO (long-chain triglycerides [LCTs]) plus medium chain triglycerides (MCT) (SO/MCT), to a SO (LCT) emulsion (Nijveldt 1998, Lindgren 2001, Garnacho-Montero 2002 and Iovinelli 2007). Additionally, 3 studies compared a mixture of soybean and olive oil (SO/OO, Clinoleic) to a SO/MCT mixture or SO (Garcia de-Lorenzo 2005, Umpierrez 2012 & Pontes-Arruda 2012). The trial by Pontes-Arruda include 3 groups: 1) multichambered bag (MCB) with OO/SO, 2) compounded PN with OO/SO and 3) compounded SO. In the meta-analysis, we have only included group 2 and 3 so as to evaluate the effect of OO and not effect of the MCB. The trial by Huschak was excluded from the meta-analysis because the PN strategies also varied by lipid and glucose composition

FO-containing lipid emulsions
The goal of FO-containing lipid emulsions was not only to lower amount the amount linoleic acid but to create a more favourable omega-3-to-omega-6 fatty acid ratio by adding a FO supplement to PN or either adding a FO containing lipid component to MCT/LCT (Lipoplus/Lipidem) or to blend of MCT/LCT and OO (SMOFlipid).[1]

[1] it is important to know that the fish oil enriched component of the two commercially available products Lipoplus and SMOFlipid comply with different European pharmacopeia (EP) monographs. Lipoplus complies with EP monograph 1352 “Omega-3-acid triglycerides” which is defined as a synthesized mixture of mono-, di- and triesters of omega-3 acids. Sum of the contents of the omega-3 acids EPA and DHA expressed as triglycerides is not less than 45%. SMOFlipid complies with EP monograph 1912 “Fish oil, rich in omega-3 acids” which describes purified fish oil rich in omega-3 fatty acids. The monograph specifies that the content of EPA is not less than 13% and a content of DHA not less than 9%. Lipoplus contains 10% omega-3 acid triglycerides and SMOFlipid contains 15% fish oil, rich in omega-3 acids. Although omega-3 fatty acids are derived from natural sources (leading to slight variations in concentration), the actual concentrations of EPA and DHA in SMOFlipid and Lipoplus are comparable according to existing literature. Both products provide approximately the same omega-3-to-omega-6 (ratio of 1:2.5 to 1:2.6).

Seven trials of patients receiving parenteral nutrition compared lipid emulsions supplemented with fish oil (FO) (i.v. FO supplement Omegaven) to SO, MCT/SO or OO/SO (Grecu 2003, Friesecke 2008, Wang 2009, Gultekin 2014, Wang 2014, Chen 2017a, and Chen 2017b). The added FO emulsion was not specified in two trials (Guo 2009 and Qu 2009). Four trials compared a ready-to-use mixture of SO, MCT and FO[2] (SO/MCT/FO, Lipoplus) to SO/MCT (Barbosa 2010, Grau-Carmona 2014, Singer 2021) or SO (Sabater 2011), and 1 study compared another ready-to-use mixture of SO, MCT, olive oil (OO) and FO[3] (SO/MCT/OO/FO, SMOFlipid) to LCT (Donoghue 2019).
Singer 2021 used an EN product enriched with fish oils in the intervention group, which was different than all other trials. The dose from parenteral fish oils was initially low (<0.05 g/kg/d on d1-5, >0.05 g/kg/d from d6) and most of the fish oils were derived from the enteral product so the effect of this trial was evaluated in a *sensitivity analysis* where it was excluded (See Table 2 on Fish Oil Dosing).

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.

Another 5 trials compared stand alone fish oil enriched IV lipid emulsions in patients fed as per usual clinical routine where the control patients received standard of care (Gupta 2011, Khor 2011, Zhao 2011, Burkhart 2013 and Hall 2014). These trials were analyzed separately.

Subgroup Analyses
We compared the effect of SO/MCT or SO/OO vs SO and FO-containing PN vs SO or SO/MCT or SO/OO. In addition, as Omegaven (10% lipid emulsion from pure fish oils) was used in 12 trials (7 were PN-fed trials and 5 were in the context of a stand-alone supplement), we performed a comparison of the trials of Omegaven vs. non-Omegaven fish oil containing strategies.

[2] FO component as Omega-3 Acid Triglycerides according to Pharm Eur Monograph 1352
[3] FO component as Fish oil, Rich in EPA and DHA according to Pharm Eur Monograph 1912

Mortality:

Overall omega-6 fatty acid reducing strategy: When all the trials that used an omega-6 fatty acid sparing strategy, excluding those in which the FO supplements were given as a stand-alone intervention, were aggregated, the use of a lower omega-6 fatty acid strategy was not associated with a significant reduction in overall mortality (RR 0.91, 95% CI 0.76, 0.10. p=0.34, test for heterogeneity I^2 = 0%.; figure 1.1). However, a trend towards reduction in 28-day mortality was observed (RR 0.79, 95% CI 0.61, 1.02, p=0.07, I^2 = 0%; figure 2.1)

When sensitivity analysis was done without the Singer 2021 trial, a similar results was observed for overall mortality (RR 0.91, 95% CI 0.75, 1.11, p=0.36, test for heterogeneity I^2 = 0%.; figure 1.2), and 28-day mortality (RR 0.77, 95% CI 0.59, 1.02, p=0.07, I^2 = 0%; figure 2.2)

In subgroup analyses, neither SO/MCT or SO/OO vs OO (RR 0.89, 95% CI 0.65, 1.23, p=0.50, test for heterogeneity I^2 = 0%.; figure 1.3) nor FO-containing PN vs SO or SO/MCT or SO/OO (RR 0.92, 95% CI 0.72, 1.16, p=0.47, test for heterogeneity I^2 = 4%.; figure 1.3) had an effect on overall mortality. The test for subgroup differences were non-significant (p=0.91).
A trend towards reduction of 28-day mortality was found for FO-containing PN vs SO or SO/MCT or SO/OO (RR 0.74, 95% CI 0.54, 1,01, p=0.06, I^2 = 0%; figure 2.3). The test for subgroup differences were non-significant (p=0.50).

SO/MCT vs. SO: A meta-analysis of the studies of SO/MCT vs. SO showed no difference in overall mortality between the groups (RR 0.90, 95% CI 0.55, 1.48, p=0.68, heterogeneity I^2=0%; figure 1.1). No studies reported 28-day mortality (figure 2.1)
SO/OO vs SO/MCT or SO: We observed no difference in overall mortality (RR 0.89, 95% CI 0.59, 1.34, p = 0.57, heterogeneity I^2=0%; figure 1.1) and 28-day mortality (RR 0.91, 95% CI 0.56, 1.47, p = 0.69, figure 2.1) between the groups receiving the OO containing emulsions compared to SO/MCT or SO
FO containing PN vs. SO or SO/MCT or SO/OO: With respect to studies of FO enriched PN vs. SO or SO/MCT or SO/OO, no significant reduction in overall mortality was observed (RR 0.92, 95% CI 0.72, 1.16, p = 0.47, test for heterogeneity I^2 =4%; figure 1.1). In the sensitivity analyses without the Singer 2021 trial, the result was similar (RR 0.90, 95% CI 0.69, 1.18, p = 0.46, test for heterogeneity I^2 =12%; figure 1.2). However, a trend towards lower 28-day mortality was observed in the main (RR 0.74, 95% CI 0.54, 1.01, p=0.06, I^2 =0%; figure 2.1 and sensivitiy (RR 0.72, 95% CI 0.51, 1.01, p=0.05, I^2 =0%; figure 2.2) analyses.

Omegaven vs. other oils:

FO containing PN: Omegaven was associated with a significant reduction in overall (RR 0.68, 95% CI 0.48, 0.95, p=0.03, test for heterogeneity I^2 =0%; figure 1.4) and 28-day mortality (RR 0.63, 95% CI 0.41, 0.99, p=0.05, I^2 =16%; figure 2.4) while other fish oil emulsions had no effect on overall (RR 1.19, 95% CI 0.87, 1.62, p=0.27, test for heterogeneity I^2 =0%; figure 1.4) and 28-day (RR 0.91, 95% CI 0.56,

1.51, p=0.74, I^2 =0%; figure 2.4) mortality. The test for subgroup differences was significant for overall (p=0.02) but not 28-day (p=0.28) mortality..

In the sensitivity analyses that excluded the Singer 2021 trial, the effects of other fish oil emulsions on overall mortality were similar for both overall (RR 1.26, 95% CI 0.90, 1.77, p=0.18, test for heterogeneity I^2 =0%; figure 1.5) and 28-day mortality (RR 0.94, 95% CI 0.49, 1.83, p=0.86, I^2 =0%; figure 2.5), test for subgroup differences was significant in overall (p=0.01) but not 28-day mortality (p=0.33).

Stand-alone FO emulsion supplement vs. standard care: When these FO trials in which the control group received no lipids were aggregated, a trend towards significant reduction in overall mortality(RR 0.76, 95% CI 0.53, 1.10, p=0.14, test for heterogeneity I^2 =0%; figure 1.6), and a significant reduction of 28-day mortality (RR 0.60, 95% CI 0.36, 0.99, p=0.04, I^2 =0%; figure 2.6) were found. All aggregated trials used omegaven FO.

In studies that reported **ICU mortality**, no differences between groups were found in the overall and the subgroup analyses. None of the trial on stand-alone FO emulsion reported ICU mortaltiy (figure 3.1 to 3.4)

In studies that reported **hospital mortality**, no differences no differences between groups were found in the overall and the subgroup analyses (figure 3.1-3.3). A trend towards reduced hospital morality was found when the 2 trials of stand-alone FO supplement were aggregated (RR 0.59, 95% CI 0.34, 1.04, p=0.07, I^2 =0%; figure 4.4)

Infections:

Overall omega-6 fatty acid reducing strategy: When all 7 studies that used an omega-6 fatty acid sparing strategy were aggregated, the use of a lower omega-6 fatty acid emulsion had no effect on infections (RR 0.94, 95% CI 0.70, 1.26, p = 0.68, I^2=32%; figure 5.1).

In subgroup analyses, **SO/OO vs SO/MCT or SO** were associated with a trend towards an increase in overall infections (RR 1.23, 95% CI 0.92, 1.63, p=0.16, I^2 = 0%.; figure 5.1) while **FO-containing PN** were associated with a significant reduction in infections (RR 0.65, 95% CI 0.44, 0.95, p=0.03, I^2 = 0%.; figure 5.1). There was a significant difference between the two subgroups (p=0.008).

Omegaven vs. other fish oils:

FO enriched PN: When the data from 3 studies of Omegaven were aggregated, there was no effect on overall infections (RR 0.77, 95% CI 0.44, 1.36, p=0.37, I^2=0%; figure 5.2) while in one study a significant reduction in infections was seen in the group receiving fish oil emulsion other than Omegaven (Grau-Carmona 2014, RR 0.56, 95% CI 0.34, 0.94, p=0.03; figure 5.2). Test for subgroup differences was not significant (p=0.43)**.**

FO vs. standard (no lipids): only one trial that used Omegaven was found, hence a subgroup comparison to non Omegaven studies was not possible (figure 5.2).

Stand-alone FO emulsion supplement vs. standard care: When examining the only trial of fish oils in which the control group received no IV soybean oil, no effect was seen on infections (Hall 2014, RR 0.60, 95% CI 0.16-2.29; p=0.45; no figure shown).

Hospital LOS:

Overall omega-6 fatty acid reducing strategy: When the 6 studies that used an omega-6 fatty acid sparing strategy were aggregated, the use of a lower omega-6 fatty acid emulsion was associated with a significant reduction in hospital LOS (WMD -6.88, 95% CI -11.27, -2.49, p=0.0.002, test for heterogeneity I^2=20%; figure 6.1).

In subgroup analyses**, SO/OO vs SO/MCT or SO** had no significant effect on hospital LOS (WMD -6.80, 95% CI -19.17, 5.57, p=0.28, test for heterogeneity I^2= 0%; figure 3.2). A trend towards shorter hospital LOS was observed with **FO enriched PN vs. SO or SO/MCT or SO/OO** (WMD -5.93, 95% CI -13.13, 1.27, p=0.11, test for heterogeneity I^2= 51%; figure 6.1). The test for subgroup differences was not significant (p=0.90).

Omegaven vs. other fish oils:

FO enriched PN: When the data from 2 studies of Omegaven were aggregated, there was no effect on hospital length of stay (WMD -5.75, 95% CI -14.61, 3.11; p=0.20, test for heterogeneity I^2=61%; figure 6.2) and a similar lack of effect was seen in the aggregated data from the two studies of other fish oil emulsions (WMD -12.87, 95% CI -42.65, 16.91, p=0.40, test for heterogeneity I^2=92%; figure 3.3). Test for subgroup differences was not significant (p=0.65)**.**

FO vs. standard (no lipids): all three studies used Omegaven, hence a subgroup comparison to non Omegaven studies was not possible.

Stand-alone FO emulsion supplement vs. standard care: Fish oil emulsions had no effect on hospital LOS when compared to standard care (WMD = 0.78, 95% CI -2.89, 4.46, p=0.68, test for heterogeneity I^2= 0%; figure 6.3).

ICU LOS

Overall omega-6 fatty acid reducing strategy: When all 12 studies that used an omega-6 fatty acid sparing strategy were aggregated, the use of a lower omega-6 fatty acid emulsion was associated with a trend towards a reduction in ICU LOS (WMD -1.94, 95% CI -4.41, 0.52, p=0.12, test for heterogeneity I^2=83%; figure 7.1).

In subgroup analysis, SO/MCT or SO/OO vs SO had no effect on ICU LOS (WMD 1.74, 95% CI -2.17, 5.66, p=0.38, test for heterogeneity I^2= 50%; figure 7.2); however, FO-containing PN vs SO or SO/MCT or SO/OO signifincantly reduced ICU LOS (WMD -3.53, 95% CI -6.16 to -0.90, p=0.009, I^2= 82%; figure 7.2) There was a significant difference between the two subgroups (p=0.03).

SO/MCT vs SO: No difference in ICU LOS between the two groups (WMD 3.03, 95% CI -2.02, 8.07, p=0.24; figure 7.1).

SO/OO vs. SO/MCT or SO: When the data from the two studies of olive oil emulsions vs SO/MCT or SO were aggregated, olive oil emulsions had no effect on ICU length of stay (WMD -2.09, 95% CI -12.17, 8.00, p=0.69, test for heterogeneity I^2=55%; figure 7.1).

FO containing PN vs. SO or MCT/SO or OO/SO: When the data from the eight studies of fish oil emulsions vs SO+ MCT or SO were aggregated, a significant reduction in ICU LOS was observed in the fish oil group (WMD -3.53, 95% CI -6.16 to -0.90, p=0.009, I^2= 82%; figure 7.1).

Omegaven vs. other fish oils:

FO enriched PN: When the data from 4 studies of Omegaven were aggregated, there was a trend towards reduction in ICU length of stay (WMD -3.15, 95% CI -6.89, 0.59, p=0.10, test for heterogeneity I^2=79%; figure 7.3). Similarly, when the data were aggregated from the four studies of other fish oil emulsions, a trend towards reduction in ICU LOS was observed (WMD -3.81, 95% CI -7.96, 0.34, p=0.07, test for heterogeneity I^2=75%; figure 7.3). Test for subgroup differences was not significant (p=0.82).

FO vs. standard (no lipids): all four studies used Omegaven, hence a subgroup comparison to non Omegaven studies was not possible.

Stand-alone FO emulsion supplement vs. standard care: When these trials were statistically aggregated, there was a trend towards reduced ICU LOS (WMD -1.38, 95% CI –4.11, 1.34, p=0.32; test for heterogeneity I^2=52%; figure 7.4).

Ventilator days:

Overall omega-6 fatty acid reducing strategy: A trend towards shoter duration of ventilation was found with Omega-6 fatty acid sparing strategies (WMD -0.87, 95% CI -1.82, 0.07, p=0.07, test for heterogeneity I^2=52%; figure 8.1).

In subgroup analyses, SO/MCT os SO/OO vs SO were associated with a significant reduction in ventilator days (WMD -3.26, 95% CI -5.32, -1.20, p=0.002, test for heterogeneity I^2= 0%; figure 8.2) while FO-containing PN had no effect on ventilator days (WMD -0.31, 95 % CI -1.07, 0.45, p=0.42, test for heterogeneity I^2= 39%; figure 8.2). The test for subgroup differences were significant (p=0.009).

SO/MCT vs SO: Only one study comparing SO+MCT to SO reported duration of ventilation and a significant reduction duration of mechanical ventilation in the SO+MCT group was observed (RR -3.30, 95% CI -5.39, -1.21, p=0.002; figure 8.1).

SO/OO vs. SO/MCT or SO: Only one study reported this outcome, and the use of olive oil emulsions had no effect on the duration of mechanical ventilation (WMD -2.00, 95% CI -13.92, 9.92, p=0.74; figure 8.1).

FO containing PN vs. SO or SO/MCT or SO/OO: When the data from the six studies of fish oils were aggregated, no effect on duration of mechanical ventilation was observed (WMD -0.31, 95% CI -1.07, 0.45, p=0.42, test for heterogeneity I^2=39%; figure 8.1).

Omegaven vs. other fish oils:

FO enriched PN: When the data from 3 studies of Omegaven were aggregated, there was no effect on ventilator days (WMD -0.87, 95 % CI -2.37, 0.63, p=0.26, test for heterogeneity I^2=35%; figure 8.3). Similar signals were seen when the three studies of other fish oil emulsions, were pooled (WMD 0.28, 95% CI -0.32, 0.88, p=0.36, test for heterogeneity I^2=0%; figure 8.3). Test for subgroup differences was not significant (p=0.16).

FO vs. standard (no lipids): both studies that reported on ventilator days used Omegaven, hence a subgroup comparison to non Omegaven studies was not possible.

Stand-alone FO emulsion supplement vs. standard care: When these two trials were statistically aggregated, no effect on ventilator days was observed (WMD 1.98, 95% CI –2.36, 6.31, p=0.37; test for heterogeneity I^2=0%; figure 8.4).

Other outcomes:

SO/MCT vs SO: A significant improvement in nutritional parameters (i.e., nitrogen balance, retinol binding protein, prealbumin) was observed in the groups receiving SO + MCT in some of the studies (Garnacho-Montero 2002, Lindgren 2001) and a significant reduction in the time of weaning was seen in one study (Iovinellei 2007).

SO/OO vs. SO/MCT or SO: No differences were found for multiple organ dysfunction score (Garcia-de-Lorenzo 2005) or other nutritional outcomes (Pontes-Arruda 2013, Umpierrez 2012)

FO containing PN vs. SO or SO/MCT or SO/OO: The use of FO 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 FO, 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). Singer 2021 reported a higher % patients tolerating EN alone at day 6 and higher catecholamine treatment free days in the omega 3 supplemented EN+PN group (p=0.34 and 0.05 respectively).

Conclusions: In critically ill patients,

1) Omega-6 FFA reducing strategies, also known as SO sparing strategies,
    a. are not associated with a significant reduction in overall, ICU or hospital mortality, but a trend towards lower 28-day mortality was observed
    b. are associated with a reduction in hospital LOS.
    c. may be associated with a reduction in ICU LOS and duration of mechanical ventilation
    d. have no effect on infections
2) SO/MCT emulsions, compared to SO, have no effect on mortality, infections, ICU or hospital length of stay in critically ill patients. There may be a significant reduction in duration of mechanical ventilation associated with SO/MCT but data points are too sparse to be sure (1 trial).
3) OO containing emulsions, compared to SO/MCT or SO,
    a. have no effect on mortality or ICU/hospital LOS or duration of mechanical ventilation.
    b. may be associated with increased infections
4) FO containing PN vs. SO or MCT/SO or OO/SO:
    a. are not associated with a significant reduction in overall, ICU or hospital mortality but a trend towards lower 28-day mortality was observed
    b. are associated with a significant reduction in infectious complications and ICU LOS.
    c. may be associated with a reduction in duration of mechanical ventilation
    d. have no effect on hospital LOS
5) Stand-alone FO emulsion supplement vs. standard care
    a. is associated with a reduction of 28-day mortality and a trend towards reduction in overall and hospital mortality/
    b. may be associated with a reduction in ICU LOS
    c. have no effect on ICU mortality, infectious complications, duration of mechanical ventilation, or hospital LOS.
6) Compared to SO/MCT or SO/OO, FO-containing lipid emulsions
    a. are associated with a significant reduction in infectious complications and ICU LOS
    b. have no impact on mortality, hospital LOS and ventilator days.
7) Compared to non-Omegaven containing PN or IV nutritional strategies, Omegaven containing PN or IV strategies
    a. May be associated with a significant reduction in mortality.

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 trials evaluating type of lipids (PN) in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
(A) SO/MCT vs. SO							
1) Nijveldt 1998	ICU, septic surgical patients, trauma N=20	C.Random: not sure ITT: yes Blinding: double (9)	PN + Lipofundin (50% MCT+ 50% SO) vs. PN + Intralipid (100% SO)	**MCT/SO Not specified** 2/12 (17)	**SO Not specified** 1/8 (13)	**MCT\SO** NR	**SO** NR
2) Lindgren 2001	ICU patients, sepsis, multi-trauma N=20	C.Random: yes ITT: No Blinding: double (7)	PN + Structolipid (36% MCT/ 64%SO) vs. PN + Intralipid (100% SO)	**MCT/SO Hospital** 4/9 (44.4)	**SO Hospital** 5/11 (45.5)	NR	NR
3) Garnacho-Montero 2002	Surgical ICU Patients with peritonitis and abdominal sepsis N=72	C.Random: No ITT: Yes Blinding: no (4)	PN + Lipofundin (50% MCT + 50% SO) vs. PN with Intralipid (100% SO) Both groups received PN with 45 % Branched chain amino acids	**MCT/SO ICU** 8/35 (23) **Hospital** 11/35 (31)	**SO ICU** 11/37 (30) **Hospital** 13/37 (35)	**MCT/SO** NR	**SO** NR
4) Iovinelli 2007	Patients with COPD requiring ventilation N=14 (of 24)	C.Random: not sure ITT: no Blinding: no (4)	PN + Lipofundin (50% MCT + 50% SO) vs. 100% SO. In both received 50% of non-protein calories given as lipids	**MCT/SO 15-d** 2/7 (28.6)	**SO 15-d** 3/7 (42.9)	**MCT/SO Catheter-related** 1/12 (8)	**SO Catheter-related** 2/12 (17)
(B) SO/OO vs. SO/MCT or SO							
5) 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% OO, 20% SO, (63% ω9, 37% ω6= restricted linoleic acid {ω6} content) vs. Lipofundin (50% MCT+ 50% SO).	**OO/SO ICU=Hosp=6-mo** 4/11 (36)	**MCT/SO ICU=Hosp=6-mo** 3/11 (27.3)	**OO/SO 6/11 (55)**	**MCT/S) 6/11 (55)**

6) 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 compounded ClinOleic 80% OO, 20% SO (n=103) vs compounded PN with a MCT/SO (n=101)	**OO/SO ICU** 19/103 (24) **28-day=Hosp*** 24/103 (27)	**MCTSO ICU** 21/101 (21) **28-day=Hosp*** 26/101 (26)	**OO/SO** **All infections** 39/103 (38) **ICU acquired infections** 28/103 (27) **VAP/lower respiratory infections** 9/103 (9)	**MCT/SO** 35/101 (35) 23/101 (23) 11/101 (11)
7) Umpierrez 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%OO, 20% SO,, ω6:ω3=9:1) vs Intralipid (100% SO, ω6:ω3=7:1)	**OO/SO Hospital** 5/51 (10)	**SO Hospital** 8/49 (16)	**OO/SO** 29/51 (57) **Pneumonia** 7/51 (14)	**SO** 21/49 (43) 5/49 (10)
(C) FO containing PN vs. SO or SO/MCT or SO/OO							
8) 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 SOs vs. PN with SO	**FO/SO ICU** 2/28 (7)	**SO ICU** 3/26 (12)	**FO/SO VAP** 0/8	**SO VAP** 1/7 (14)
9) Friesecke 2008	Medical ICU patients N=166	C.Random: yes ITT: yes Blinding: double (10)	PN + Lipofundin (50% MCT + 50% SO) + Omegaven (10% fish oil) vs. Lipofundin MCT (50% MCT + 50% SO)	**FO/MCT/SO 28 day** 18/83 (22)	**MCT/SO 28 day** 22/82 (27)	**FO/MCT/SO** 10/83 (12)	**MCT/SO** 11/82 (13)
10) Guo 2008	Septic ICU patients with APACHE II > 12 N=80 (of 88)	C.Random: no ITT: no Blinding: no (4)	PN with 20% lipid emulsion with an added 100 ml of Omega-3 PUFAs (product not specified) vs PN with 20% lipid emulsion	**FO 28 day** 6/38	**SO 28 day** 8/42	NR	NR
11) Qu 2009	Severe sepsis patients N=40	C.Random: no ITT: no Blinding: no (5)	Routine PN + omega 3 FO emulsion (product not specified) at 1-2 ml/kg/d vs routine PN.	**FO 28 day** 4/20 (20)	**Standard 28 day** 2/20 (10)	NR	NR
12) Wang 2009	Severe acute pancreatitis patients in ICU N=56	C.Random: no ITT: yes Blinding: double (11)	PN + Omegaven (10% FO) plus Lipovenos (SO) (ω3:ω6 ratio was 1:4) vs. PN with Lipovenos (SO). Both received same amounts of lipids (1 gm/kg/day) Note: Lipovenos contains 20% MCT	**FO ICU** 0/28 (0)	**SO ICU** 2/28 (7)	**FO** 6/28 (21)	**SO** 9/28 (32)

13) 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%SO, 10% FO) vs. Nutriflex LipidSpecial (50% MCT, 50% SO). Both received same amounts of lipids (~1 gm/kg/day)	**FO/MCT/SO** **5 day** 2/13 (15) **28 day** 4/13 (31)	**MCT/SO** **5 day** 1/10 **(**10) **28 day** 4/10 (40)	**FO/MCT/SO** NR	**MCT/SO** NR
14) Sabater 2011	ARDS pts requiring MV and PN	C.Random: unknown ITT: yes Blinding: unknown (9)	Group A: Lipoplus 20% B. Braun Medical (50% MCT, 40% LCT, 10% FO). Group B: Intralipid 20% Fresenius Kabi (100% LCT). The lipids emulsions were administered for 12h at 0.12 g/kg/h in both groups	**FO/MCT/SO** **not specified** 4/8 (50)	**SO** **not specified** 2/8 (25)	NR	NR
15) Grau Carmona 2014	Medical and surgical pts requiring TPN N=159 (of 175)	C.Random: yes ITT: no Blinding: double (8)	PN + Lipoplus (50% MCT, 40% SO, 10% FO vs PN + Lipofundin (50% MCT + 50% SO)	**FO/MCT/SO** **ICU** 26/81 (32.5) **Hospital** 32/81 (39.5) **6-month** 34/81 (42)	**MCT/SO** **ICU** 16/78 (20.5) **Hospital** 22/78 (28.3) **6-month** 24/78 (30.8)	**FO/MCT/SO** 17/81 (21)	**MCT/SO** 29/78 (37.2)
16) Gultekin 2014	ICU pts needing TPN N=32 (of 58)	C.Random: unknown ITT: other Blinding: double (4)	PN + 100ml/day Omegaven (10% FO) plus Clinoleic (80% OO, 20% SO) vs PN + Clinoleic. Both groups were prescribed IV lipids to provide 30-40% of total energy requirements.	**FO/OO/SO** **Not specified** 7/16 (44)	**OO/SO** **Not specified** 8/16 (50)	NR	NR
17) Wang 2014	Abdominal sepsis patients needing TPN for ≥5 days N=53	C.Random: unknown ITT: yes Blinding: unknown (6)	Routine PN + Omegaven 0.2 g/kg/day to replace part of routine PN lipid emulsion for 5 days vs Routine PN	NR	NR	NR	NR
18) Chen 2017a	ICU patients with SIRS N=78	C.Random: unknown ITT: yes Blinding: single (9)	PN containing 50g LCFA + 100 m/day containing 10g FO as Omegaven vs PN containing 50g LCFA. Both groups dosed at 20 kcal/kg for first 7 days, slowly increased to 30 kcal/kg afterwards	**FO/SO** **28 day** 10/41 **60 day** 11/41	**SO** **28 day** 15/37 **60 day** 18/37	NR	NR
19) Chen 2017b	Mechanically ventilated patients with systemic inflammation reaction syndrome and intestinal failure N=48	C.Random: no ITT: yes Blinding: double (9)	PN with 10 gms/day Omega-3 fatty acids (100 mls Omegaven) vs. standard PN (assumed to be LCT) Isocaloric (20 Kcal/kg/day in first 7 days)	**FO** **28 day** 3/24 (12.5%)	**SO** **28 day** 10/24 (41.7%) p =0.023	NR	NR

20) Donoghue 2019	Critically ill patients with SIRS, sepsis and/or ARDS N=68 (of 75)	C.Random: no ITT: no Blinding: double (7)	PN with SMOF lipid emulsion (30% SO, 30% MCT, 25% OO and 15% FO, ω6:ω3=2.5:1) vs. LCT Intralipid (100% SO ω6:ω3=7:1)	**SMOF ICU** 6/35 (18.4%)	**SO ICU** 5/33 (15.2%); p=0.71	NR	NR
21) Singer 2021	Mechanically ventilated patients, receiving <80% by EN alone N=95 (of 100)	C.Random: yes ITT: no Blinding: double (9)	Supplemental PN (Nutriflex Omega Special) with MCT/SO: Omega-3 PUFA of 4:5:1 (EPA+DHA: 1.8 g/ml) plus EN enriched with fish oils, borage oil & gamma linolenic acid (Oxepa) vs. Supplemental PN (Nutriflex lipid) with MCT/SO of 1:1 plus EN without fish oils (Pulmocare)	**FO EN+PN 28 day** 10/48 (20.8%) **90 day** 15/48 (31.3%)	**MCT/SO 28 day** 11/47 (23.4%); p=0.81 **90 day** 19/47 (40.4%); p=0.52	NR	NR
(D) Stand-alone FO emulsion supplement vs. standard care							
22) 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)	**FO 28-d** 7/31 (23) **Hospital** 9/31 (29)	**Standard 28-d** 13/30 (43) **Hospital** 14/30 (47)	NR	NR
23) Khor 2011	ICU patients with severe sepsis/septic shock N = 27 (of 28)	C.Random: yes ITT: No Blinding: double (8)	EN and/or oral diet supplemented with 100 ml 10% Omegaven (10g refined FO, 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	**FO** NR	**Standard** NR	NR	NR
24) Zhao 2011	ICU patients with sepsis N=116	C.Random: no ITT: no Blinding:no (5)	Omega-3 FO lipid emulsion (Omegaven), 100 ml qd for 5-7 days vs standard treatment	**FO 28-d** 8/56 (14)	**Standard 28-d** 11/60 (18)	NR	NR
25) Burkhart 2013	ICU Septic patients N=50	C.Random: unknown ITT: yes Blinding: single (assessor) (8)	2 ml.kg/d Omegaven vs no parenteral FO. Both groups received EN and/or PN without added fish oils at the discretion of the clinician.	**FO 1-year#** 13/25 (52)	**Standard 1-year#** 13/25 (52)	NR	NR
26) Hall 2014	ICU Septic patients N=60	C.Random: not sure ITT: yes Blinding: no (10)	Omegaven at 0.2 g FO /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.	**FO Hospital** 4/30 (13.3) **28 day** 4/30 (13.3)	**Standard Hospital** 9/30 (30) **28 day** 8/30 (26.7)	**FO** 3/30 (10)	**Standard** 5/30 (16.7)

#Burkhart 2013: Discharged patients were contacted by telephone after 1 year or later to determine survivorship; median follow-up time 109 (9-408 days)
*Info from author

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

Study	LOS days		Ventilator days		Other
SO/MCT vs. SO					
1) Nijveldt 1998	**MCT/SO** NR	**SO** NR	**MCT/SO** 13.8 ± 2.9 (12)	**SO** 17.4 ± 3.0 (8)	NR
2) Lindgren 2001	**MCT/SO** **ICU** 26±6 (9)	**SO** **ICU** 20±5 (11)	**MCT/SO** NR	**SO** NR	**MCT/SO** **SO** **Adverse effects** 6/9 (67) 4/11 (36.3) **Nitrogen balance at day 3** 2.6 ± 5.6 gms -11.7 ± 4.8 gms; p=0.061 **Nitrogen balance at day 6** 1.6±11.6 gms -29.3±11.1 gms; p=0.08
3) Garnacho-Montero 2002	**MCT/SO** **ICU** 16.6 ± 6.1 (35)	**SO** **ICU** 15.8 ± 7 (37)	**MCT/SO** NR	**SO** NR	**MCT/SO** **SO** **Retinol binding protein** 1.7 ± 1 0.8 ± 0.6 **Nitrogen balance** 14.2 ± 2.9 11.6 ± 4
4) Iovinelli 2007	**MCT/SO** NR	**SO** NR	**MCT/SO** 10.6 ± 3.0 (7)	**SO** 13.4 ± 3.5 (7)	**MCT/SO** **SO** **Time before weaning** 52 ± 36 hrs 127 ± 73 hrs
SO/OO vs. SO/MCT or SO					
5) Garcia-de-Lorenzo 2005	**OO/SO** **ICU** 32.9 ± 10.61[a] (11) **Hospital** 57 ± 15.26[a] (11)	**MCT/SO** **ICU** 41.8 ± 16.57[a] (11) **Hospital** 64.9 ± 27.20[a] (11)	**OO/SO** 11.0 ± 11.94[a] (11)	**MCT/SO** 13.0 ± 16.25[a](11)	**OO/SO** **MCT/SO** **Multiple organ dysfunction score** 11.0 ± 3.6 13.0 ± 4.9
6) Pontes-Arruda 2013	**OO/SO** **ICU** 12 (7-17) **Hospital** 21 (15-25)	**MCTSO** **ICU** 11 (5-14) **Hospital** 18 (13-23)	NR	NR	**OO/SO** **MCTSO** **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)

7) Umpierrez 2012	**OO/SO** **ICU** 17 ± 18 (51) **Hospital** 40.8 ± 36 (51)	**SO** **ICU** 15.2 ± 14 (49) **Hospital** 46.7 ± 48 (49)	NR	NR	**OO/SO** **SO** **Total Energy Intake (kcal/kg)** 22 ± 6 22 ± 5
FO containing PN vs. SO or SO/MCT or SO/OO					
8) Grecu 2003*	**FO/SO** **ICU** 3.32 ± 1.48 (8) **Hospital** 11.68 ± 2.04 (28)	**SO** **ICU** 9.28 ± 3.08 (7) **Hospital** 20.46 ± 3.27 (26)	**FO/SO** 2.83 ± 1.62 (8)	**SO** 5.23 ± 2.80 (7)	**FO/SO** **SO** **Patients undergoing reoperation for septic episode** 2/28 (7) 8/26 (31)
9) Friesecke 2008	**FO/MCT/SO** **ICU** 28 ± 25 (83)	**MCT/SO** **ICU** 23 ± 20 (82)	**FO/MCT/SO** 22.8 ± 22.9 (83)	**MCT/SO** 20.5 ± 19.0 (82)	**FO/MCT/SO** **MCT/SO** **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
10) Guo 2008	**FO** **ICU** 21.1±2.9	**SO** **ICU** 28.4±4.2	NR	NR	NR
11) Qu 2009	NR	NR	NR	NR	NR
12) Wang 2009	NR	NR	NR	NR	**FO** **SO** **Surgery of infected pancreatic necrosis** 3/28 (11) 6/28 (21)
13) Barbosa 2010	**FO/MCT/SO** **ICU** 12 ± 14.4[a] (13) **Hospital** 22 ± 25.2[a] (13)	**MCT/SO** **ICU** 13 ± 12.6 [a] (10) **Hospital** 55 ± 50.6 [a] (10)	**FO/MCT/SO** 10 ± 14.4 (13)	**MCT/SO** 11 ± 12.64 (10)	**FO/MCT/SO** **MCT/SO** 2057± 418 kcals 1857 ± 255 kcals **PO2/FiO2 ratio at day 6** 331±71 vs 245±107 (p=0.047)
14) Sabater 2011	NR	NR	NR	NR	NR
15) Grau Carmona 2014	**FO/MCT/SO** **ICU** 18.9±15.5 (81)	**MCT/SO** **ICU** 21.8±20.9 (78)	**FO/MCT/SO** 8.4±6.6 (67)	**MCT/SO** 9.2±6.9 (64)	**FO/MCT/SO** **MCT/SO** **Parenteral lipid intake [(g/kg BW)/d]** 1.04 ± 0.12 1.05 ± 0.13 **PN kcal**

	Hospital 41.1±41.0 (81)	**Hospital** 42.5±28.5 (78)			1,737 ± 353 1,782 ± 312
16) Gultekin 2014	**FO/OO/SO** **Hospital** 31.6 ± 17.2 (16)	**OO/SO** **Hospital** 30.6 ± 17.2 (16)	NR	NR	**FO/OO/SO OO/SO** **Kcal/kg/day** 27.5±1.5 15.8±1.5 **g protein/kg/d** 1.3±0.2 1.1±0.1
17) Wang 2014	**Routine TPN+ FO** 7.75±1.90 (25)	**Routine TPN** 10.03±2.15 (28); p<0.01	**Routine TPN+ FO** 2.43±1.06 (25)	**Routine TPN** 2.94±1.37 (28); p>0.05	**Routine TPN+ FO Routine TPN** **Days on CRRT** 3.15±1.98 3.83±1.32; p>0.05
18) Chen 2017a	NR	NR	NR	NR	NR
19) Chen 2017b	**FO** **ICU** 13.8 ± 9.9	**SO** **ICU** 24.4 ± 23.2, p =0.046	NR	NR	**FO SO** **APACHE II day 7** 16.1 ± 6.1 21.5 ± 8, p=0.019 **MARSHALL score** 6.2 (2.5) 8.6 (4.3), p=0.026
20) Donoghue 2019	**SMOF** **ICU** 9.5 ± 7.09	**SO** **ICU** 10.7 ± 7.6; p= 0.49	**SMOF** 1.24 ± 0.83	**SO** 0.88 ± 1.63; p=0.39	**SMOF SO** **Day 3 maximum intake of PN before start of EN** **Energy, kcal** 2249.9 ± 386.1 vs. 2222.6 ± 352.4; p=0.76 **Protein, g/kg** 1.33±0.16 vs. 1.39 ± 0.2; p=0.16
21) Singer 2021	**FO** **ICU** 23 (15-28) **Hospital** 33 (24-57)	**MCT/SO** **ICU** 24 (17-36); p=0.68 **Hospital** 39 (26-65); p=0.45	**Ventilation free days, Omega 3** **FO** 9.2 ±9.4 (48)	**Ventilation free days,** **MCT/SO** 7.3 ± 9.3 (47); p=0.33	**FO MCT/SO** **Days on supplemental PN and EN** PN 7.1±4.0 , EN 12.3±7.6 vs. PN 7.9±4.7, EN 10.6±6.7 **Change in blood oxygenation, Day 1-4** **-1.3**±83.7 vs. 13.3± 86.1; p=0.78 **Catecholamine treatment free days** Higher in Omega 3 EN+PN group; p=0.05 **% patients tolerating EN alone at day 6** 51% vs. 29.8%; p=0.034
Stand-alone FO emulsion supplement vs. standard care					
22) Gupta 2011	**FO** **ICU** 15.27 ± 9.54 (31) **Hospital** 19.00 ± 13.26 (31)	**Standard** **ICU** 13.70 ± 11.56 (30) **Hospital** 19.30 + 16.65 (30)	**FO** 13.39 ± 8.30 (31)	**Standard** 11.30 ± 10.44 (30)	
23) Khor 2011	**FO** **ICU** 10.3 ± 7.4 (14)	**Standard** **ICU** 8.4 ± 5.7 (13)	NR	NR	NR

	Hospital 19.6 ± 6.5 (14)	**Hospital** 17.5 ± 5.3 (13)			
24) Zhao 2011	**FO** **ICU** 8.0 ± 2.02 (56)	**Standard** **ICU** 10.97 ± 2.02 (60)	NR	NR	NR
25) Burkhart 2013	**FO** **ICU** 5 (3-22)	**Standard** **ICU** 6 (2-33)	NR	NR	**FO** **Standard** **Subsyndromal delirium** 5 (25) 6(29) **Sepsis associated delirium** 15 (75) 15 (71)
26) Hall 2014	**FO** **I CU** 8.8±7.7 **Hospital** 26.7±18.2	**Standard** **I CU** 12.3±12.4 **Hospital** 33.5±30.4	NR (reported as free ventilator days)	NR (reported as free ventilator days)	NR

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
[a] converted Standard Error Mean (SEM) to Standard deviation (SD)

Table 2: Dose of Fish Oils in PN Trials

Study	Design	Patients	N	Nutrition / Products	Dose of FO (g/kg/d or g/d)
Grecu 2003 (abstract)	RCT, DB	Abdominal sepsis	54 (15 ICU)	**PN** LCT + Omegaven vs. LCT	0.15 g/kg/d
Friesecke 2008	RCT, DB	115 SIRS, 52 non-SIRS	166	**PN** Lipofundin MCT + Omegaven vs. Lipofundin MCT	0.15 g/kg/d
Guo 2008	RCT	Septic ICU pts APACHE II>12	88	**PN** 20% ILE + ω-3 vs. 20% ILE	10 g/day
Wang 2009	RCT, DB	Severe acute pancreatitis in ICU	56	**PN** Lipovenoes + Omegaven vs. Lipovenoes	0.16 on day 1, then 0.2 g/kg/d
Barbosa 2010	RCT, SB	ICU, SIRS or sepsis requiring PN	25	**PN** Lipoplus vs. Nutriflex lipid special	0.09 g/kg/d
Sabater 2011	RCT	ARDS requiring MV and PN	16	**PN** Lipoplus 20% vs Intralipid 20%	0.12 g/kg/h
Grau Carmona 2014	RCT, DB	Medical and surgical ICU pts requiring TPN	175	**PN** Lipoplus vs. Lipofundin MCT	0.1 g/kg/d
Gultekin 2014	RCT, DB	Severe sepsis or septic shock	58	**PN** ClinOleic + Omegaven vs. ClinOleic	10 g/day
Wang 2014	RCT	Abdominal sepsis and require TPN for ≥5 days	53	**PN** Routine PN + Omegaven to replace part of routine PN lipid emulsion for 5 days vs Routine PN	0.2 g/kg/day
Chen 2017a	RCT, SB	ICU pts with SIRS and ID	78	**PN** SO + Omegaven vs. SO	10 g/day
Chen 2017b	RCT, SB	ICU pts with SIRS and ID	48	**PN** Standard PN + Omegaven vs. Standard PN	10 g/day
Singer 2021	RCT, DB	ICU pts on MV	100	**sPN+ EN** Nutriflex Omega special + Oxepa vs. Nutriflex Lipid + Pulmocare	<0.05 g/kg/d on d1-5 >0.05 g/kg/d from d6
Donoghue 2019	RCT, DB	Critically ill, SIRS, sepsis and/ or ARDS	75	**PN** SMOFlipid vs. Intralipid	0.09 – 0.19

Overall mortality

Figure 1.1: Overall Mortality in Trials Using an Omega-6 Reducing Strategy

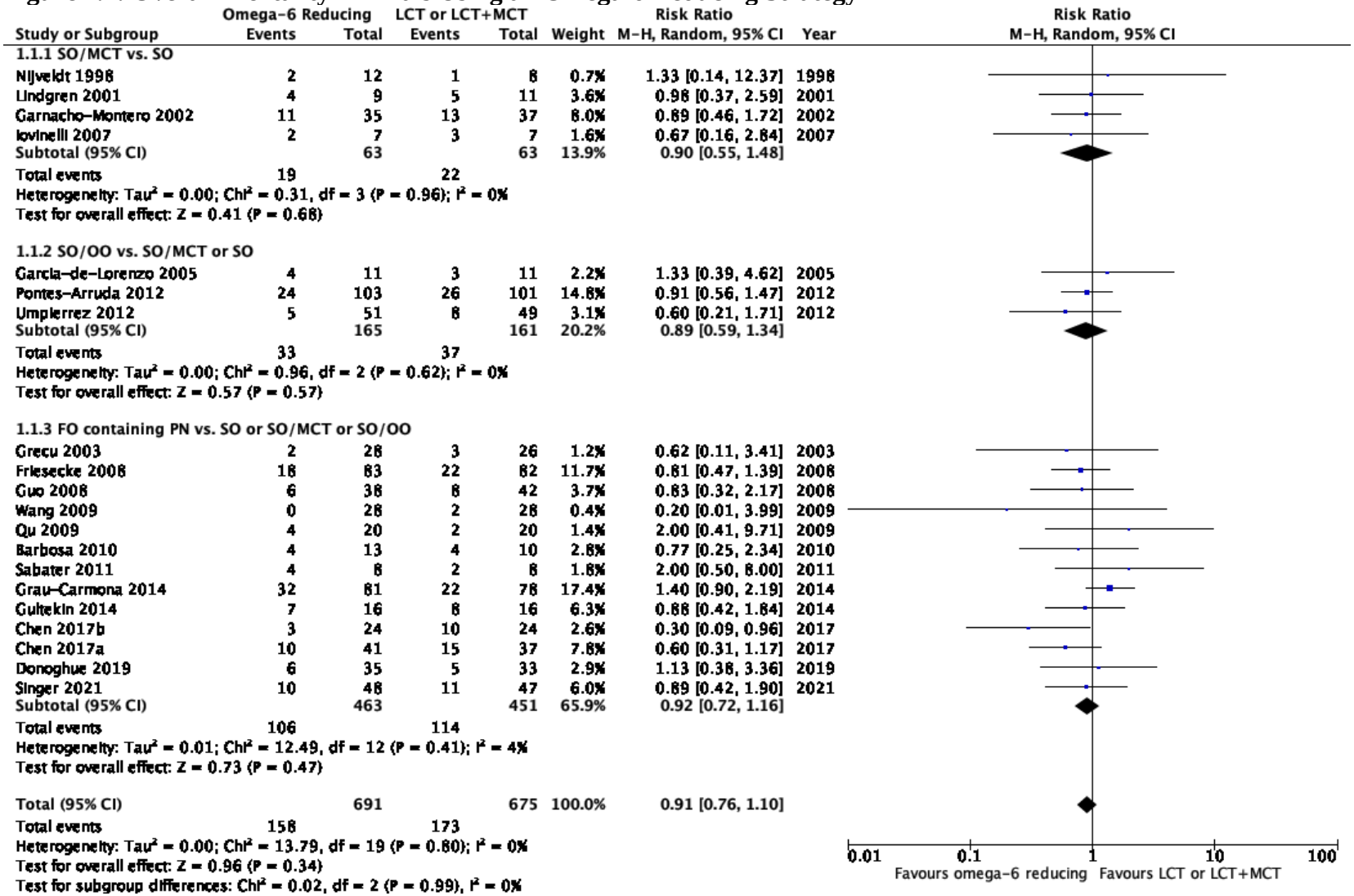


Figure 1.2 Overall Mortality in Trials Using an Omega-6 Reducing strategy: Sensitivity Analyses Without Singer 2021

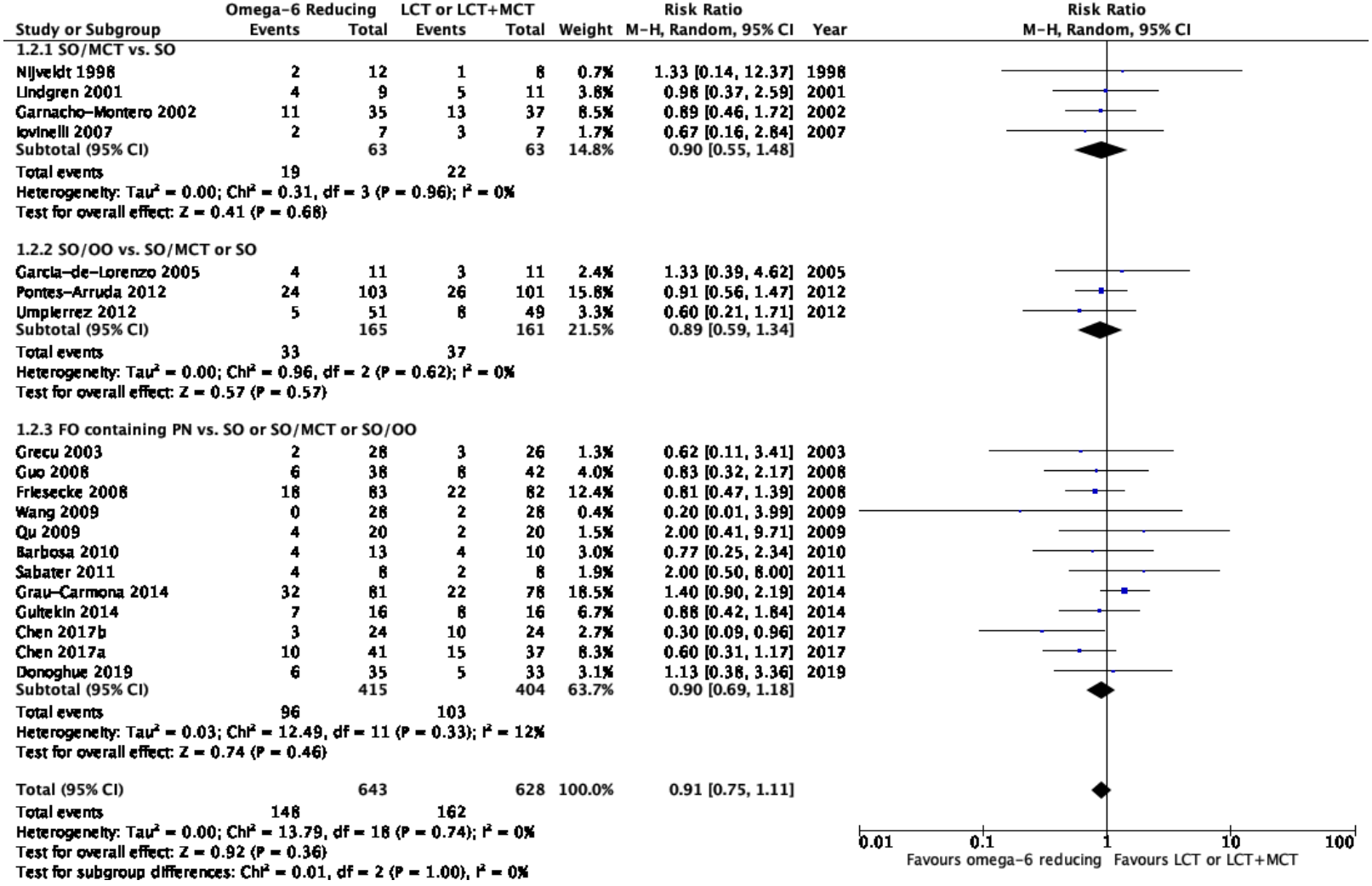


Figure 1.3 Overall Mortality in Trials Using an Omega-6 Reducing Strategy: Subgroup Analyses of SO/MCT or SO/OO vs. SO and FO vs SO or SO/MCT or SO/OO

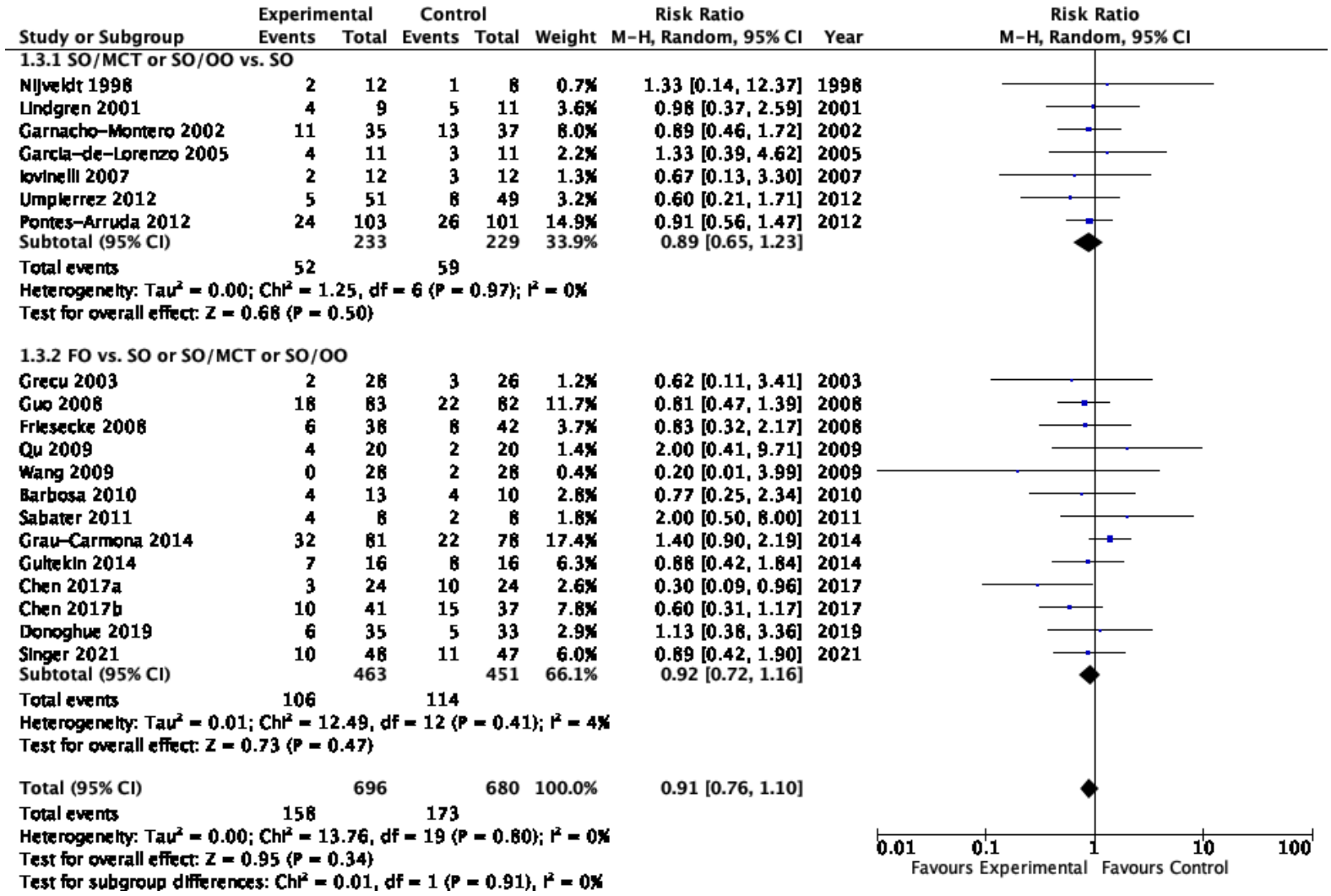


Figure 1.4 Overall Mortality in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

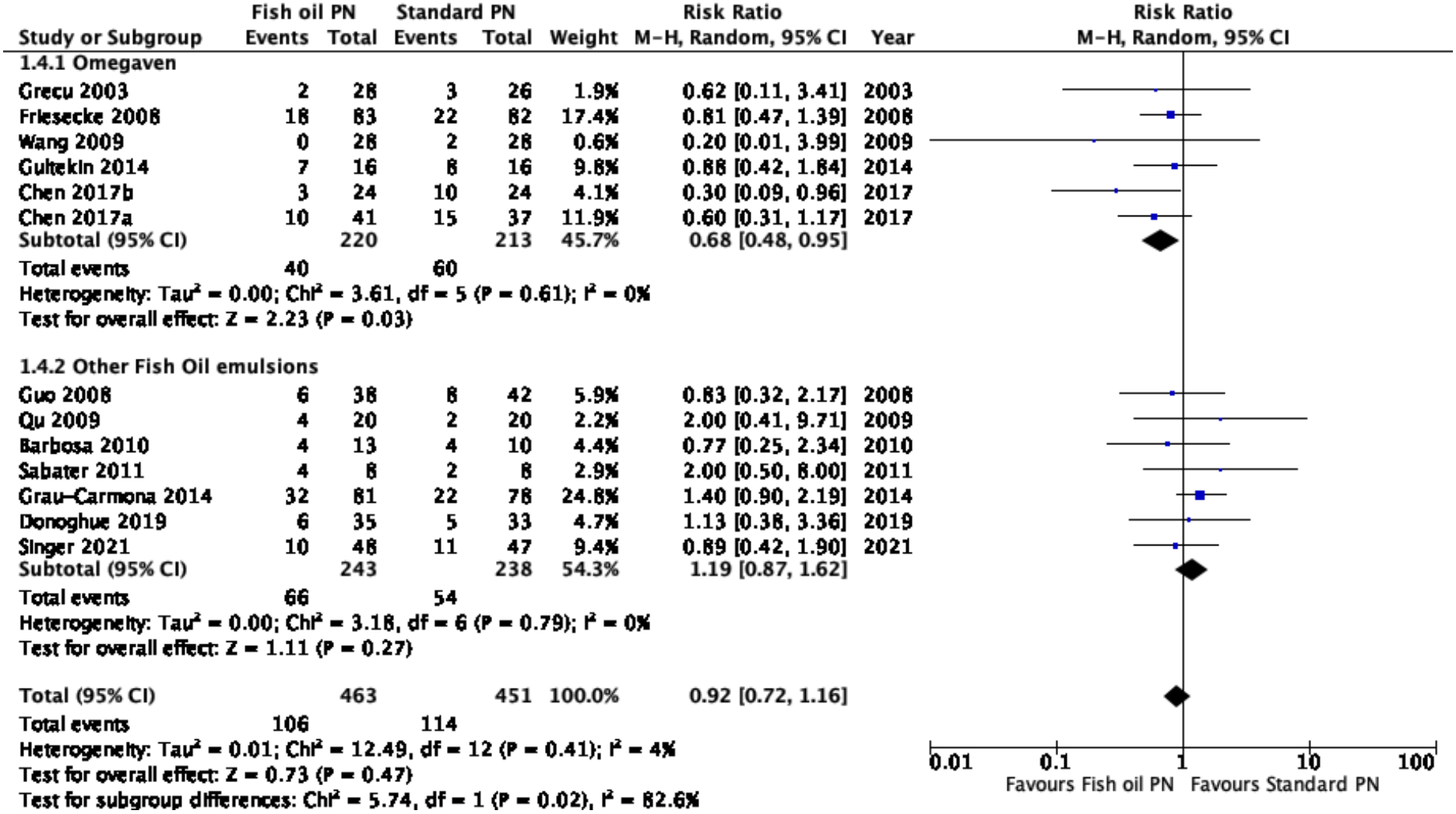


Figure 1.5 Overall Mortality in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions: Sensitivity Analyses Without Singer 2021

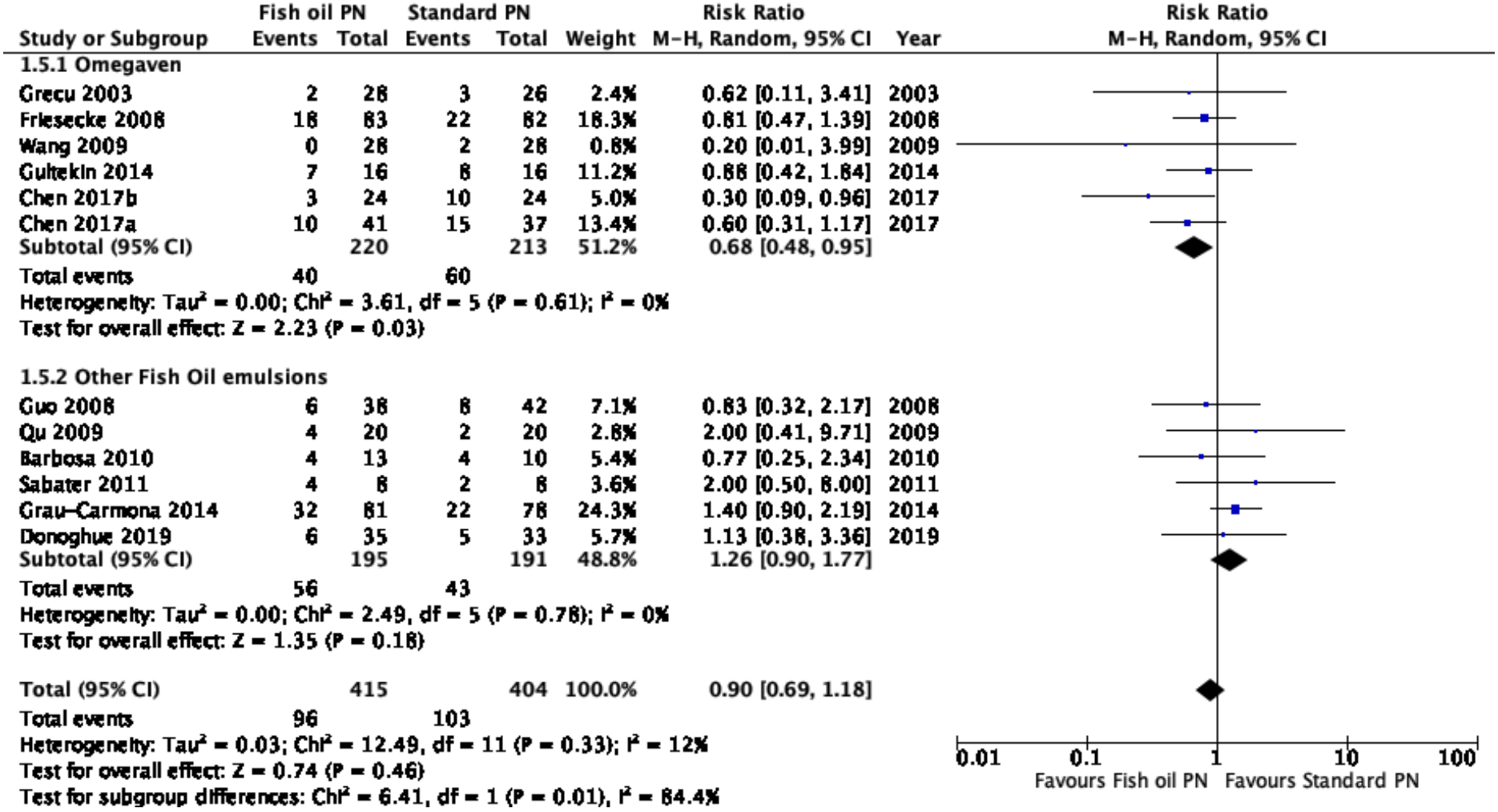
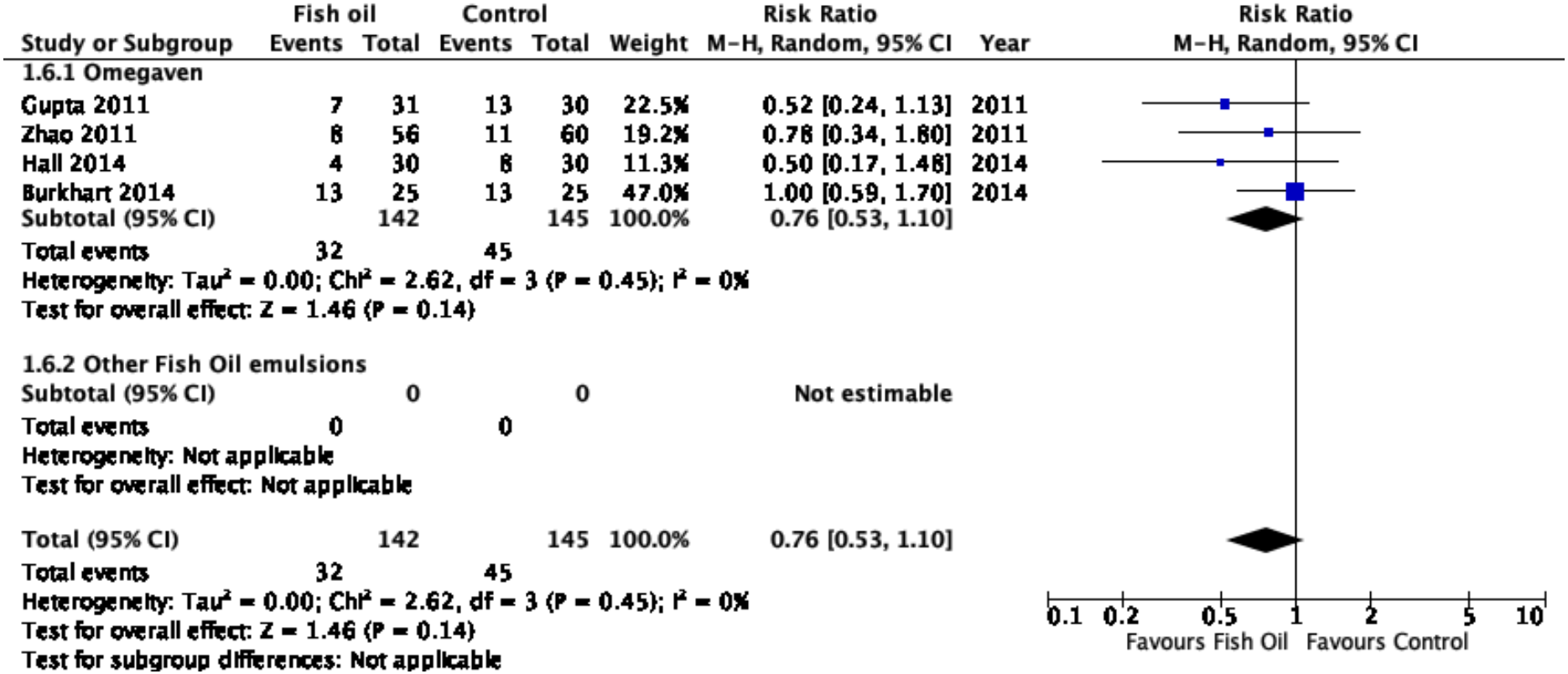


Figure 1.6 Overall Mortality in Trials Comparing Stand-Alone Fish Oil Emulsions to Standard of Care



28-day mortality

Figure 2.1: 28-day Mortality in Trials Using an Omega-6 Reducing Strategy

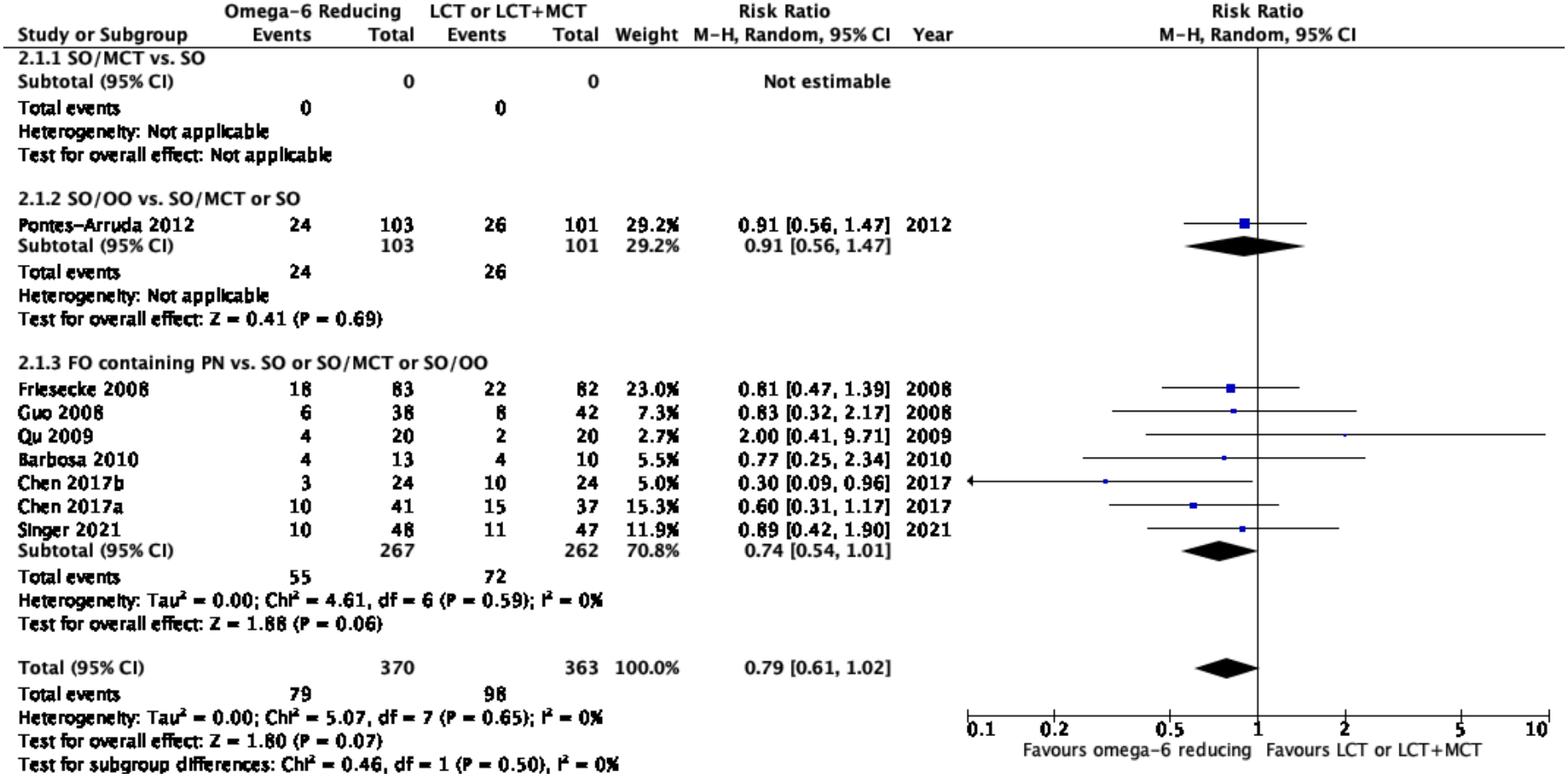


Figure 2.2 28-day Mortality in Trials Using an Omega-6 Reducing strategy: Sensitivity Analyses Without Singer 2021

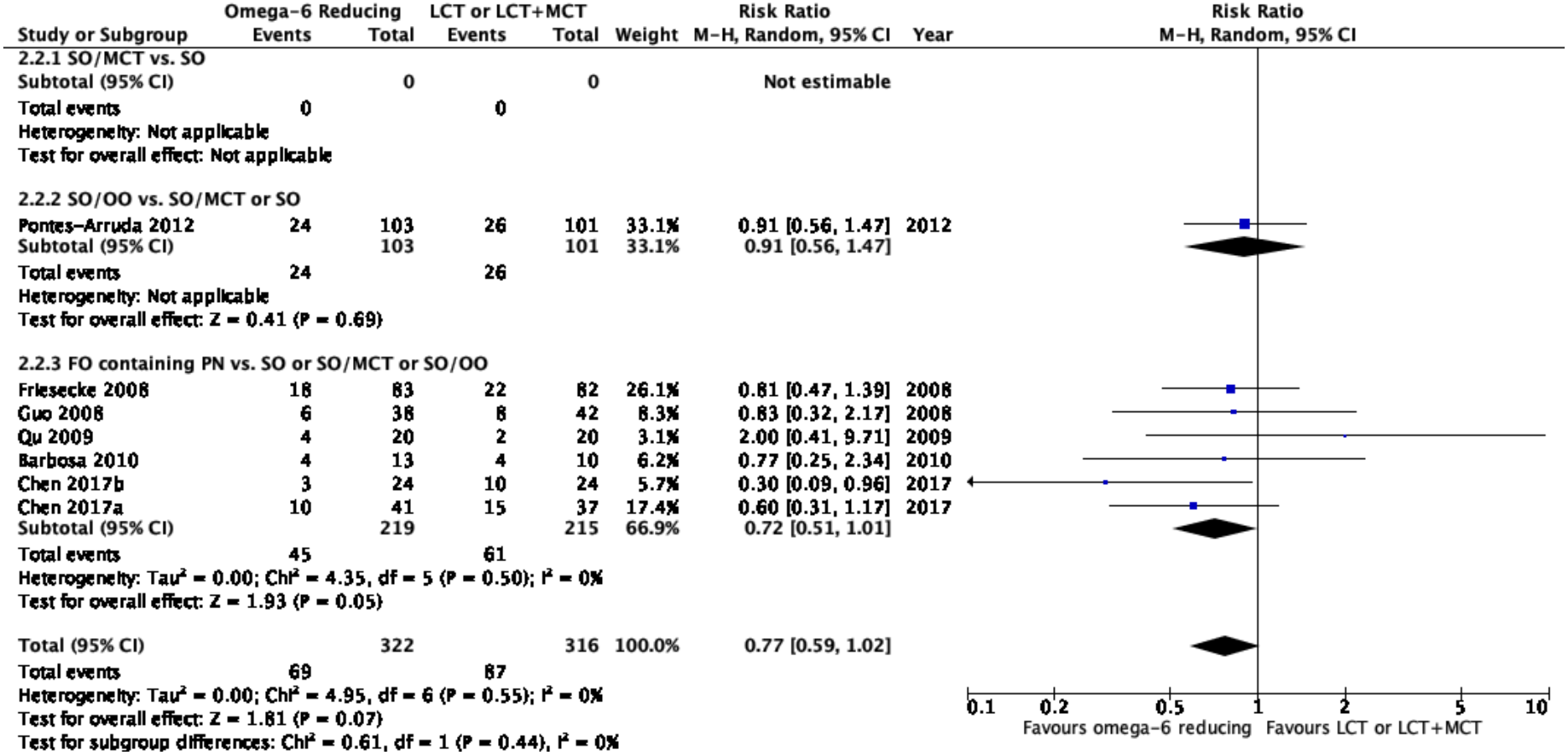


Figure 2.3 28-day Mortality in Trials Using an Omega-6 Reducing Strategy: Subgroup Analyses of SO/MCT or SO/OO vs. SO and FO vs SO or SO/MCT or SO/OO

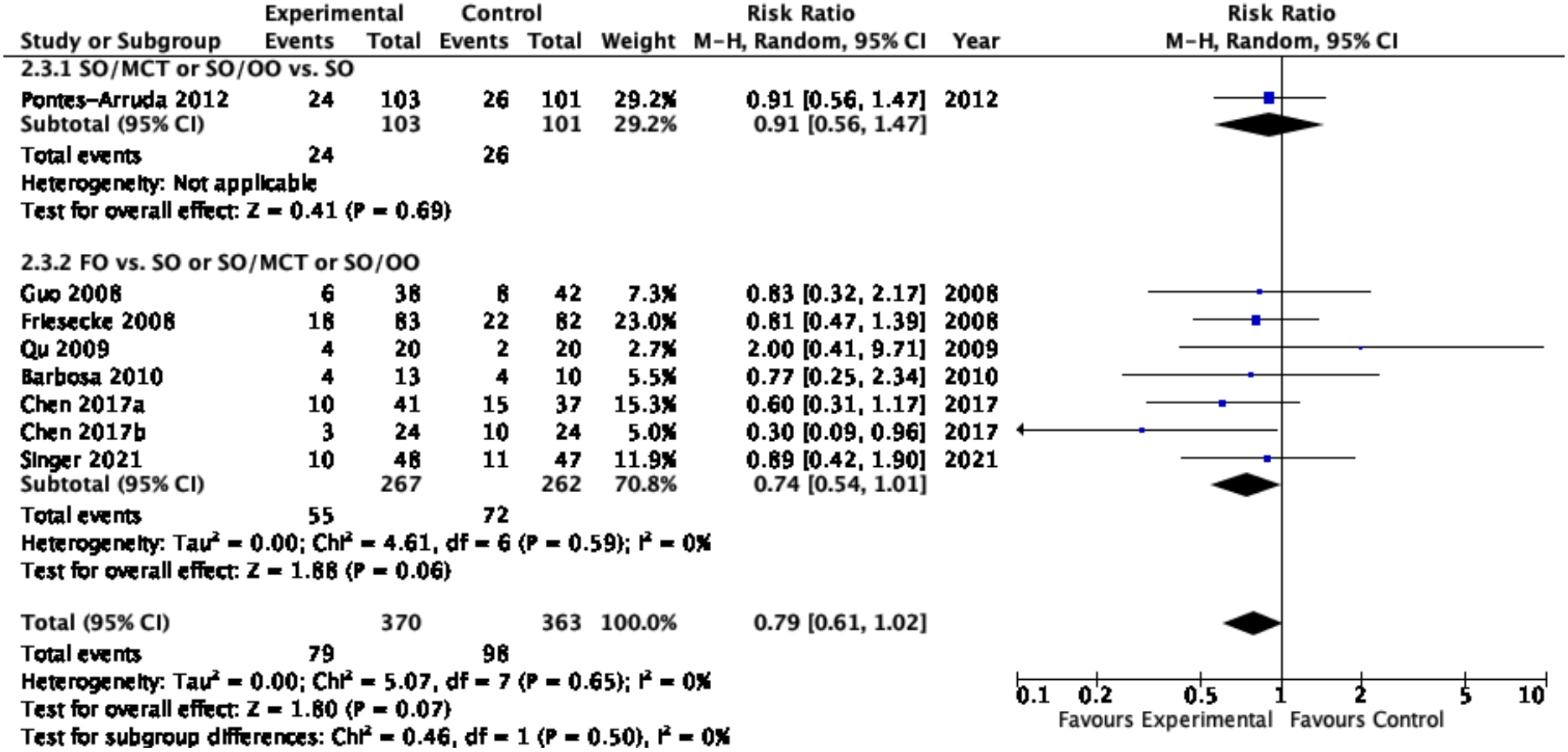


Figure 2.4 28-day Mortality in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

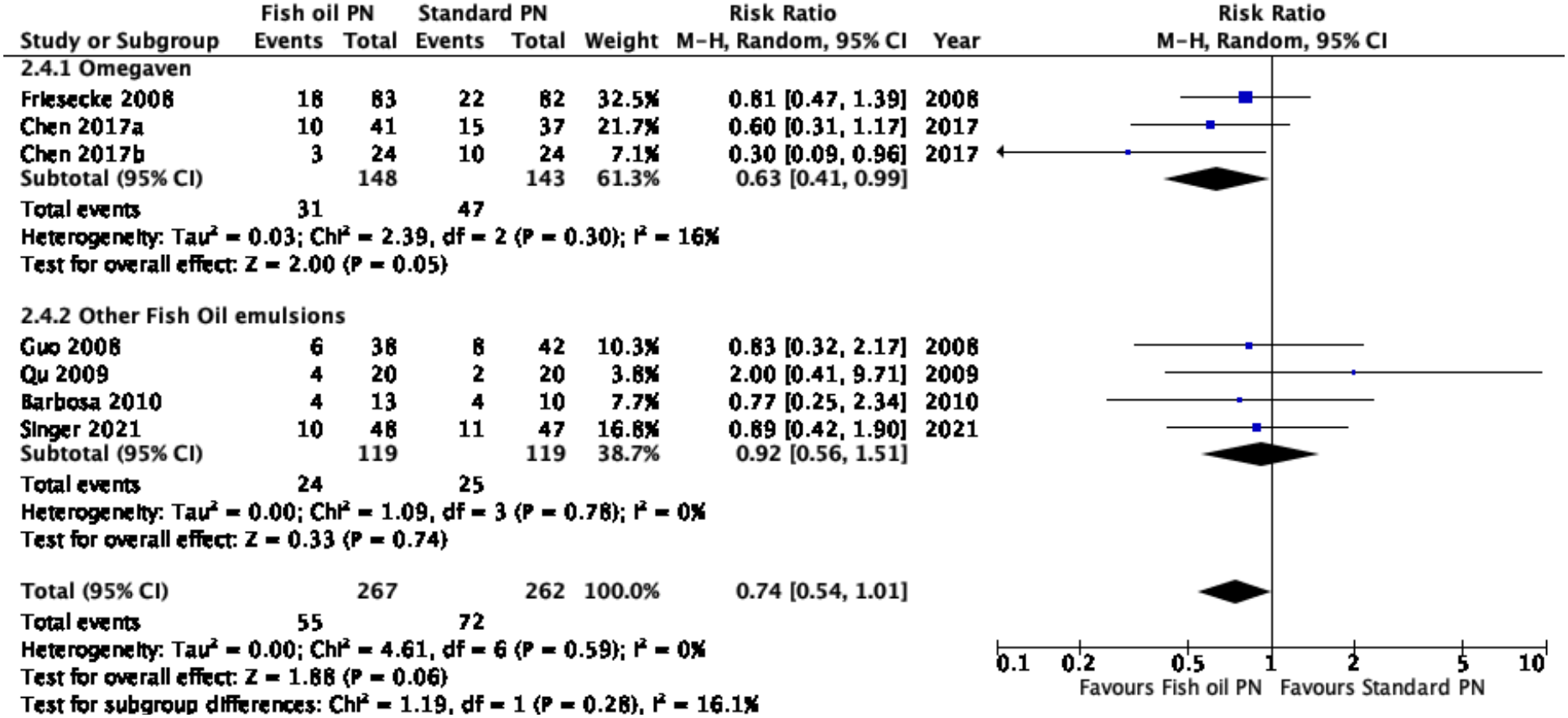


Figure 2.5 28-day Mortality in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions: Sensitivity Analyses Without Singer 2021

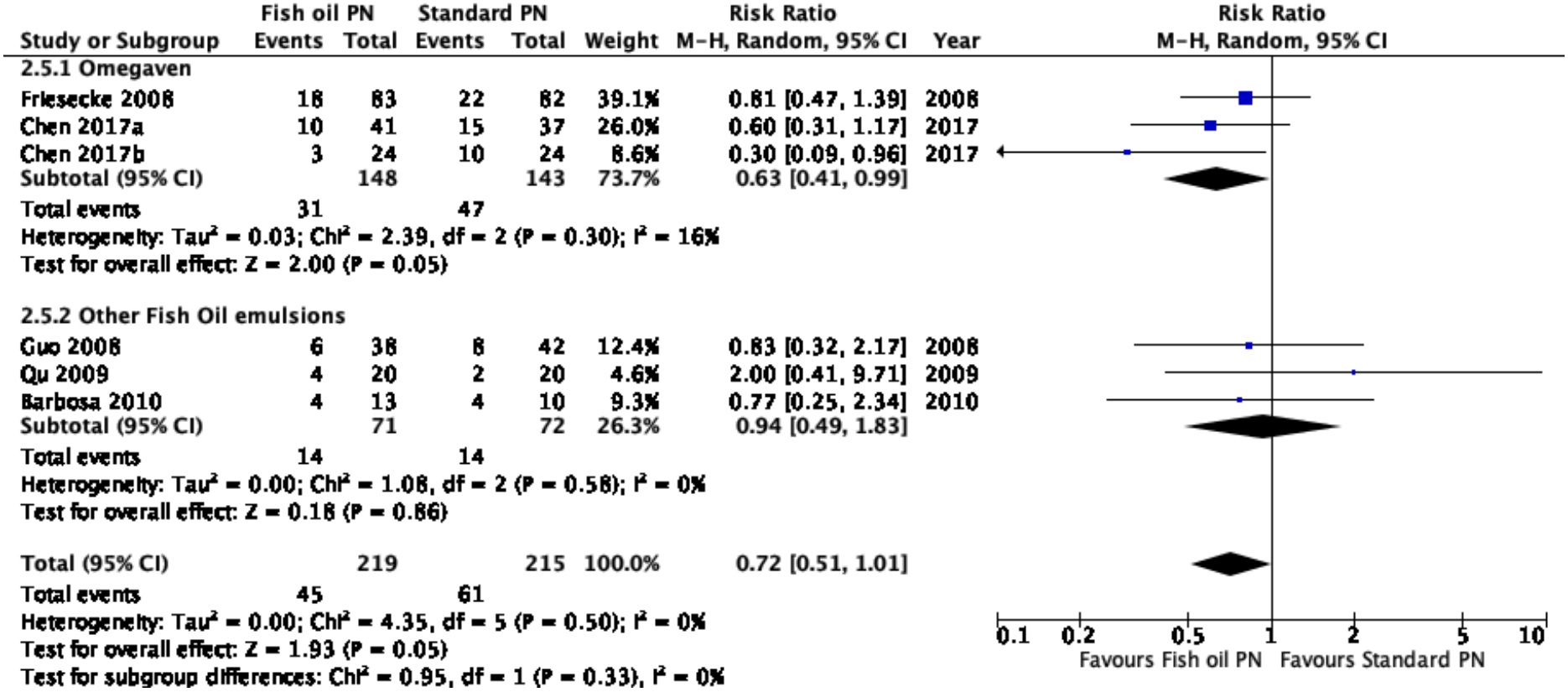
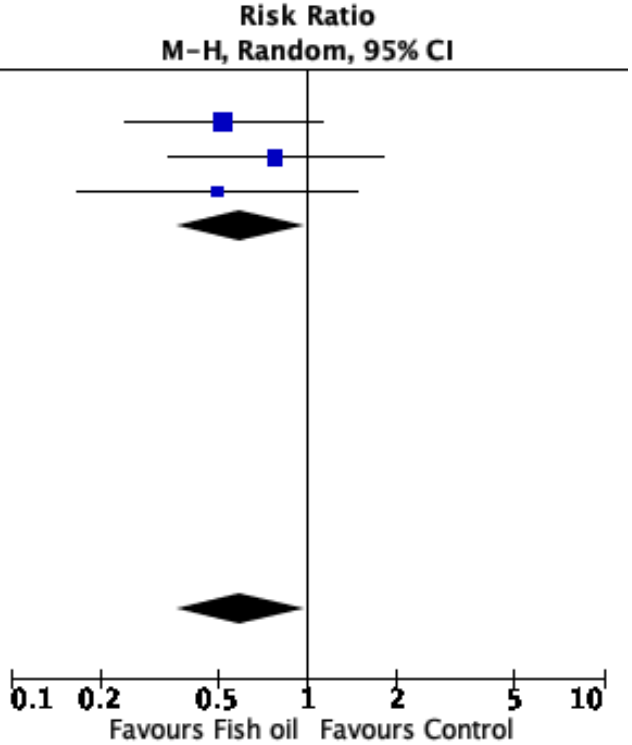


Figure 2.6 28-day Mortality in Trials Comparing Stand-Alone Fish Oil Emulsions to Standard of Care

Study or Subgroup	Fish oil Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.6.1 Omegaven							
Gupta 2011	7	31	13	30	42.6%	0.52 [0.24, 1.13]	2011
Zhao 2011	8	56	11	60	36.2%	0.78 [0.34, 1.80]	2011
Hall 2014	4	30	8	30	21.3%	0.50 [0.17, 1.48]	2014
Subtotal (95% CI)		117		120	100.0%	0.60 [0.36, 0.99]	
Total events	19		32				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.61$, df = 2 (P = 0.74); $I^2 = 0\%$							
Test for overall effect: Z = 2.01 (P = 0.04)							
2.6.2 Other Fish Oil emulsions							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		117		120	100.0%	0.60 [0.36, 0.99]	
Total events	19		32				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.61$, df = 2 (P = 0.74); $I^2 = 0\%$							
Test for overall effect: Z = 2.01 (P = 0.04)							
Test for subgroup differences: Not applicable							



ICU Mortality

Figure 3.1 ICU Mortality in Trials Using an Omega-6 Reducing Strategy

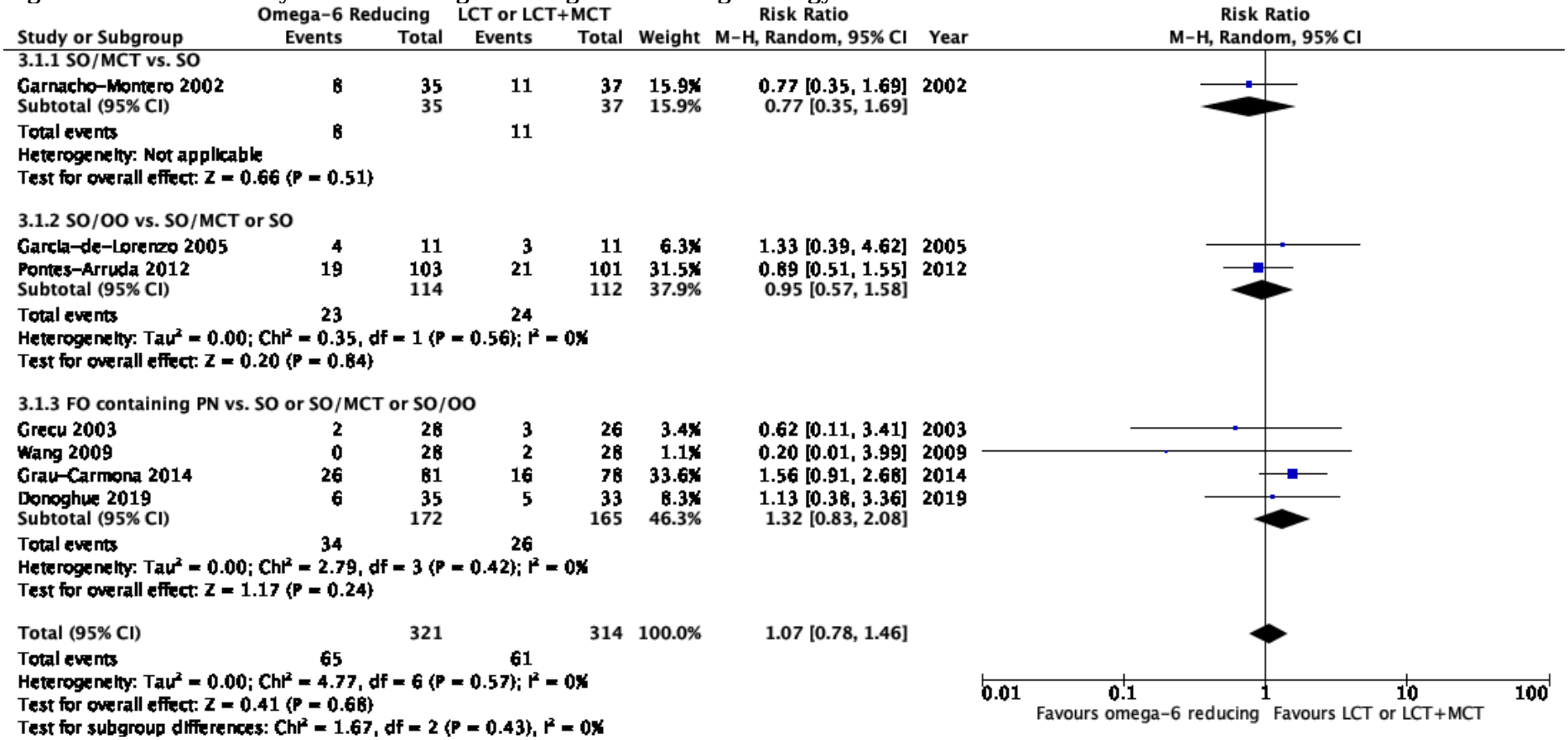


Figure 3.2 ICU Mortality in Trials Using an Omega-6 Reducing Strategy: Subgroup Analyses of SO/MCT or SO/OO vs. SO and FO vs SO or SO/MCT or SO/OO

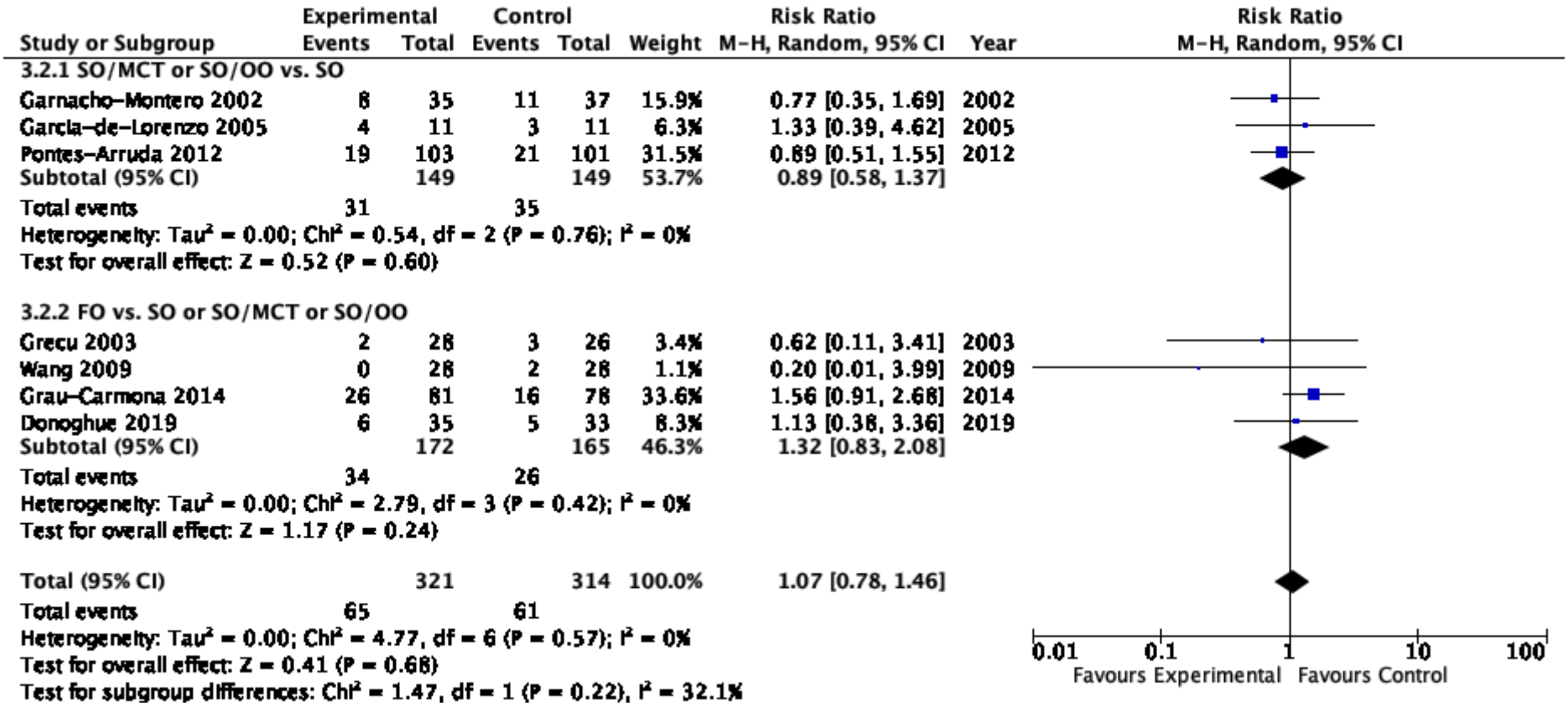


Figure 3.3 ICU Mortality in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

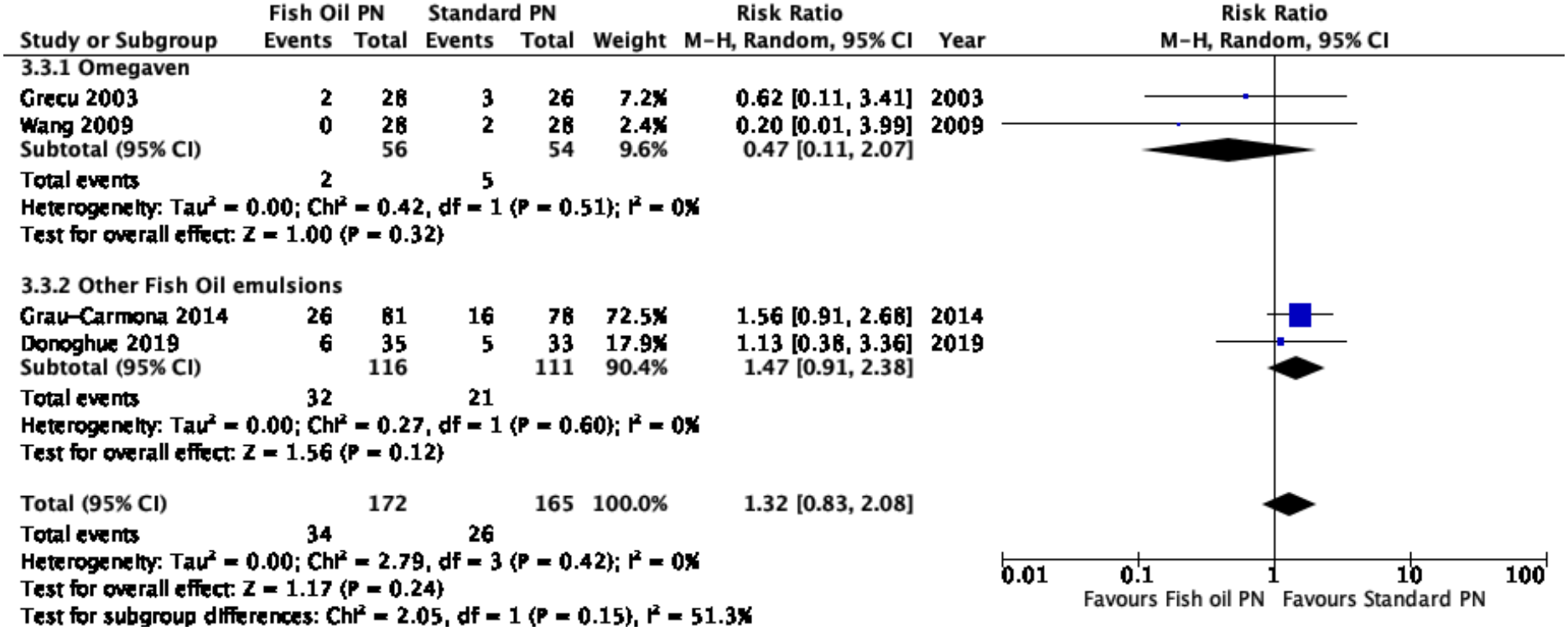


Figure 3.4 ICU Mortality in Trials Comparing Stand-Alone Fish Oil Emulsions to Standard of Care
None reported ICU mortality

Hospital Mortality

Figure 4.1 Hospital Mortality in Trials Using an Omega-6 Reducing Strategy

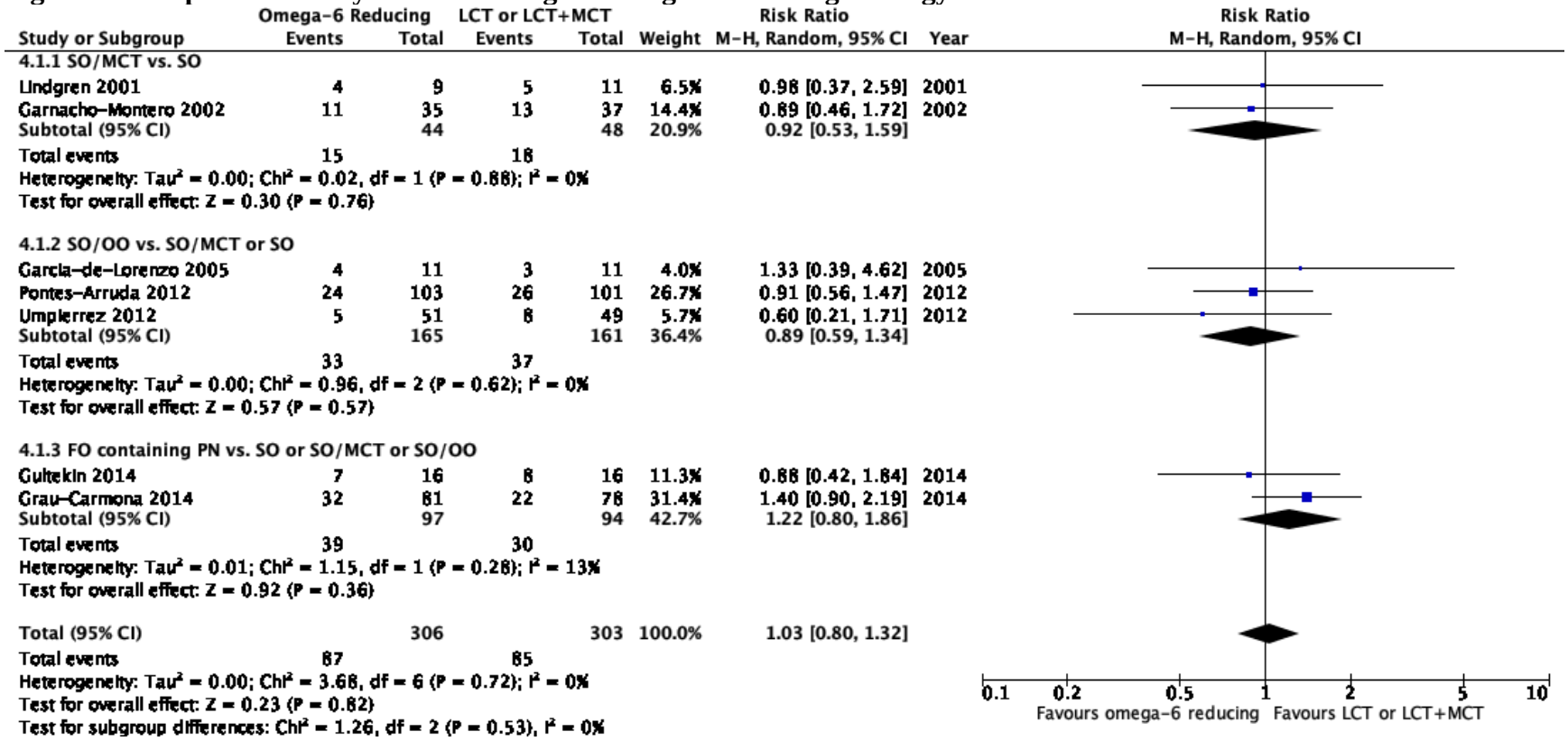


Figure 4.2 Hospital Mortality in Trials Using an Omega-6 Reducing Strategy: Subgroup Analyses of SO/MCT or SO/OO vs. SO and FO vs SO or SO/MCT or SO/OO

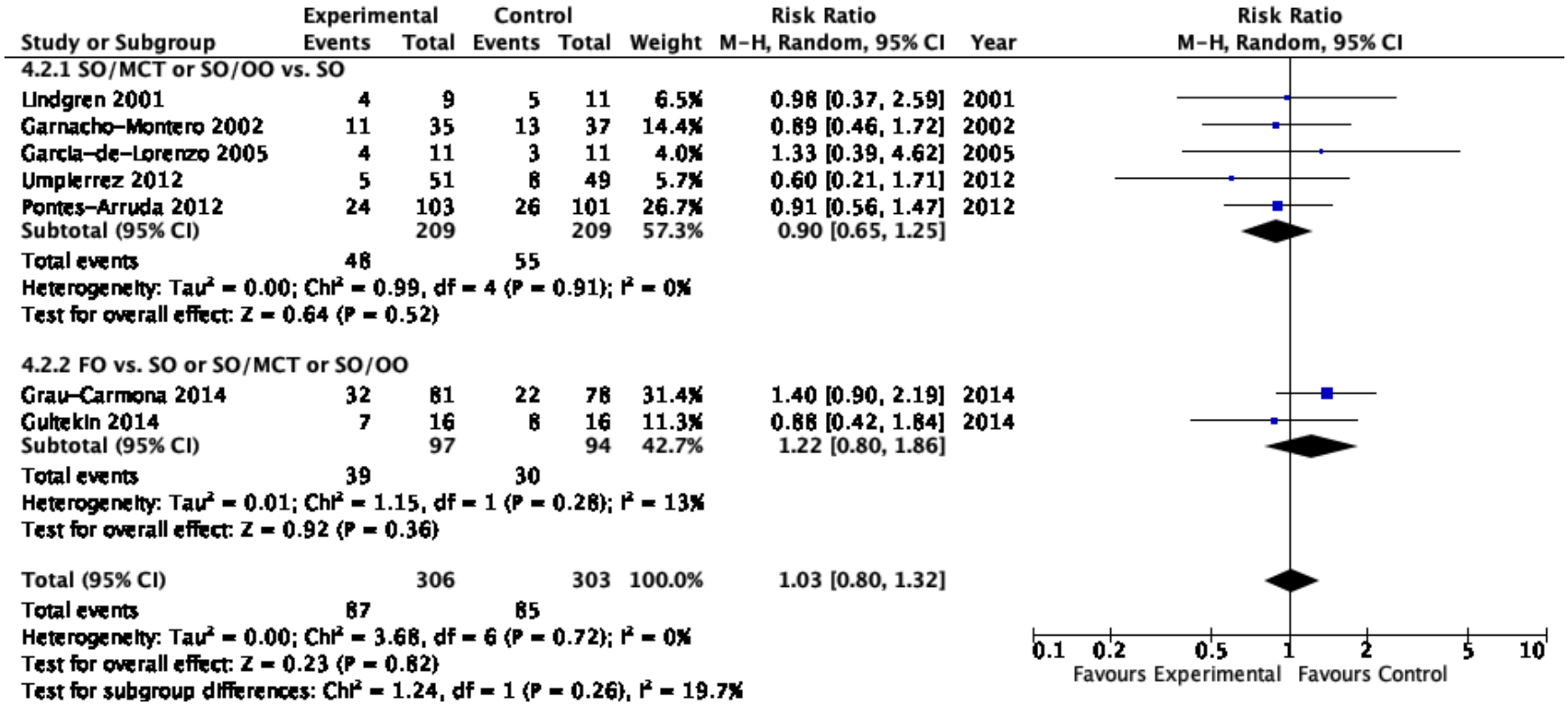


Figure 4.3 Hospital Mortality in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

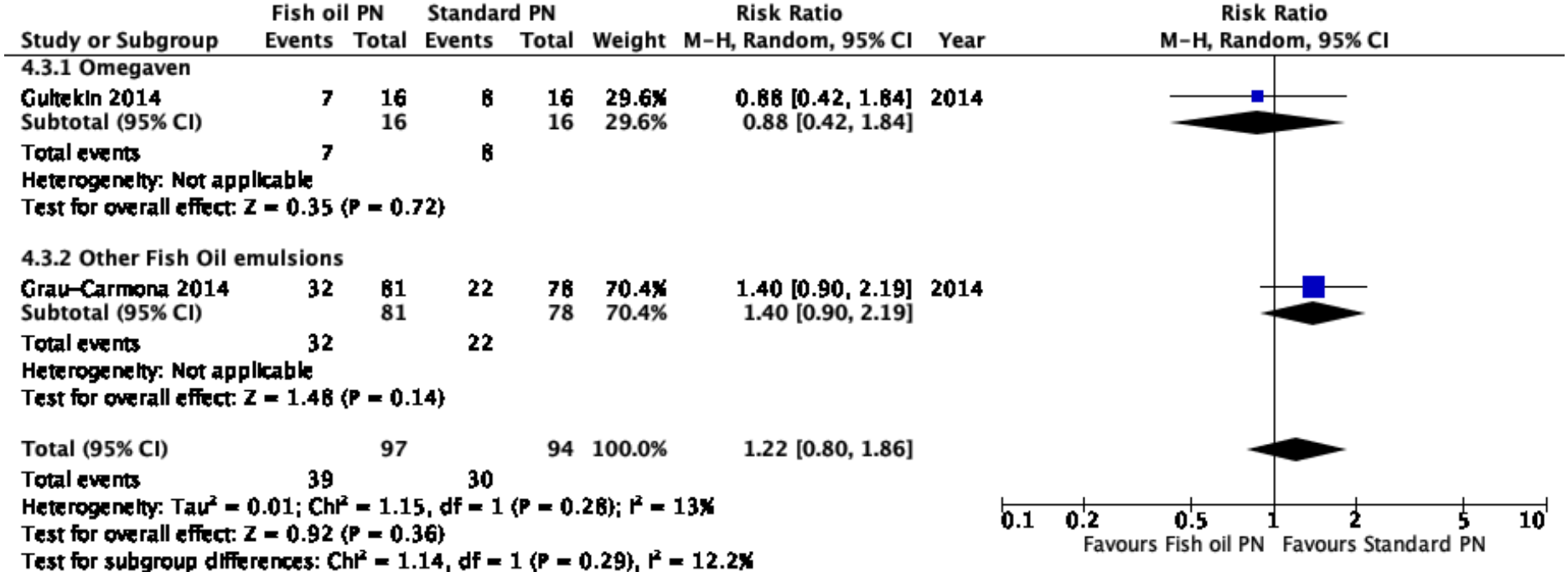


Figure 4.4 Hospital Mortality in Trials Comparing Stand-Alone Fish Oil Emulsions to Standard of Care

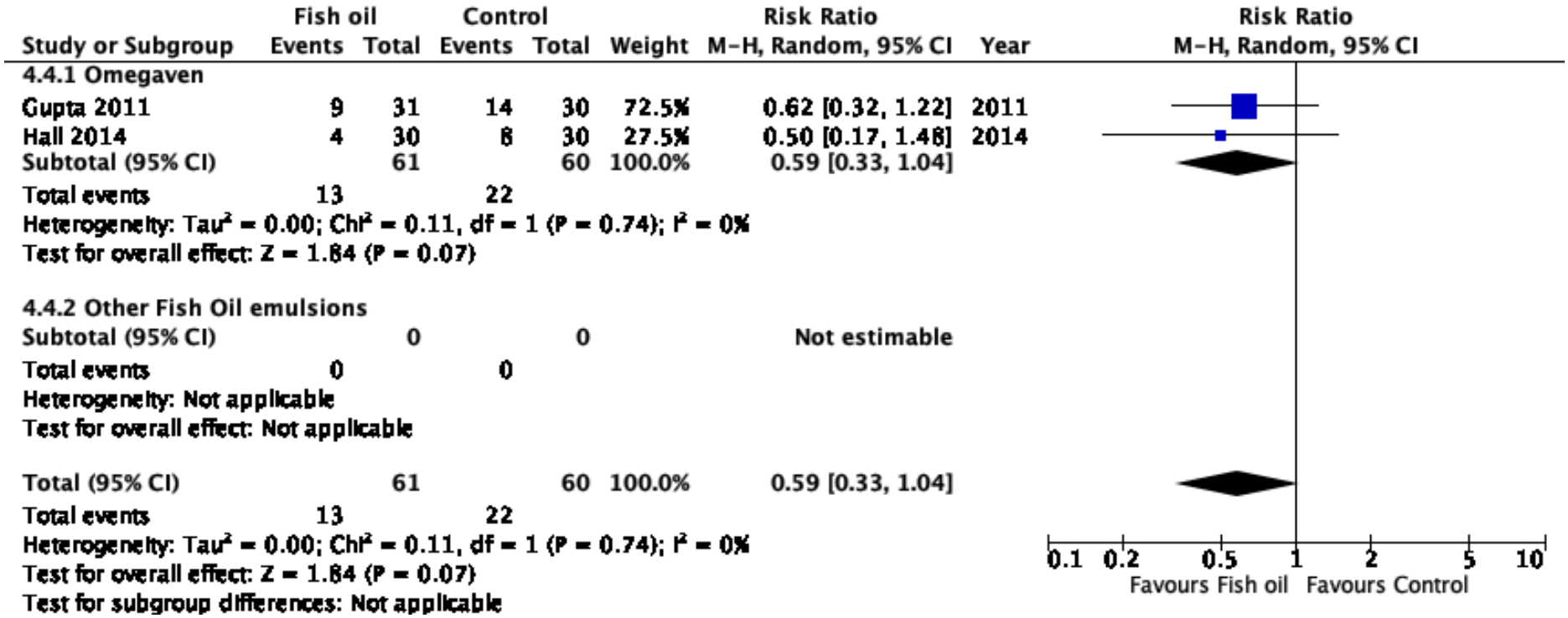


Figure 5.1 Overall Infections in Trials Using an Omega-6 Reducing strategy

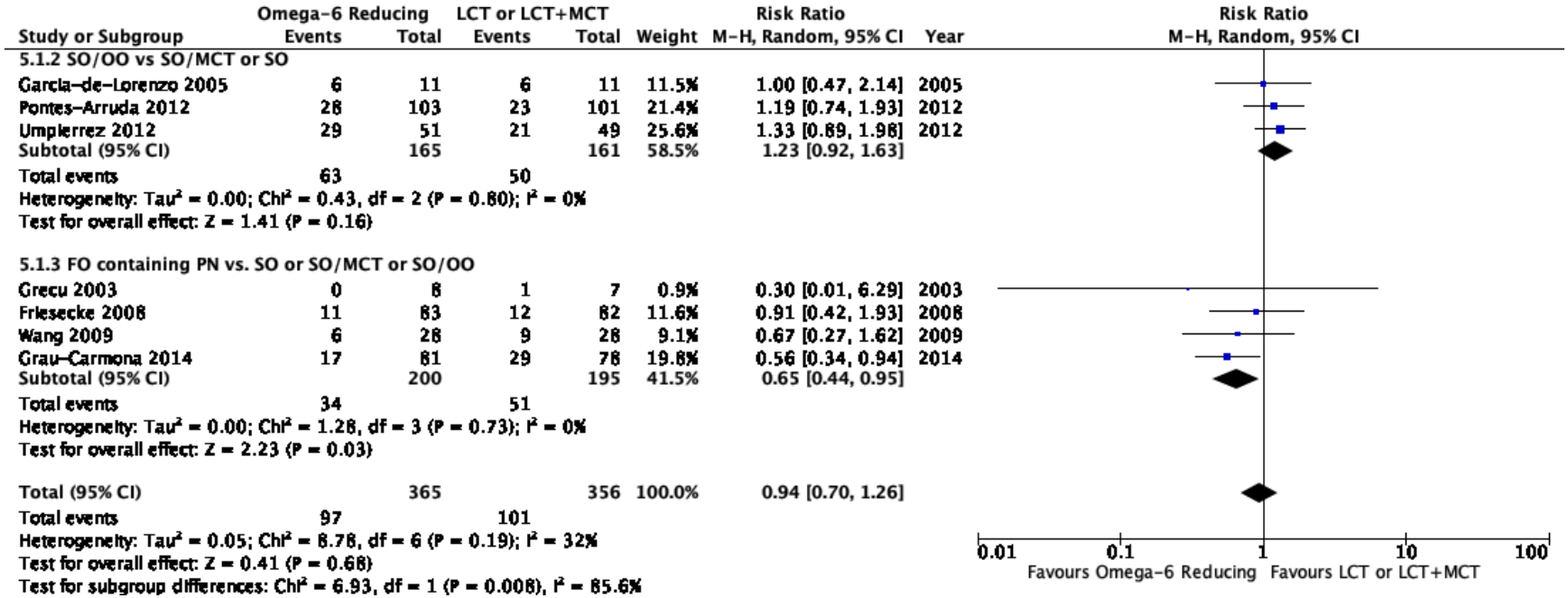


Figure 5.2 Overall Infections in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

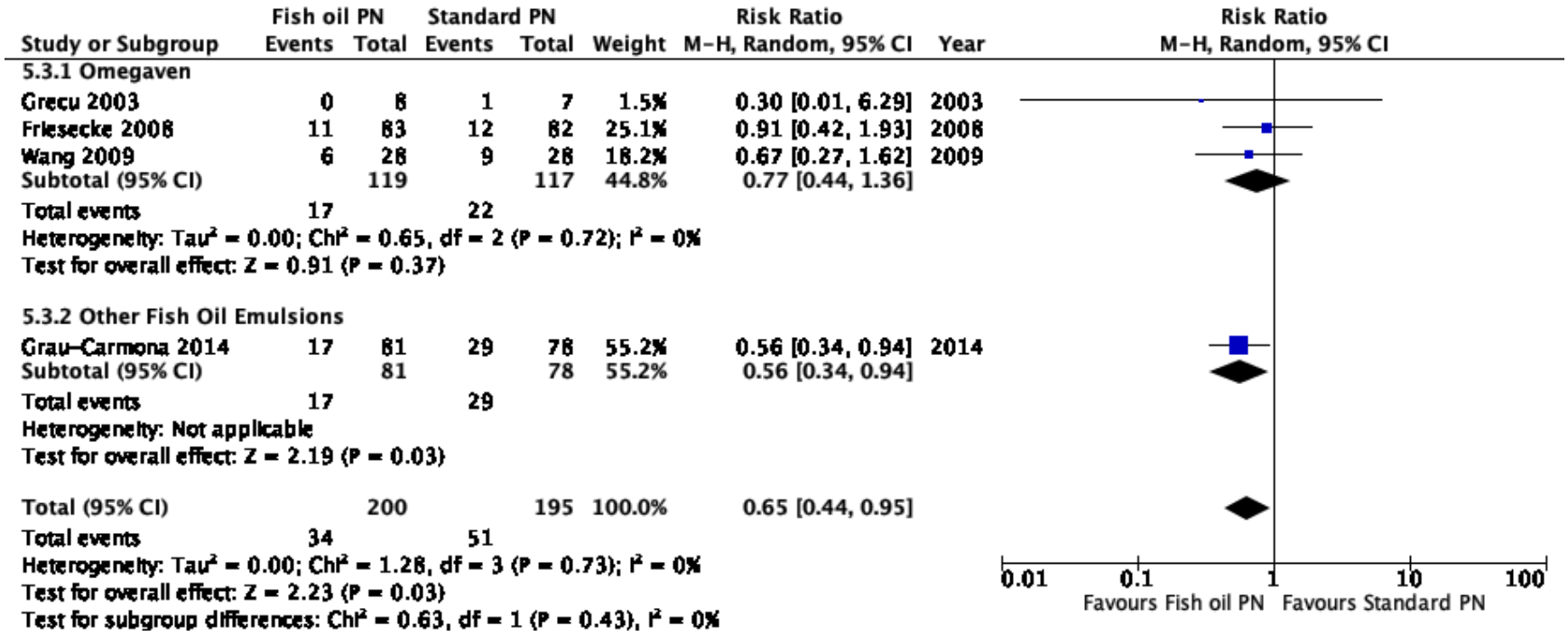


Figure 6.1 Hospital LOS in Trials Using an Omega-6 Reducing Strategy

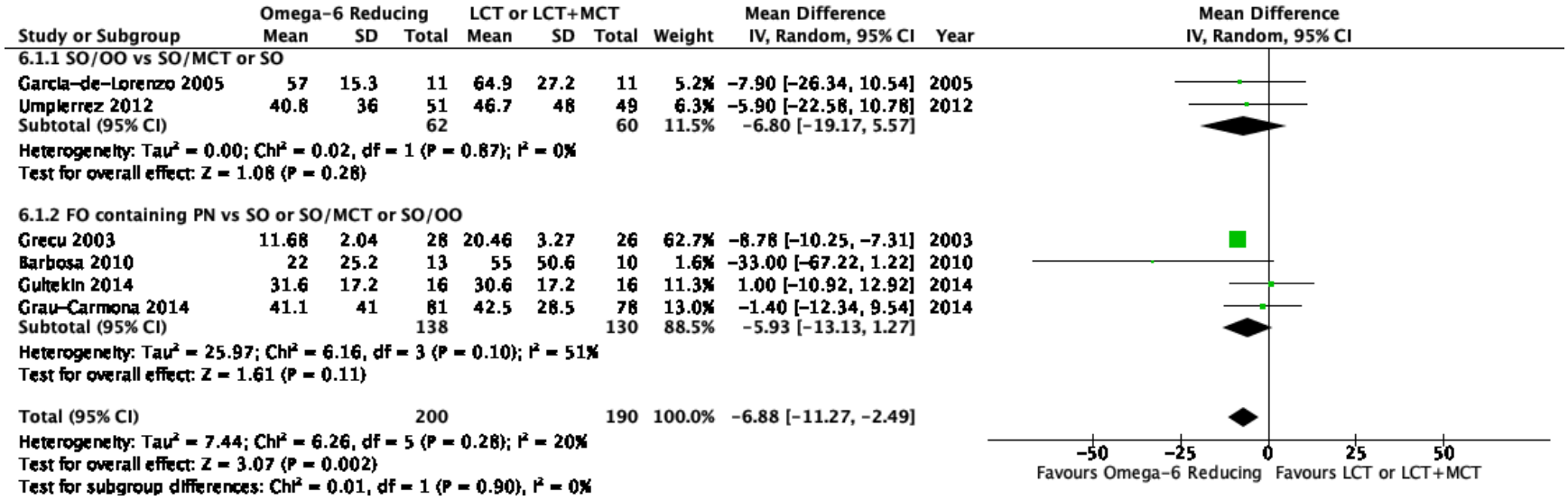


Figure 6.2 Hospital LOS in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

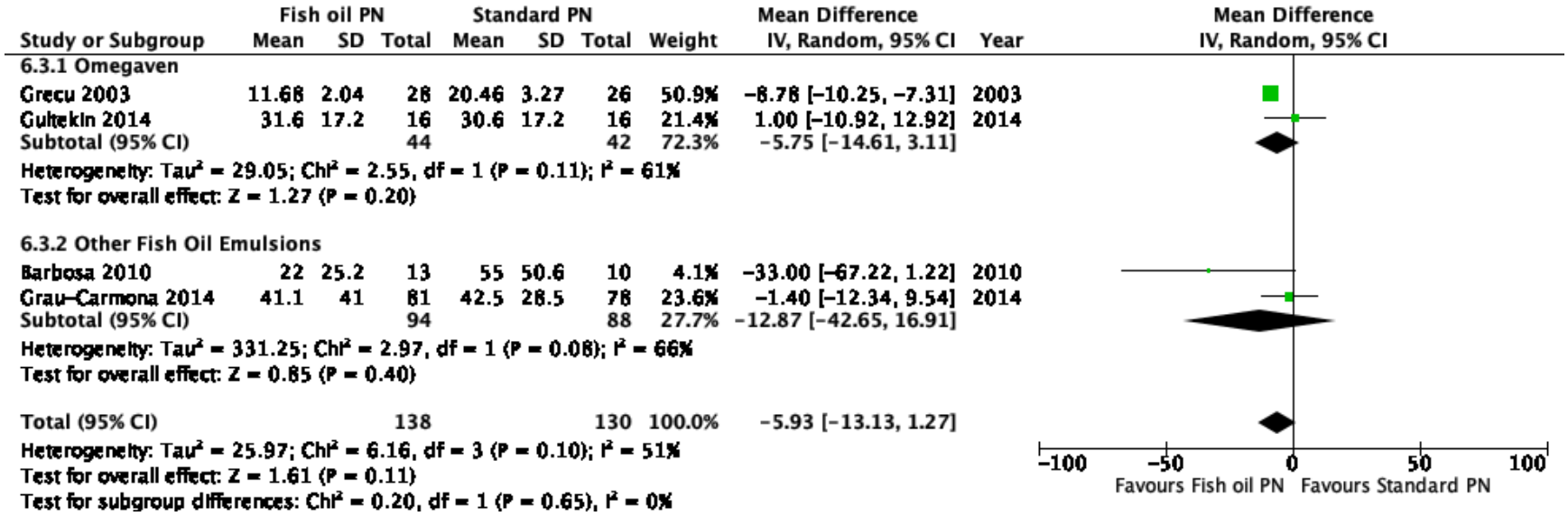


Figure 6.3 Hospital LOS in Trials Comparing Stand-Alone Fish Oil Emulsions to Standard of Care

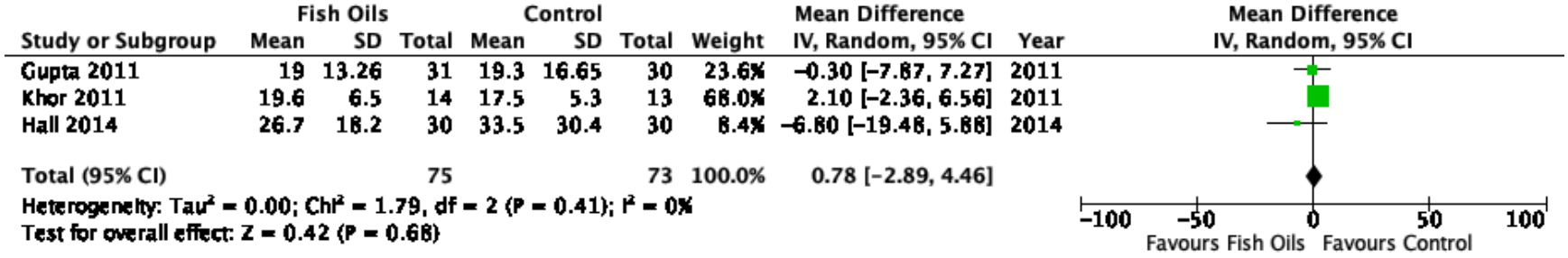


Figure 7.1 ICU LOS in Trials Using an Omega-6 Reducing Strategy

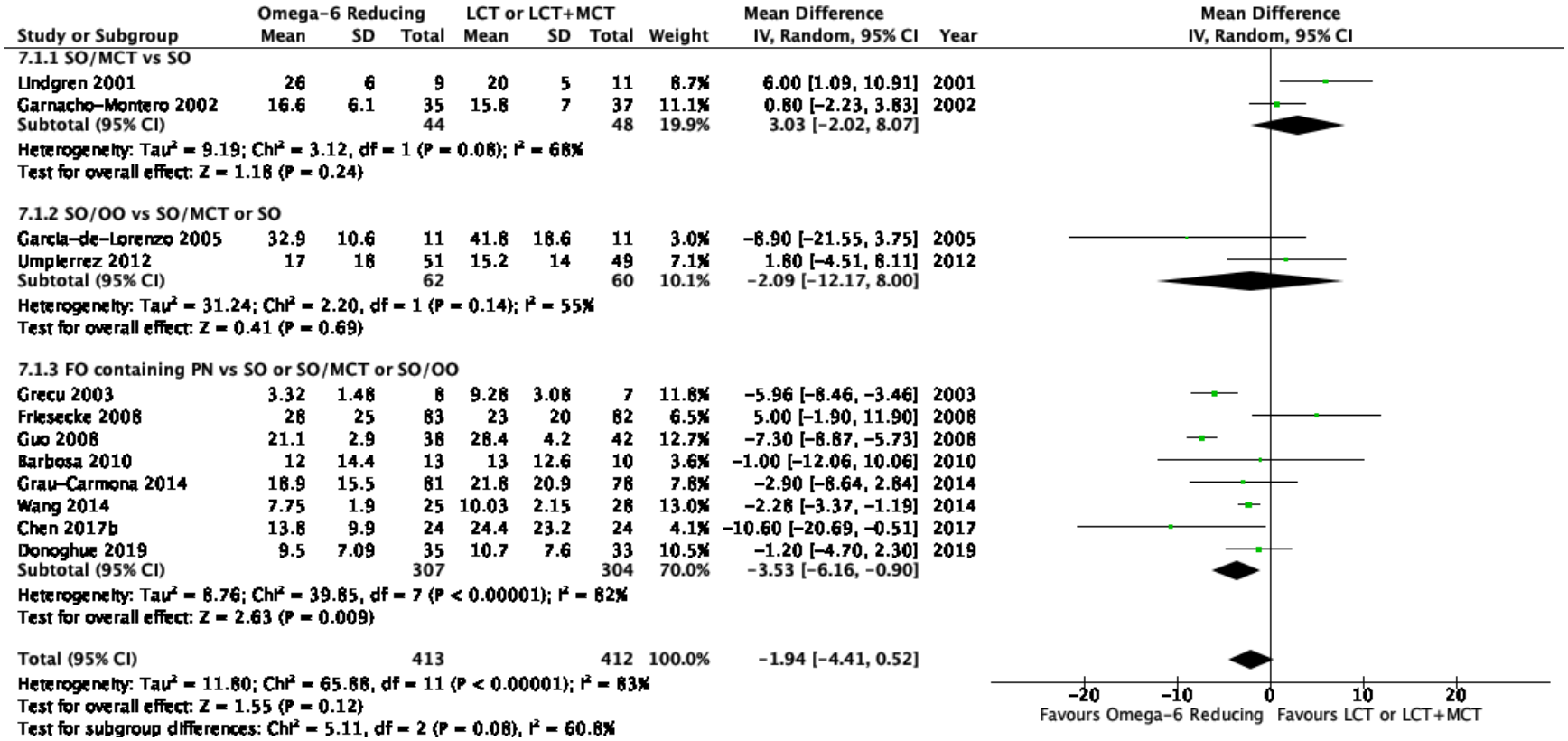


Figure 7.2 ICU LOS in Trials Using an Omega-6 Reducing Strategy: Subgroup Analyses of SO/MCT or SO/OO vs. SO and FO vs SO or SO/MCT or SO/OO

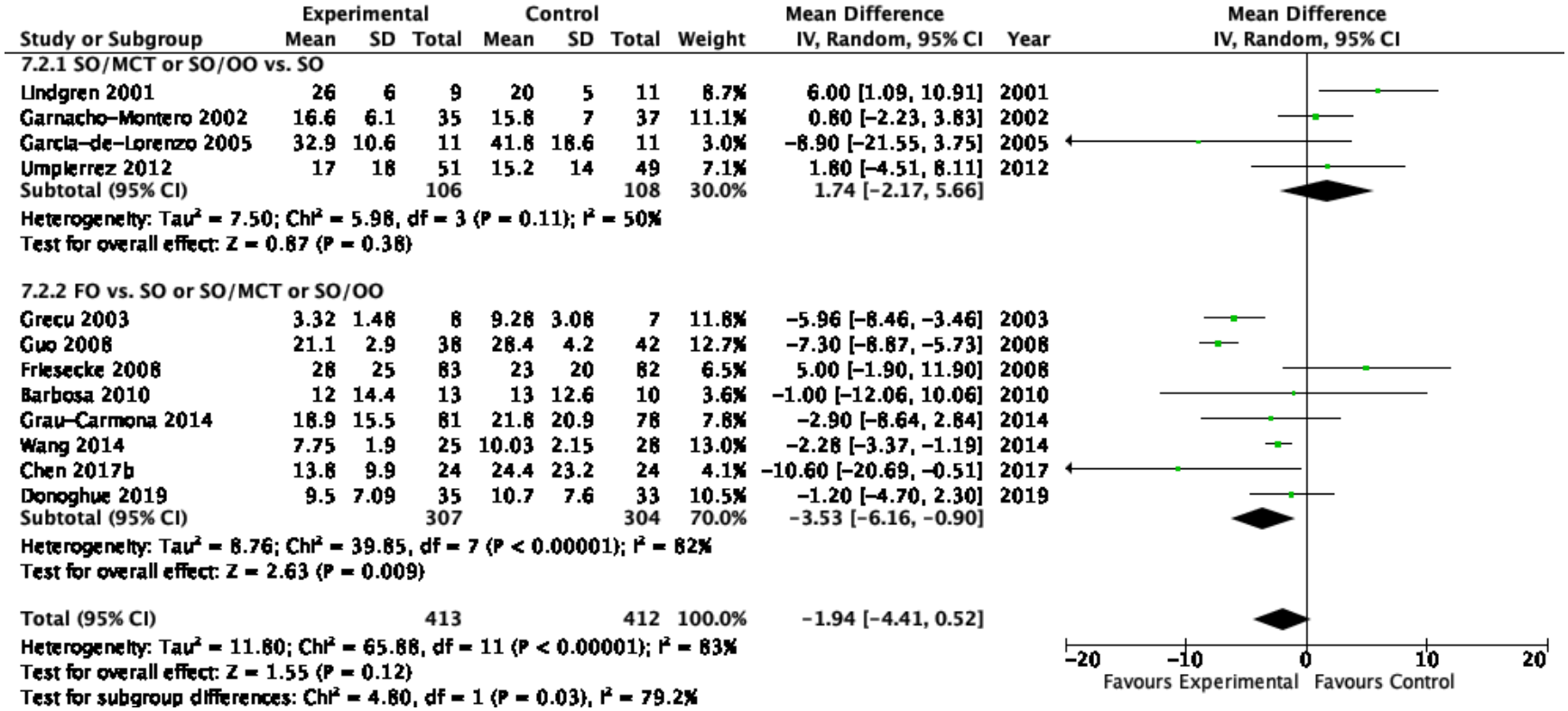


Figure 7.3. ICU LOS in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

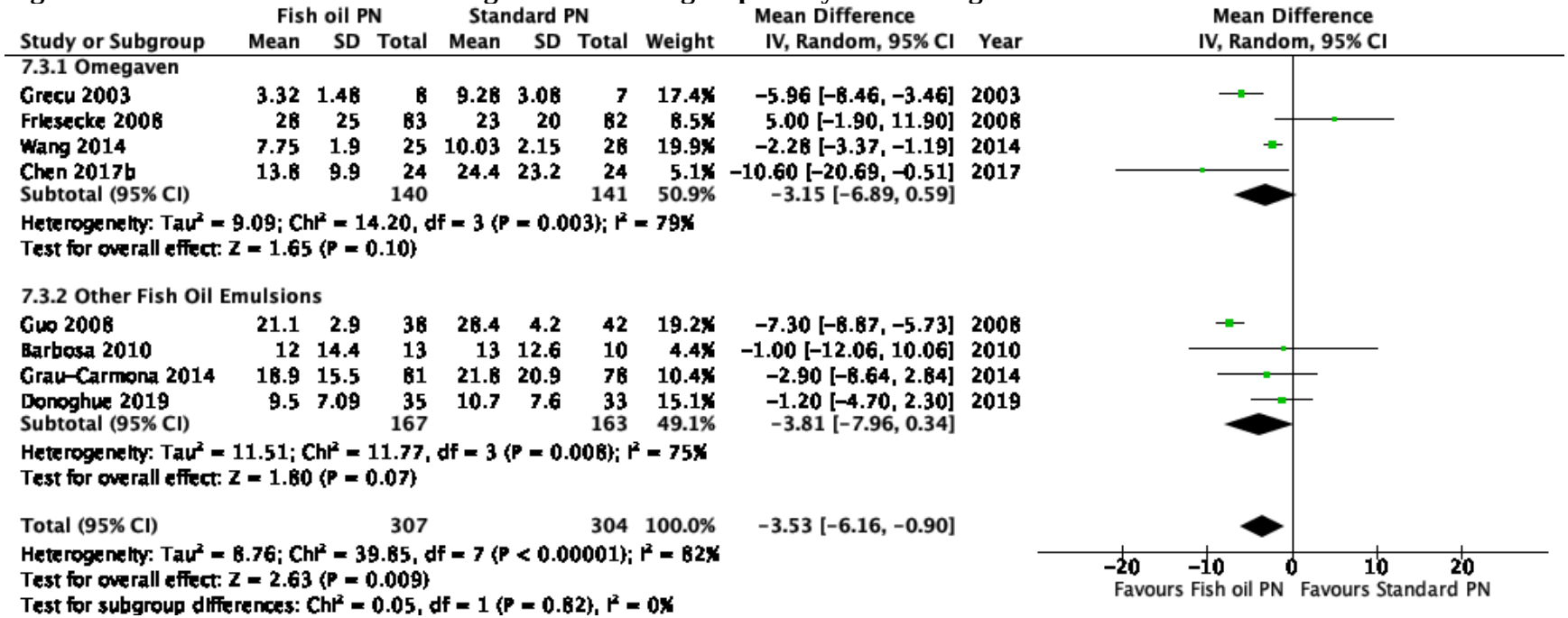


Figure 7.4. ICU LOS in Trials Comparing Stand-alone Fish Oil Emulsions to Standard of Care

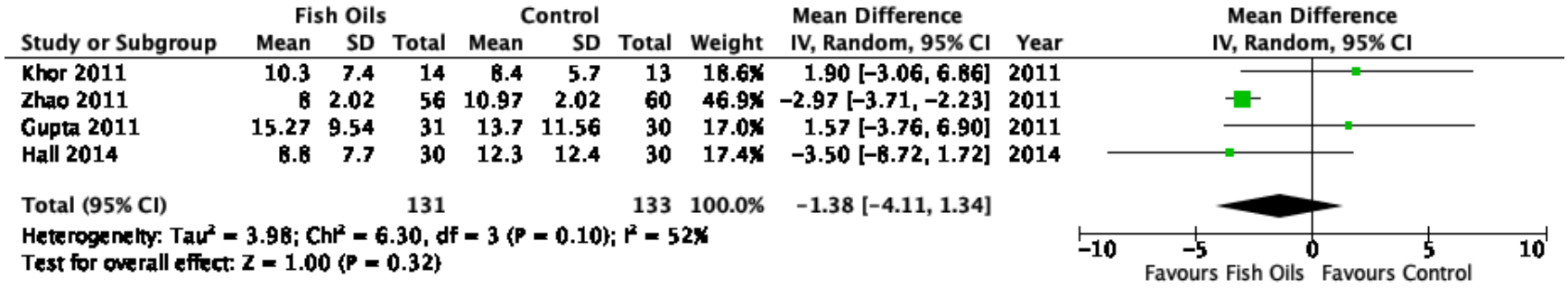


Figure 8.1 Ventilator Days in Trials Using an Omega-6 Reducing Strategy

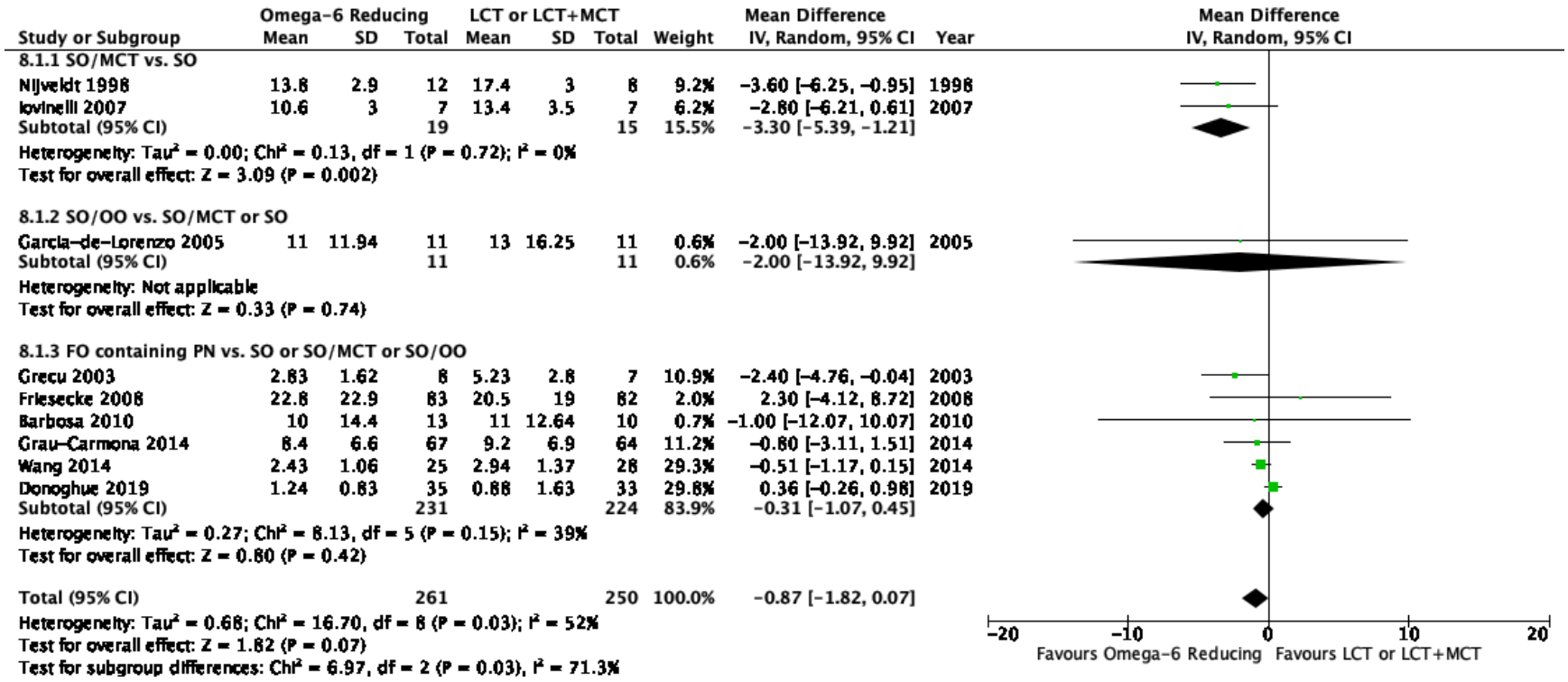


Figure 8.2 Ventilator Days in Trials Using an Omega-6 Reducing Strategy: Subgroup Analyses of SO/MCT or SO/OO vs. SO and FO vs SO or SO/MCT or SO/OO

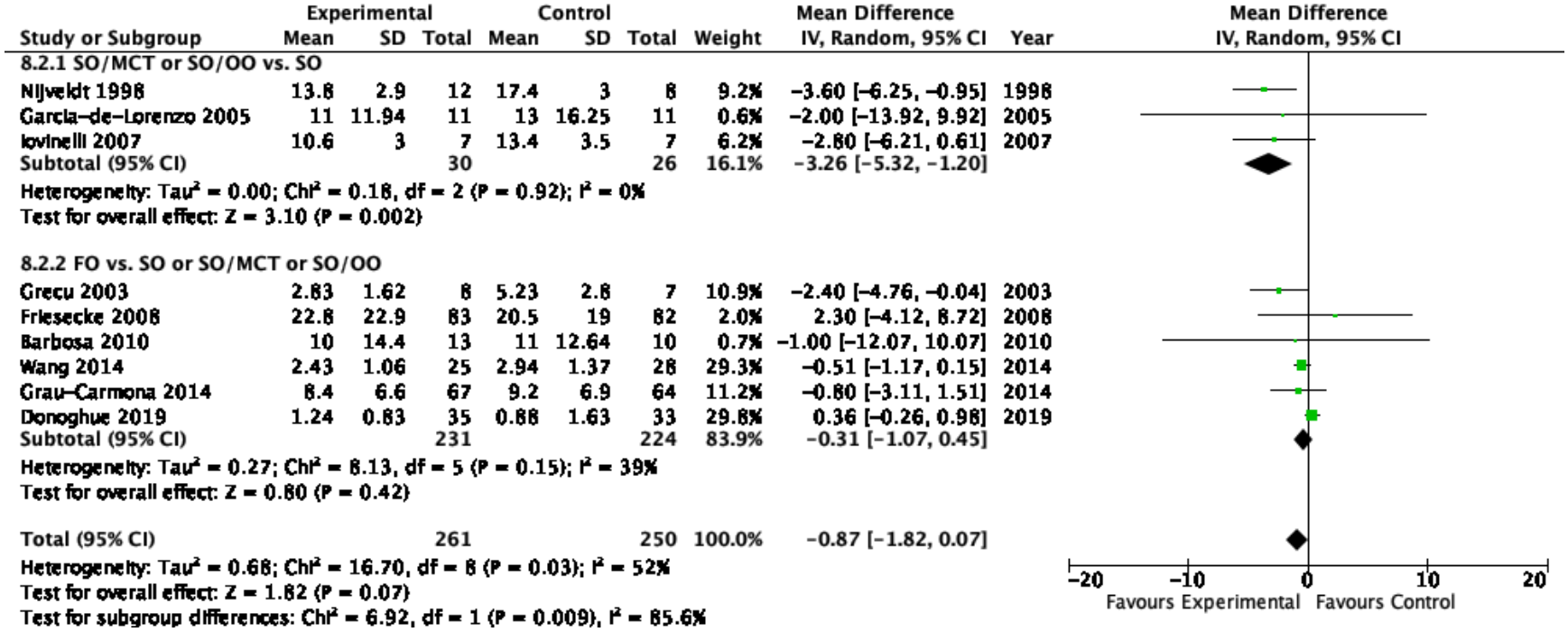


Figure 8.3 Ventilator Days in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

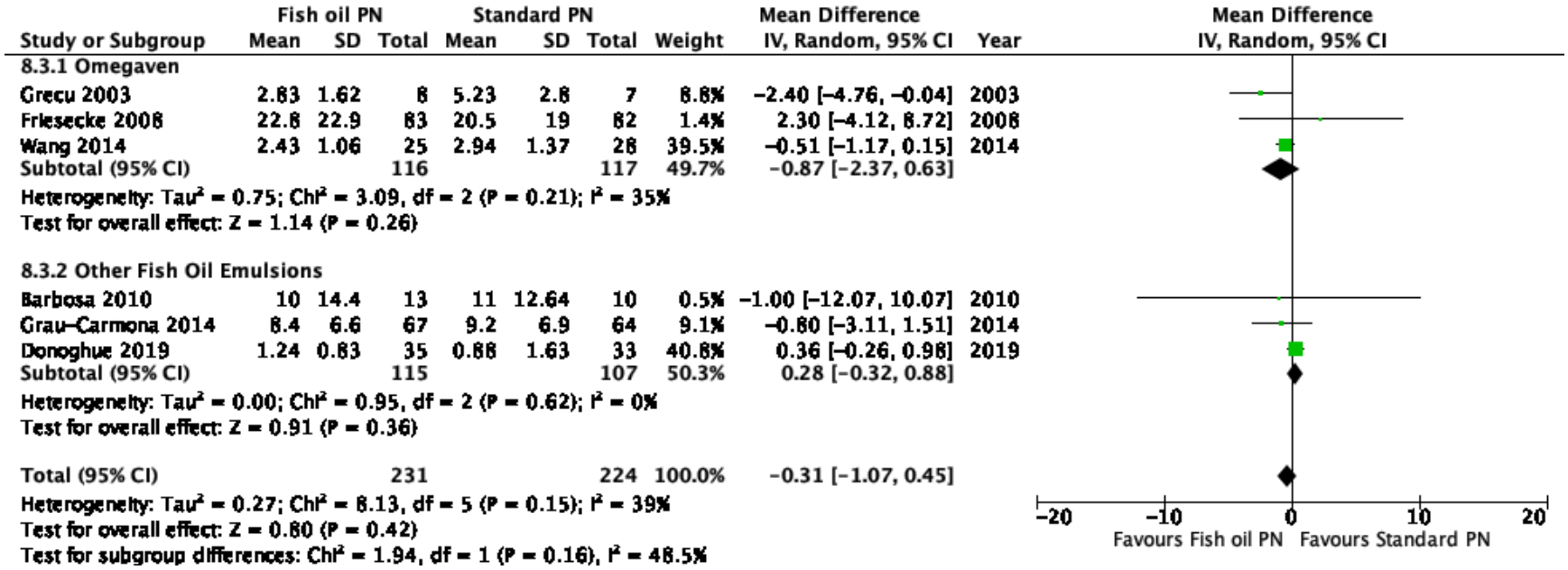
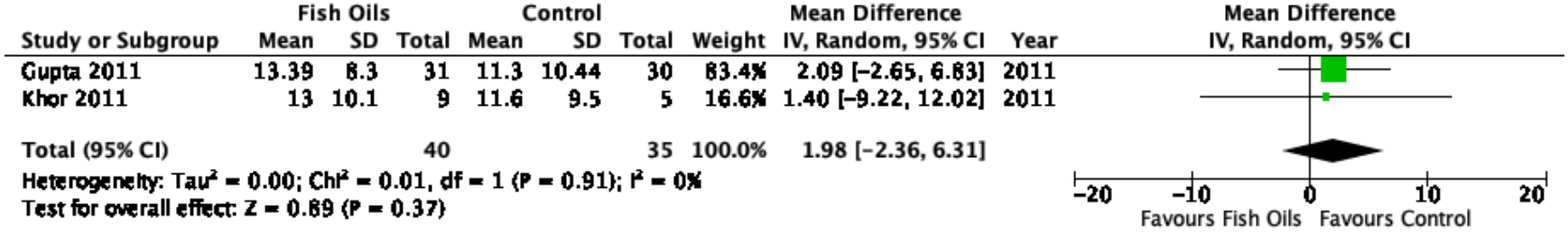


Figure 8.4 Ventilator Days in Trials Comparing Stand-Alone Fish Oil Emulsions to Standard of Care



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Stand alone Fish Oil

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Exclusion list

#	Reason excluded	Citation
1	Duplicate of Wang 2009	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;32(3):236-241. doi:10.1177/0148607108316189
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