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-, diand 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 FO² (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 FO³ (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% Cl 0.65, 1.23, p=0.50, test for heterogeneity $l^2 = 0\%$.; figure 1.3) nor FO-containing PN vs SO or SO/MCT or SO/OO (RR 0.92, 95% Cl 0.72, 1.16, p=0.47, test for heterogeneity $l^2 = 4\%$.; 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, I² = 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 I²=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 I²=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 $l^2 = 4\%$; 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 $l^2 = 12\%$; 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, $l^2 = 0\%$; figure 2.1 and sensivity (RR 0.72, 95% CI 0.51, 1.01, p=0.05, $l^2 = 0\%$; 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, l² =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 I² =0%; figure 1.6), and a significant reduction of 28-day mortality (RR 0.60, 95% CI 0.36, 0.99, p=0.04, I² =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 standalone FO emulsion reported ICU mortality (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, $l^2=0\%$; figure 4.4)

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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, I²=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, I²=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 I²=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 I²= 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 I²= 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 I²=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 I²=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 I²= 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 I²=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 I²= 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, I²= 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 I²=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, I²= 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 I²=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 I²=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 I²=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 I²=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 I²= 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 I²= 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 I²=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 I²=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 I²=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 I²=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 (lovinellei 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.

| 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) lovinelli 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% ω 9, 37% ω 6= restricted linoleic acid { ω 6} 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) | | | |

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

| 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 infe 39/103 (38) ICU acquired 28/103 (27) VAP/lower respir 9/103 (9) | 35/101 (35) I infections 23/101 (23) |
|--------------------------|--|---|--|---|---|--|--|
| 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 SO 29/51 (57) 21/49 (43) Pneumonia 7/51 (14) 5/49 (10) | |
| | | (C) F | FO containing PN vs. SO or SO/N | ICT 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 FO SO (SO) (ω 3: ω 6 ratio was 1:4) vs. PN with ICU ICU Lipovenos (SO). Both received same amounts 0/28 (0) 2/28 (7) of lipids (1 gm/kg/day) Note: Lipovenos contains 20% MCT ICU | | 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 |
| | <u> </u> | (D) Stand-alc | one FO emulsion suppleme | ent vs. stand | dard 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

| Study | LOS days | | Ventilato | or 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 | $\begin{array}{c c} \textbf{MCT/SO} & \textbf{SO} \\ \textbf{Retinol binding protein} \\ 1.7 \pm 1 & 0.8 \pm 0.6 \\ \textbf{Nitrogen balance} \\ 14.2 \pm 2.9 & 11.6 \pm 4 \end{array}$ | |
| 4) lovinelli 2007 | MCT/SO NR | SO NR | MCT/SO 10.6 ± 3.0 (7) | SO 13.4 ± 3.5 (7) | MCT/SOSOTime before weaning52 ± 36 hrs127 ± 73 hrs | |
| | | | SO/OO vs. SO/MCT or SO | | | |
| 5) Garcia-de- Lorenzo 2005 | OO/SO ICU 32.9 ± 10.61ª (11) Hospital 57 ± 15.26ª (11) | MCT/SO ICU 41.8 ± 16.57ª (11) Hospital 64.9 ± 27.20 ° (11) | OO/SO 11.0 ± 11.94ª (11) | MCT/SO 13.0 ± 16.25ª(11) | OO/SOMCT/SOMultiple 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) 12 (8-15) 11 (7-15) Dextrose (g/day) 288 (275-303) 288 (275-303) 281 (273-301) AAs (g/day) 87 (84-90) | |

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

| 7) Umpierrez 2012 | $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$ | | NR NR | | OO/SO SO Total Energy Intake (kcal/kg) 22 ± 6 22 ± 5 |
|--------------------------|--|--|--------------------------------------|--|---|
| | | FO containir | ng PN vs. SO or SO/MC | T 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) | $\begin{array}{c c} \textbf{FO/MCT/SO} & \textbf{MCT/SO} \\ \textbf{Urinary Tract Infections} \\ 6/83 (7) & 4/82 (5) \\ \textbf{Catheter-related infections} \\ 1/83 (1) & 3/83 (4) \\ \textbf{Total EN Energy Intake (kcal/kg)} \\ 22.2 \pm 5.5 & 21.6 \pm 5.6 \\ \end{array}$ |
| 10) Guo 2008 | FO ICU 21.1 <u>+</u> 2.9 | SO ICU 28.4 <u>+</u> 4.2 | NR | NR | NR |
| 11) Qu 2009 | NR | NR | NR | NR | NR |
| 12) Wang 2009 | NR | NR | NR | NR | FOSOSurgery of infected pancreatic necrosis3/28 (11)6/28 (21) |
| 13) Barbosa 2010 | FO/MCT/SO ICU 12 ± 14.4ª (13) Hospital 22 ± 25.2ª (13) | MCT/SO ICU 13 ± 12.6 ° (10) Hospital 55 ± 50.6 ° (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 <u>+</u> 15.5 (81) | MCT/SO ICU 21.8 <u>+</u> 20.9 (78) | FO/MCT/SO 8.4 <u>+</u> 6.6 (67) | MCT/SO 9.2 <u>+</u> 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 |

1

1

| | Hospital 41.1 <u>+</u> 41.0 (81) | Hospital 42.5 <u>+</u> 28.5 (78) | | | 1,737 ± 353 1,782 ± 312 |
|----------------------|--|---|---|--|--|
| 16) Gultekin 2014 | FO/OO/SO Hospital 31.6 <u>+</u> 17.2 (16) | OO/SO Hospital 30.6 <u>+</u> 17.2 (16) | NR | NR | FO/OO/SO OO/SO Kcal/kg/day 27.5±1.5 27.5±1.5 15.8±1.5 g protein/kg/d 1.3±0.2 |
| 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 <u>+</u> 9.9 | SO ICU 24.4 <u>+</u> 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 ve | s. 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 <u>+</u> 7.4 (14) | Standard ICU 8.4 <u>+</u> 5.7 (13) | NR | NR | NR |

| | Hospital 19.6 <u>+</u> 6.5 (14) | Hospital 17.5 <u>+</u> 5.3 (13) | | | |
|-------------------|--|---|--|---------------------------------------|---|
| 24) Zhao 2011 | FO ICU 8.0 <u>+</u> 2.02 (56) | Standard ICU 10.97 <u>+</u> 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 <u>+</u> 7.7 Hospital 26.7 <u>+</u> 18.2 | Standard I CU 12.3 <u>+</u> 12.4 Hospital 33.5 <u>+</u> 30.4 | NR (reported as free ventilator days) | NR (reported as free ventilator days) | NR |

C.Random: concealed randomization ITT: intent to treat

MCT: medium chain triglycerides LCT: long chain triglycerides

† hospital mortality unless specified ‡ number of patients with infections unless specified

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)

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

| | Omega-6 Re | | LCT or LCT | | | Risk Ratio | | Risk Ratio |
|--|----------------|-------------|---------------------------|--------|---------|---------------------|------|---|
| tudy or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M–H, Random, 95% CI |
| .1.1 SO/MCT vs. SO | | | - | - | | | | |
| lijveldt 1998 | 2 | 12 | 1 | 6 | 0.7% | | | |
| Indgren 2001 | 4 | 9 | 5 | 11 | 3.6% | | | |
| arnacho-Montero 2002 | 11 | 35 | 13 | 37 | 8.0% | | | |
| ovinelli 2007 | 2 | 7 | 3 | 7 | 1.6% | | 2007 | |
| ubtotal (95% CI) | | 63 | | 63 | 13.9% | 0.90 [0.55, 1.48] | | - |
| otal events | 19 | | 22 | | | | | |
| eterogeneity: Tau ² = 0.00; | | | = 0.96); i ^z = | - 0% | | | | |
| est for overall effect: Z = 0 | .41 (P = 0.68) | | | | | | | |
| .1.2 SO/OO vs. SO/MCT o | or SO | | | | | | | |
| Garcia-de-Lorenzo 2005 | 4 | 11 | 3 | 11 | 2.2% | 1.33 [0.39, 4.62] | 2005 | |
| ontes-Arruda 2012 | 24 | 103 | 26 | 101 | 14.6% | | | |
| Implerrez 2012 | 5 | 51 | 8 | 49 | 3.1% | | | |
| ubtotal (95% CI) | - | 165 | - | 161 | 20.2% | | - | • |
| otal events | 33 | | 37 | | | | | |
| leterogeneity: Tau ² = 0.00; | | df = 2 (P • | | 0% | | | | |
| est for overall effect: $Z = 0$ | | | | | | | | |
| .1.3 FO containing PN vs. | SO or SO/MC | T or SO/C | 0 | | | | | |
| irecu 2003 | 2 | 28 | 3 | 26 | 1.2% | 0.62 [0.11, 3.41] | 2003 | |
| riesecke 2008 | 16 | 63 | 22 | 82 | 11.7% | 0.61 [0.47, 1.39] | 2008 | |
| Juo 2008 | 6 | 38 | 6 | 42 | 3.7% | 0.83 [0.32, 2.17] | 2008 | |
| Vang 2009 | 0 | 28 | 2 | 28 | 0.4% | 0.20 [0.01, 3.99] | 2009 | · · · · · · · · · · · · · · · · · · · |
| Qu 2009 | 4 | 20 | 2 | 20 | 1.4% | 2.00 [0.41, 9.71] | 2009 | |
| arbosa 2010 | 4 | 13 | 4 | 10 | 2.6% | 0.77 [0.25, 2.34] | 2010 | |
| abater 2011 | 4 | 8 | 2 | 8 | 1.6% | 2.00 [0.50, 8.00] | 2011 | |
| Grau-Carmona 2014 | 32 | 61 | 22 | 78 | 17.4% | 1.40 [0.90, 2.19] | 2014 | |
| iultekin 2014 | 7 | 16 | 6 | 16 | 6.3X | 0.66 [0.42, 1.64] | 2014 | |
| hen 2017b | 3 | 24 | 10 | 24 | 2.6% | 0.30 [0.09, 0.96] | 2017 | |
| hen 2017a | 10 | 41 | 15 | 37 | 7.6% | 0.60 [0.31, 1.17] | 2017 | |
| onoghue 2019 | 6 | 35 | 5 | 33 | 2.9% | | | |
| inger 2021 | 10 | 48 | 11 | 47 | 6.0% | | 2021 | |
| ubtotal (95% CI) | | 463 | | 451 | 65.9% | 0.92 [0.72, 1.16] | | • |
| otal events | 106 | | 114 | | | | | |
| leterogeneity: $Tau^2 = 0.01$; est for overall effect: $Z = 0$ | | | P = ().41); | r = 4% | | | | |
| otal (95% CI) | | 691 | | 675 | 100.0% | 0.91 [0.76, 1.10] | | |
| otal events | 158 | 001 | 173 | 0.5 | 200.0/0 | 0.01 [0.00] 1.10] | | • |
| leterogeneity: Tau ² = 0.00; | | df = 10 / | - | P - 08 | | | | |
| est for overall effect: Z = 0 | | | · - 0.00); | | | | | 0.01 0.1 1 10 |
| | .50 (7 = 0.34) | | | | | | | Favours omega-6 reducing Favours LCT or LCT+MCT |

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

| 8 | Omega-6 Red | ducing | LCT or LCT | +мст | e | Risk Ratio | | Risk Ratio |
|--|-------------------------------|-----------|---------------------------|---------|--------|---------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M-H, Random, 95% Cl |
| 1.2.1 SO/MCT vs. SO | | | | | | | | |
| Nijvekit 1998 | 2 | 12 | 1 | 8 | 0.7% | 1.33 [0.14, 12.37] | 1998 | |
| Undgren 2001 | 4 | 9 | 5 | 11 | 3.6% | 0.98 [0.37, 2.59] | | |
| Garnacho-Montero 2002 | 11 | 35 | 13 | 37 | 8.5% | 0.89 [0.46, 1.72] | 2002 | _ |
| ovinelli 2007 | 2 | 7 | 3 | 7 | 1.7% | 0.67 [0.16, 2.84] | 2007 | |
| Subtotal (95% CI) | | 63 | | 63 | 14.8% | 0.90 [0.55, 1.48] | | - |
| Fotal events | 19 | | 22 | | | | | |
| Heterogeneity: Tau ² = 0.00 |); Chl ² = 0.31, c | if = 3 (P | = 0.96); 1 ² = | 0% | | | | |
| Test for overall effect: Z = | | | | | | | | |
| 1.2.2 SO/OO vs. SO/MCT | or SO | | | | | | | |
| Garcia-de-Lorenzo 2005 | 4 | 11 | 3 | 11 | 2.4% | 1.33 [0.39, 4.62] | 2005 | |
| Pontes-Arruda 2012 | 24 | 103 | - | | 15.8% | | | _ _ |
| Umplerrez 2012 | 5 | 51 | 6 | 49 | | | | |
| Subtotal (95% CI) | | 165 | | 161 | 21.5% | 0.89 [0.59, 1.34] | | + |
| Fotal events | 33 | | 37 | | | | | - |
| Heterogeneity: $Tau^2 = 0.00$ |): $Cht^2 = 0.96$. c | if = 2 (P | = 0.62); l ² = | 0% | | | | |
| Test for overall effect: Z = | 0.57 (P = 0.57) | | | | | | | |
| 1.2.3 FO containing PN vs | . SO or SO/MC | T or SO/ | 00 | | | | | |
| Grecu 2003 | 2 | 28 | 3 | 26 | 1.3× | 0.62 [0.11, 3.41] | 2003 | |
| Guo 2008 | 6 | 36 | 6 | 42 | 4.0% | 0.83 [0.32, 2.17] | 2008 | |
| riesecke 2008 | 18 | 83 | 22 | 82 | 12.4% | 0.81 [0.47, 1.39] | 2008 | _ - + |
| Wang 2009 | 0 | 28 | 2 | 28 | 0.4% | 0.20 [0.01, 3.99] | 2009 | |
| Qu 2009 | 4 | 20 | 2 | 20 | 1.5% | 2.00 [0.41, 9.71] | 2009 | |
| Sarbosa 2010 | 4 | 13 | 4 | 10 | 3.0% | 0.77 [0.25, 2.34] | 2010 | |
| Sabater 2011 | 4 | 8 | 2 | 8 | 1.9% | 2.00 [0.50, 8.00] | 2011 | |
| Grau-Carmona 2014 | 32 | 61 | 22 | 78 | 18.5% | 1.40 [0.90, 2.19] | | + - - |
| Guitekin 2014 | 7 | 16 | 6 | 16 | 6.7% | 0.88 [0.42, 1.84] | 2014 | _ |
| Chen 2017b | 3 | 24 | 10 | 24 | 2.7% | 0.30 [0.09, 0.96] | 2017 | |
| Chen 2017a | 10 | 41 | 15 | 37 | 8.3X | 0.60 [0.31, 1.17] | 2017 | |
| Donoghue 2019 | 6 | 35 | 5 | 33 | 3.1% | 1.13 [0.38, 3.36] | 2019 | |
| Subtotal (95% CI) | | 415 | | 404 | 63.7% | 0.90 [0.69, 1.18] | | ◆ |
| Fotal events | 96 | | 103 | | | | | |
| Heterogeneity: Tau ² = 0.03 Fest for overall effect: Z = 1 | | | (P = 0.33); I | ² = 12% | | | | |
| | | | | | | | | |
| | | 643 | | 628 | 100.0% | 0.91 0.75. 1.111 | | - |
| Fotal (95% CI) | 14R | 643 | | 628 | 100.0% | 0.91 [0.75, 1.11] | | • |
| Fotal (95% CI) Fotal events | 146): Chế - 13 70 | | 162 | | 100.0% | 0.91 [0.75, 1.11] | | • • |
| otal (95% CI) |); Chl ² = 13.79, | df = 18 | 162 | | 100.0% | 0.91 [0.75, 1.11] | | 0.01 0.1 1 10 1 Favours omega-6 reducing Favours LCT or LCT+MCT |

| 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 |

| 6 | Experim | | Cont | | M/-1-1 - | Risk Ratio | | Risk Ratio |
|--|---------------|------------|-----------|------------|----------------|--|------|--------------------------------------|
| Study or Subgroup | | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M-H, Random, 95% Cl |
| 1.3.1 SO/MCT or SO/OO | | | _ | | · | | | |
| Nijveldt 1996 | 2 | 12 | 1 | 6 | 0.7% | 1.33 [0.14, 12.37] | | |
| Lindgren 2001 | 4 | 9 | 5 | 11 | 3.6% | 0.98 [0.37, 2.59] | | |
| Garnacho-Montero 2002 | 11 | 35 | 13 | 37 | 8.0% | 0.89 [0.46, 1.72] | | |
| Garcia-de-Lorenzo 2005 | 4 | 11 | 3 | 11 | 2.2% | 1.33 [0.39, 4.62] | | |
| iovinelli 2007 | 2 | 12 | | 12 | 1.3% | 0.67 [0.13, 3.30] | | |
| Umplerrez 2012 | 5 | 51 | 6 | 49 | 3.2% | 0.60 [0.21, 1.71] | | |
| Pontes-Arruda 2012 Subtotal (95% CI) | 24 | 103 233 | 26 | 101 229 | 14.9X 33.9% | 0.91 [0.56, 1.47] 0.89 [0.65, 1.23] | 2012 | • |
| Total events | 52 | | 59 | | | | | |
| Heterogeneity: Tau ² = 0.04 Test for overall effect: Z = | | | = 6 (P = | 0.97); | r = 0% | | | |
| 1.3.2 FO vs. SO or SO/MC | CT or SO/O | 00 | | | | | | |
| Grecu 2003 | 2 | 28 | 3 | 26 | 1.2% | 0.62 [0.11, 3.41] | 2003 | |
| Guo 2008 | 16 | 63 | 22 | 82 | 11.7% | 0.81 [0.47, 1.39] | 2008 | _ - + |
| Friesecke 2008 | 6 | 38 | 8 | 42 | 3.7% | 0.83 [0.32, 2.17] | 2008 | |
| Qu 2009 | 4 | 20 | 2 | 20 | 1.4% | 2.00 [0.41, 9.71] | 2009 | |
| Wang 2009 | 0 | 28 | 2 | 28 | 0.4% | 0.20 [0.01, 3.99] | 2009 | |
| Barbosa 2010 | 4 | 13 | 4 | 10 | 2.6% | 0.77 [0.25, 2.34] | 2010 | |
| Sabater 2011 | 4 | 6 | 2 | 6 | 1.6% | 2.00 [0.50, 8.00] | 2011 | |
| Grau-Carmona 2014 | 32 | 81 | 22 | 78 | 17.4% | 1.40 [0.90, 2.19] | 2014 | + |
| Gultekin 2014 | 7 | 16 | 8 | 16 | 6.3X | 0.88 [0.42, 1.84] | 2014 | - |
| Chen 2017a | 3 | 24 | 10 | 24 | 2.6% | 0.30 [0.09, 0.96] | 2017 | |
| Chen 2017b | 10 | 41 | 15 | 37 | 7.6% | 0.60 [0.31, 1.17] | 2017 | |
| Donoghue 2019 | 6 | 35 | 5 | 33 | 2.9% | 1.13 [0.38, 3.36] | 2019 | |
| Singer 2021 | 10 | 48 | 11 | 47 | 6.0% | 0.89 [0.42, 1.90] | 2021 | - |
| Subtotal (95% CI) | | 463 | | 451 | 66.1% | 0.92 [0.72, 1.16] | | • |
| Total events | 106 | | 114 | | | | | |
| Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = | | | f = 12 (P | P = 0.43 | 1); | 4 | | |
| Total (95% CI) | | 696 | | 680 | 100.0% | 0.91 [0.76, 1.10] | | • |
| Total events | 158 | | 173 | | | | | |
| Heterogeneity: $Tau^2 = 0.00$ | $0: Ch^2 = 1$ | 3.76. d | f = 19 (P | P = 0.80 | $0); t^2 = 03$ | í | | |
| Test for overall effect: Z = | | | | | | | | 0.01 0.1 1 10 1 |
| lest for subgroup different | | | if _ 1 /P | - 0.91 | 1 6-04 | | | Favours Experimental Favours Control |

| | Fish oi | | Standar | | | Risk Ratio | | Risk Ratio |
|-----------------------------------|------------|--------------------|-----------|-------------------------|-------------------------|---------------------|------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | Year | M–H, Random, 95% CI |
| 1.4.1 Omegaven | | | | | | | | |
| Grecu 2003 | 2 | 28 | 3 | 26 | 1.9% | 0.62 [0.11, 3.41] | | |
| Friesecke 2008 | 16 | 63 | 22 | 82 | 17.4% | 0.81 [0.47, 1.39] | | |
| Wang 2009 | 0 | 26 | 2 | 28 | 0.6% | 0.20 [0.01, 3.99] | | |
| Gultekin 2014 | 7 | 16 | 6 | 16 | 9.6X | 0.66 [0.42, 1.64] | | |
| Chen 2017b | 3 | 24 | 10 | 24 | 4.1% | 0.30 [0.09, 0.96] | | |
| Chen 2017a | 10 | 41 | 15 | 37 | 11.9% | 0.60 [0.31, 1.17] | 2017 | |
| Subtotal (95% CI) | | 220 | | 213 | 45.7% | 0.68 [0.48, 0.95] | | • |
| Total events | 40 | _ | 60 | | _ | | | |
| Heterogeneity: Tau ² = | - | | - | $\langle P=0.$ | 61); ř = 0 |)% | | |
| Test for overall effect: | Z = 2.23 (| (P=0.) | 03) | | | | | |
| 1.4.2 Other Fish Oil e | mulsions | | | | | | | |
| Guo 2008 | 6 | 38 | 8 | 42 | 5.9% | 0.83 [0.32, 2.17] | 2008 | |
| Qu 2009 | 4 | 20 | 2 | 20 | 2.2% | 2.00 [0.41, 9.71] | 2009 | |
| Barbosa 2010 | 4 | 13 | 4 | 10 | 4.4% | 0.77 [0.25, 2.34] | 2010 | |
| Sabater 2011 | 4 | 6 | 2 | 6 | 2.9% | 2.00 [0.50, 8.00] | 2011 | |
| Grau-Carmona 2014 | 32 | 81 | 22 | 78 | 24.8X | 1.40 [0.90, 2.19] | 2014 | + - |
| Donoghue 2019 | 6 | 35 | 5 | 33 | 4.7% | 1.13 [0.38, 3.36] | 2019 | |
| Singer 2021 | 10 | 48 | 11 | 47 | 9.4% | 0.89 [0.42, 1.90] | 2021 | . |
| Subtotal (95% CI) | | 243 | | 238 | 54.3% | 1.19 [0.87, 1.62] | | ◆ |
| Total events | 66 | | 54 | | | | | |
| Heterogeneity: Tau ² = | 0.00; Chř | ² = 3.1 | 8, df = 6 | $\langle \mathbf{P}=0,$ | 79); i ² = 0 |)% | | |
| Test for overall effect: | Z = 1.11 (| (P= 0) | 27) | | | | | |
| Total (95% CI) | | 463 | | 451 | 100.0% | 0.92 [0.72, 1.16] | | • |
| Total events | 106 | | 114 | | | | | |
| Heterogeneity: Tau ² = | 0.01; Chř | ² = 12. | 49, df = | 12 (P = | 0.41); l ² • | - 4% | | 0.01 0.1 1 10 10 |
| Test for overall effect: | | | | - | | | | 0.01 0.1 1 10 10 Favours Fish oil PN Favours Standard PN |
| Fest for subgroup diffe | | - | • | 1 (P = 1) | 0.02). i ² = | 82.6% | | ravours rish on river ravours standard PN |

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

| | Fish oi | | Standa | | | Risk Ratio | | | Risk Ratio |
|-----------------------------------|-----------|----------------|-----------|------------------|-----------------------|---------------------|------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | Year | | M–H, Random, 95% Cl |
| 1.5.1 Omegaven | | | | | | | | | |
| Grecu 2003 | 2 | 28 | 3 | 26 | 2.4% | 0.62 [0.11, 3.41] | 2003 | | |
| Friesecke 2008 | 18 | 63 | 22 | 82 | 18.3X | 0.81 [0.47, 1.39] | 2008 | | |
| Wang 2009 | 0 | 28 | 2 | 28 | 0.6% | 0.20 [0.01, 3.99] | 2009 | | |
| Gultekin 2014 | 7 | 16 | 6 | 16 | 11.2% | 0.88 [0.42, 1.84] | 2014 | | |
| Chen 2017b | 3 | 24 | 10 | 24 | 5.0% | 0.30 [0.09, 0.96] | 2017 | | |
| Chen 2017a | 10 | 41 | 15 | 37 | 13.4% | 0.60 [0.31, 1.17] | 2017 | | |
| Subtotal (95% CI) | | 220 | | 213 | 51.2% | 0.68 [0.48, 0.95] | | | • |
| Total events | 40 | | 60 | | | | | | |
| Heterogeneity: $Tau^2 =$ | 0.00; Chř | ² = 3.6 | 1, df = 5 | $(\mathbf{P}=0)$ | 61); i ² = | 0% | | | |
| Test for overall effect: | Z = 2.23 | (P=0.) | 03) | | | | | | |
| 1.5.2 Other Fish Oil e | mulsions | | | | | | | | |
| Guo 2008 | 6 | 38 | 8 | 42 | 7.1% | 0.83 [0.32, 2.17] | 2008 | | |
| Qu 2009 | 4 | 20 | 2 | 20 | 2.8% | 2.00 [0.41, 9.71] | 2009 | | |
| Barbosa 2010 | 4 | 13 | 4 | 10 | 5.4% | 0.77 [0.25, 2.34] | 2010 | | |
| Sabater 2011 | 4 | 6 | 2 | 6 | 3.6% | 2.00 [0.50, 8.00] | 2011 | | |
| Grau-Carmona 2014 | 32 | 81 | 22 | 76 | 24.3% | 1.40 [0.90, 2.19] | 2014 | | + |
| Donoghue 2019 | 6 | 35 | 5 | 33 | 5.7% | 1.13 [0.38, 3.36] | 2019 | | |
| Subtotal (95% CI) | | 195 | | 191 | 48.8% | 1.26 [0.90, 1.77] | | | ◆ |
| Total events | 56 | | 43 | | | | | | |
| Heterogeneity: Tau ² = | 0.00; Chř | ² = 2.4 | 9, df = 5 | $(\mathbf{P}=0)$ | 78); i ² = | 0% | | | |
| Test for overall effect: | Z = 1.35 | (P= 0) | 16) | | | | | | |
| Total (95% CI) | | 415 | | 404 | 100.0% | 0.90 [0.69, 1.18] | | | • |
| Total events | 96 | | 103 | | | | | | |
| Heterogeneity: $Tau^2 =$ | 0.03; Chř | ² = 12. | 49, df = | 11 (P = | 0.33); P | = 12% | | 0.01 | 0.1 1 10 10 |
| Test for overall effect: | | | | - | | | | 0.01 | 0.1 1 10 10 Favours Fish oil PN Favours Standard PN |
| Test for subgroup diffe | | | | 1 (P = | 0.01), P | = 64.4% | | | ravours rish oli PN ravours standard PN |

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| | Fish | oil | Cont | rol | | Risk Ratio | | Risk Ratio | |
|---|---|--|---------------------|-------|--------|------------------------------------|------|---|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M–H, Random, 95% Cl | |
| 1.6.1 Omegaven | | | | | | | | | |
| Gupta 2011 | 7 | 31 | 13 | 30 | 22.5% | 0.52 [0.24, 1.13] | 2011 | | |
| Zhao 2011 | 6 | 56 | 11 | 60 | 19.2% | 0.78 [0.34, 1.80] | 2011 | | |
| Hall 2014 | 4 | 30 | 6 | 30 | 11.3% | 0.50 [0.17, 1.48] | 2014 | | |
| Burkhart 2014 | 13 | 25 | 13 | 25 | 47.0% | 1.00 [0.59, 1.70] | 2014 | | |
| Subtotal (95% CI) | | 142 | | 145 | 100.0% | 0.76 [0.53, 1.10] | | | |
| Total events | 32 | | 45 | | | | | | |
| Heterogeneity: Tau ² | | | | - | | | | | |
| 1.6.2 Other Fish Oil | | - | 1.14) | 0 | | Not estimable | | | |
| 1.6.2 Other Fish Oil Subtotal (95% CI) | emulsion | IS | - | 0 | | Not estimable | | | |
| 1.6.2 Other Fish Oil Subtotal (95% CI) Total events Heterogeneity: Not a | l emulsion 0 pplicable | 0 | 0 | 0 | | Not estimable | | | |
| Test for overall effect 1.6.2 Other Fish Oil Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect Total (95% CI) | l emulsion 0 pplicable | 0 | - | - | 100.0% | Not estimable 0.76 [0.53, 1.10] | | | |
| 1.6.2 Other Fish Oil Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect | l emulsion 0 pplicable | o Icable | - | - | 100.0% | | | | |
| 1.6.2 Other Fish Oil Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect Total (95% CI) | l emulsion 0 pplicable t: Not appl 32 | o Icable 142 | 0 | 145 | | 0.76 [0.53, 1.10] | | | |
| 1.6.2 Other Fish Oil Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect Total (95% CI) Total events | l emulsion 0 pplicable t: Not appl 32 = 0.00; Cł | 0 icable 142 1 ² = 2.1 | 0 45 62, df = | 145 | | 0.76 [0.53, 1.10] | 0.1 | 0.2 0.5 1 2 5 Favours Fish Oil Favours Control | 10 |

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

28-day mortality

| udy or Subgroup | _ | | | F+MCT | | Risk Ratio | | | Risk Ratio |
|---|---------------|-----------|--------------|-------|---------|---------------------|------|-----|---------------------------------------|
| | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | | M–H, Random, 95% Cl |
| 1.1 SO/MCT vs. SO | | | | | | | | | |
| ıbtotal (95% CI) | | 0 | | 0 | | Not estimable | | | |
| otal events | 0 | | 0 | | | | | | |
| eterogeneity: Not applic | able | | | | | | | | |
| est for overall effect: No | t applicable | | | | | | | | |
| 1.2 SO/OO vs. SO/MC | T or SO | | | | | | | | |
| ontes-Arruda 2012 | 24 | 103 | 26 | 101 | 29.2% | 0.91 [0.56, 1.47] | 2012 | | |
| ıbtotal (95% CI) | | 103 | | 101 | 29.2% | 0.91 [0.56, 1.47] | | | |
| otal events | 24 | | 26 | | | | | | |
| eterogeneity: Not applic | able | | | | | | | | |
| est for overall effect: Z = | = 0.41 (P = 0 |).69) | | | | | | | |
| 1.3 FO containing PN | vs. SO or SO | /MCT or | so/oo | | | | | | |
| lesecke 2008 | 16 | 83 | 22 | 82 | 23.0% | 0.81 [0.47, 1.39] | 2008 | | |
| uo 2006 | 6 | 36 | 6 | 42 | 7.3% | 0.83 [0.32, 2.17] | 2008 | | |
| u 2009 | 4 | 20 | 2 | 20 | 2.7% | 2.00 [0.41, 9.71] | 2009 | | · · · · · · · · · · · · · · · · · · · |
| urbosa 2010 | 4 | 13 | 4 | 10 | 5.5% | 0.77 [0.25, 2.34] | 2010 | | |
| ren 2017b | 3 | 24 | 10 | 24 | 5.0% | 0.30 [0.09, 0.96] | | ← | |
| nen 2017a | 10 | 41 | 15 | 37 | 15.3% | 0.60 [0.31, 1.17] | | | |
| nger 2021 | 10 | 48 | 11 | 47 | 11.9% | 0.89 [0.42, 1.90] | 2021 | | |
| ibtotal (95% CI) | | 267 | | 262 | 70.8% | 0.74 [0.54, 1.01] | | | |
| otal events | 55 | | 72 | - | | | | | |
| eterogeneity: Tau ² = 0.0 est for overall effect: Z = | | | 6 (P = 0.59) | ; | | | | | |
| otal (95% CI) | | 370 | | 363 | 100.0% | 0.79 [0.61, 1.02] | | | |
| otal events | 79 | 5.0 | 98 | | 20010/0 | 0.0 5 [0.02] 1.02] | | | - |
| eterogeneity: Tau ² = 0.0 | | 07 df - 1 | | | | | | 0.1 | 1 0.2 0.5 1 2 5 |

| | Omega-6 Re | - | | | | Risk Ratio | | Risk Ratio |
|-------------------------------------|--------------------|------------|---------------|---------------|--------|---------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | Year | M–H, Random, 95% Cl |
| 2.2.1 SO/MCT vs. SO | | | | | | | | |
| Subtotal (95% CI) | | 0 | | 0 | | Not estimable | | |
| iotal events | 0 | | 0 | | | | | |
| leterogeneity: Not appl | kable | | | | | | | |
| Fest for overall effect: N | iot applicable | | | | | | | |
| 2.2.2 SO/OO vs. SO/M | CT or SO | | | | | | | |
| Pontes-Arruda 2012 | 24 | 103 | 26 | 101 | 33.1% | 0.91 [0.56, 1.47] | 2012 | |
| Subtotal (95% CI) | | 103 | | 101 | 33.1% | 0.91 [0.56, 1.47] | | |
| iotal events | 24 | | 26 | | | | | |
| leterogeneity: Not appl | kable | | | | | | | |
| est for overall effect: Z | |).69) | | | | | | |
| 2.2.3 FO containing PN | l vs. SO or SO | /MCT or s | so/oo | | | | | |
| Friesecke 2008 | 18 | 83 | 22 | 82 | 26.1% | 0.81 [0.47, 1.39] | 2008 | _ |
| Guo 2008 | 6 | 38 | 8 | 42 | | 0.83 [0.32, 2.17] | | _ |
| 2u 2009 | 4 | 20 | 2 | 20 | 3.1% | 2.00 [0.41, 9.71] | | |
| arbosa 2010 | 4 | 13 | 4 | 10 | 6.2% | 0.77 [0.25, 2.34] | | _ |
| hen 2017b | 3 | 24 | 10 | 24 | 5.7% | 0.30 [0.09, 0.96] | | |
| chen 2017a | 10 | 41 | 15 | 37 | 17.4% | 0.60 [0.31, 1.17] | | _ |
| ubtotal (95% CI) | - | 219 | - | 215 | 66.9% | 0.72 [0.51, 1.01] | | |
| otal events | 45 | | 61 | | | | | |
| Heterogeneity: $Tau^2 = 0$ | $1.00; Chl^2 = 4.$ | 35, df = 5 | 5 (P = 0.50) | ; i² = 0% | | | | |
| lest for overall effect: Z | = 1.93 (P = 0 |).05) | | | | | | |
| Total (95% CI) | | 322 | | 316 | 100.0% | 0.77 [0.59, 1.02] | | ◆ |
| fotal events | 69 | | 87 | | | | | |
| leterogeneity: Tau ² = 0 | $1.00; Chl^2 = 4.$ | 95, df = 6 | 6 (P = 0.55) | ; i² = 0% | | | 0. | 1 0.2 0.5 1 2 5 1 |
| est for overall effect: Z | = 1.81 (P = 0) |).07) | | | | | Ų. | Favours omega-6 reducing Favours LCT or LCT+MCT |
| est for subgroup differ | | | = 1 (P = 0.4) | 4), $t^2 = 0$ | × | | | ravours onlega-o reducing ravours LCT or LCT+MCT |

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

| | Experim | ental | Cont | rol | | Risk Ratio | | Risk Ratio |
|---|------------------------|------------|-----------|------------------|-------------------------|--|--------|--|
| Study or Subgroup | Events | | | | Weight | M-H, Random, 95% CI | Year | M-H, Random, 95% Cl |
| 2.3.1 SO/MCT or SO/ | 00 vs. S0 | | | | | | | |
| Pontes-Arruda 2012 Subtotal (95% CI) | 24 | 103 103 | 26 | 101 101 | 29.2% 29.2% | 0.91 [0.56, 1.47] 0.91 [0.56, 1.47] | | |
| Total events | 24 | | 26 | | | | | |
| Heterogeneity: Not app | licable | | - | | | | | |
| Test for overall effect: | | P = 0.6 | i9) | | | | | |
| 2.3.2 FO vs. SO or SO | /MCT or S | 00/00 | | | | | | |
| Guo 2008 | 6 | 38 | 8 | 42 | 7.3% | 0.83 [0.32, 2.17] | 2008 | |
| Friesecke 2008 | 16 | 83 | 22 | | 23.0% | | | |
| Qu 2009 | 4 | 20 | 2 | 20 | 2.7% | | | |
| Barbosa 2010 | 4 | 13 | 4 | 10 | 5.5% | 0.77 [0.25, 2.34] | 2010 | |
| Chen 2017a | 10 | 41 | 15 | 37 | 15.3% | 0.60 [0.31, 1.17] | 2017 | |
| Chen 2017b | 3 | 24 | 10 | 24 | 5.0% | | | |
| Singer 2021 | 10 | 48 | 11 | 47 | 11.9% | 0.89 [0.42, 1.90] | 2021 | |
| Subtotal (95% CI) | | 267 | | 262 | 70.8% | 0.74 [0.54, 1.01] | | ◆ |
| Total events | 55 | | 72 | | | | | |
| Heterogeneity: Tau ² = | 0.00; Chl ² | = 4.61 | l, df = 6 | $(\mathbf{P}=0)$ | 59); l ² = I | 0% | | |
| Test for overall effect: | Z = 1.88 (| P = 0.0 | 6) | | | | | |
| Total (95% CI) | | 370 | | 363 | 100.0% | 0.79 [0.61, 1.02] | | • |
| Total events | 79 | | 98 | | | | | |
| Heterogeneity: Tau ² = | 0.00; Chl ² | = 5.07 | | $(\mathbf{P}=0)$ | 65); l ² = l | 0% | ج ا | 0.1 0.2 0.5 1 2 5 10 |
| Test for overall effect: | | | | _ | | | U U | 1.1 0.2 0.5 1 2 5 10 Favours Experimental Favours Control |
| Test for subgroup diffe | - | | • | 1 (P = | 0.50), i ² • | - 0% | | ravours experimental ravours control |

| | Fish oi | I PN | Standar | 'd PN | | Risk Ratio | | | | Risk | Ratio | | |
|-----------------------------------|------------|------------------------|------------|----------|-------------|---------------------|------|--------|-----------|----------|----------|----------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | | M | -H, Rano | lom, 95% | CI | |
| 2.4.1 Omegaven | | | | | | | | | | | | | |
| Friesecke 2008 | 18 | 63 | 22 | 82 | 32.5% | 0.81 [0.47, 1.39] | 2008 | | | - | + | | |
| Chen 2017a | 10 | 41 | 15 | 37 | 21.7% | 0.60 [0.31, 1.17] | 2017 | | | - | + | | |
| Chen 2017b | 3 | 24 | 10 | 24 | 7.1% | | | ← | | - | - | | |
| Subtotal (95% CI) | | 148 | | 143 | 61.3% | 0.63 [0.41, 0.99] | | | - | | - | | |
| Total events | 31 | | 47 | | | | | | | | | | |
| Heterogeneity: Tau ² - | • 0.03; Ch | $ t^2 = 2.$ | 39, df = 1 | 2 (P = (|).30); l² = | • 16X | | | | | | | |
| Test for overall effect | : Z = 2.00 | $(\mathbf{P}=0)$ | .05) | | | | | | | | | | |
| 2.4.2 Other Fish Oil | emulsion | s | | | | | | | | | | | |
| Guo 2008 | 6 | 38 | 6 | 42 | 10.3% | 0.83 [0.32, 2.17] | 2008 | | | | | - | |
| Qu 2009 | 4 | 20 | 2 | 20 | 3.8% | 2.00 [0.41, 9.71] | 2009 | | - | | | | |
| Sarbosa 2010 | 4 | 13 | 4 | 10 | 7.7% | 0.77 [0.25, 2.34] | 2010 | | | | | _ | |
| Singer 2021 | 10 | 46 | 11 | 47 | 16.6% | 0.89 [0.42, 1.90] | 2021 | | - | | | | |
| Subtotal (95% CI) | | 119 | | 119 | 38.7% | 0.92 [0.56, 1.51] | | | | | | | |
| Fotal events | 24 | | 25 | | | | | | | | | | |
| Heterogeneity: Tau ² - | • 0.00; Ch | $l^2 = 1.0$ | 09, df = : | 3 (P = (|).78); l² = | - 0% | | | | | | | |
| lest for overall effect | : Z = 0.33 | $\langle \mathbf{P}=0$ | .74) | | | | | | | | | | |
| Fotal (95% CI) | | 267 | | 262 | 100.0% | 0.74 [0.54, 1.01] | | | | • | - | | |
| Fotal events | 55 | | 72 | | | | | | | | | | |
| Heterogeneity: Tau ² - | • 0.00; Ch | $t^2 = 4.6$ | 61, df = (| 6 (P = (|).59); l² = | • 0% | | 0.1 0. | 2 | 0.5 | | | 5 1 |
| Fest for overall effect | | | | | - | | | | | | Eavours | Standard | |
| Fest for subgroup diff | | - | | = 1 (P = | 0.28). P | = 16.1% | | | ravours r | | ravours | Stanuaru | FIN |

ality in DN Trials Using Fish Ails, Subgroup Analyses of Amagan Fig 2 4 20 4 .

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

| • | Fish oi | I PN | Standar | d PN | | Risk Ratio | | Risk Ratio |
|-----------------------------------|-------------|----------------------|------------|----------|-------------------------|---------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M-H, Random, 95% CI |
| 2.5.1 Omegaven | | | | | | | | |
| Friesecke 2008 | 16 | 83 | 22 | 82 | 39.1% | 0.61 [0.47, 1.39] | 2008 | |
| Chen 2017a | 10 | 41 | 15 | 37 | 26.0% | 0.60 [0.31, 1.17] | 2017 | |
| Chen 2017b | 3 | 24 | 10 | 24 | 8.6X | 0.30 [0.09, 0.96] | 2017 | · · · · · · · · · · · · · · · · · · · |
| Subtotal (95% CI) | | 148 | | 143 | 73.7% | 0.63 [0.41, 0.99] | | |
| Total events | 31 | | 47 | | | | | |
| Heterogeneity: Tau ² = | • 0.03; Cł | 11 ² = 2. | 39, df = 1 | 2 (P = C |).30); l² = | 16% | | |
| Test for overall effect: | Z = 2.00 | $(\mathbf{P}=0)$ | 1.05) | | | | | |
| 2.5.2 Other Fish Oil | emulsion | s | | | | | | |
| Guo 2008 | 6 | 38 | 8 | 42 | 12.4% | 0.83 [0.32, 2.17] | 2008 | |
| Qu 2009 | 4 | 20 | 2 | 20 | 4.6% | 2.00 [0.41, 9.71] | 2009 | |
| Barbosa 2010 | 4 | 13 | 4 | 10 | 9.3% | 0.77 [0.25, 2.34] | 2010 | |
| Subtotal (95% CI) | | 71 | | 72 | 26.3% | 0.94 [0.49, 1.83] | | |
| Total events | 14 | | 14 | | | | | |
| Heterogeneity: Tau ² = | • 0.00; Cł | $\mathbf{h}^2 = 1.$ | 08, df = : | 2 (P = C |).58); l ² = | • 0X | | |
| Test for overall effect: | Z = 0.16 | i (P = 0 | .86) | | | | | |
| Total (95% CI) | | 219 | | 215 | 100.0% | 0.72 [0.51, 1.01] | | - |
| Total events | 45 | | 61 | | | | | |
| Heterogeneity: Tau ² = | 0.00; Cl | $1^2 = 4.$ | 35, df = : | 5 (P = C |).50); l ² = | • 0% | | 0.1 0.2 0.5 1 2 5 1 |
| Test for overall effect: | - | | - | - | | | | 0.1 0.2 0.5 1 2 5 1 Favours Fish oil PN Favours Standard PN |
| Test for subgroup diff | ferences: (| Cht ² = (| 0.95, df - | - 1 (P - | 0.33), P | = 0% | | ravours risti oli rivi ravours statiuatu riv |

| | Fish | oil | Cont | rol | | Risk Ratio | | Risk Ratio |
|-----------------------------------|----------|------------|----------|--------|-----------------------|---------------------|------|----------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M–H, Random, 95% CI | Year | M–H, Random, 95% CI |
| 2.6.1 Omegaven | | | | | | | | |
| Gupta 2011 | 7 | 31 | 13 | 30 | 42.6% | 0.52 [0.24, 1.13] | 2011 | |
| Zhao 2011 | 6 | 56 | 11 | 60 | 36.2% | 0.78 [0.34, 1.80] | 2011 | |
| Hall 2014 | 4 | 30 | 6 | 30 | 21.3% | 0.50 [0.17, 1.48] | 2014 | |
| Subtotal (95% CI) | | 117 | | 120 | 100.0% | 0.60 [0.36, 0.99] | | \bullet |
| Total events | 19 | | 32 | | | | | |
| Heterogeneity: Tau ² = | 0.00; Cł | $t^2 = 0.$ | 61, df = | 2 (P = | 0.74); f ² | - 0% | | |
| Test for overall effect: | Z = 2.01 | (P = 0 |).04) | | | | | |
| 2.6.2 Other Fish Oil | emulsion | s | | | | | | |
| Subtotal (95% CI) | | 0 | | 0 | | Not estimable | | |
| Total events | 0 | | 0 | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | |
| Test for overall effect: | Not appl | icable | | | | | | |
| Total (95% CI) | | 117 | | 120 | 100.0% | 0.60 [0.36, 0.99] | | - |
| Total events | 19 | | 32 | | | | | |
| Heterogeneity: Tau ² = | 0.00; Ch | $d^2 = 0.$ | 61, df = | 2 (P = | 0.74); f ² | - 0% | L L | |
| Test for overall effect: | - | | - | • | | | 0 | 0.1 0.2 0.5 1 2 5 10 |
| I CALIOI OVCIAII CIICUL | | – . | | | | | | Favours Fish oil Favours Control |

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

ICU Mortality

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

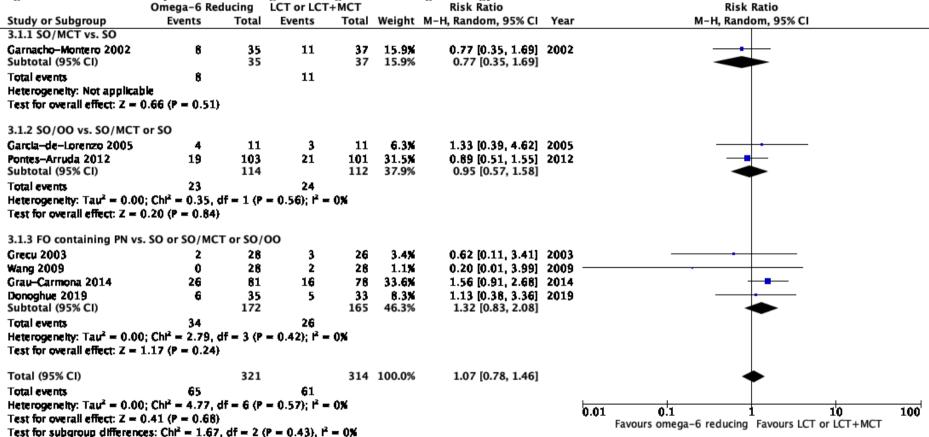


Figure 3.2 ICU Mortality in Trials Using an Omega-6 Reducing Strategy: Subgroup Analyses of SO/MCT or SO/OO vs. SO and FO vs SO or SO/MCT or SO/OO

| | ental | Cont | | | Risk Ratio | | Risk Ratio |
|-------------------------|---|---|--|--|--|--|--|
| Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M–H, Random, 95% Cl |
| s. SO | | | | | | | |
| 6 | 35 | 11 | 37 | 15.9X | 0.77 [0.35, 1.69] | 2002 | |
| 4 | 11 | 3 | 11 | 6.3X | 1.33 [0.39, 4.62] | 2005 | - |
| 19 | 103 149 | 21 | 101 149 | | | | • |
| 31 | | 35 | | | | | |
| - | - | = 2 (P = | 0.76); | r ² = 0% | | | |
| Γ or SO/O | 0 | | | | | | |
| 2 | 28 | 3 | 26 | 3.4% | 0.62 [0.11, 3.41] | 2003 | |
| 0 | 28 | 2 | 28 | 1.1% | 0.20 [0.01, 3.99] | 2009 | |
| 26 | 61 | 16 | 78 | 33.6X | 1.56 [0.91, 2.68] | 2014 | + |
| 6 | 35 | 5 | 33 | 8.3X | 1.13 [0.38, 3.36] | 2019 | |
| | 172 | | 165 | 46.3% | 1.32 [0.83, 2.08] | | ◆ |
| 34 | | 26 | | | | | |
| - | - | = 3 (P = | 0.42); | i² = 0% | | | |
| | 321 | | 314 | 100.0% | 1.07 [0.78, 1.46] | | ◆ |
| 65 | | 61 | | | | | |
| ; Cht ² = 4. | 77, df | = 6 (P = | 0.57); | l ² = 0% | | | 0.01 0.1 1 10 10 |
|).41 (P = 0) | 0.68) | | | | | | 0.01 0.1 1 10 10 Favours Experimental Favours Control |
| | s. SO 8 4 19 31 ; Chi ² = 0. 52 (P = 0 2 0 26 6 34 ; Chi ² = 2. .17 (P = 0 65 ; Chi ² = 4. 1.41 (P = 0 | s. SO 8 35 4 11 19 103 149 31 ; Chi ² = 0.54, df 0.52 (P = 0.60) F or SO/OO 2 28 0 28 26 81 6 35 172 34 ; Chi ² = 2.79, df 17 (P = 0.24) 321 65 ; Chi ² = 4.77, df 0.41 (P = 0.68) | s. SO 6 35 11 4 11 3 19 103 21 149 31 35 ; Chi ² = 0.54, df = 2 (P = 0.52 (P = 0.60) F or SO/OO 2 28 3 0 28 2 26 81 16 6 35 5 172 34 26 ; Chi ² = 2.79, df = 3 (P = 17 (P = 0.24) 321 65 61 ; Chi ² = 4.77, df = 6 (P = 0.41 (P = 0.68) | s. SO 6 35 11 37 4 11 3 11 19 103 21 101 149 149 31 35 ; Chi ² = 0.54, df = 2 (P = 0.76); 0.52 (P = 0.60) T or SO/OO 2 28 2 28 26 81 16 78 6 35 5 33 172 165 34 26 ; Chi ² = 2.79, df = 3 (P = 0.42); 17 (P = 0.24) 321 314 65 61 ; Chi ² = 4.77, df = 6 (P = 0.57); 0.41 (P = 0.68) | s. SO 6 35 11 37 15.9% 4 11 3 11 6.3% 19 103 21 101 31.5% 149 149 53.7% 31 35 ; Ch ² = 0.54, df = 2 (P = 0.76); $r^2 = 0\%$ 0.52 (P = 0.60) F or SO/OO 2 28 3 26 3.4% 0 28 2 28 1.1% 26 81 16 78 33.6% 6 35 5 33 8.3% 172 165 46.3% 34 26 ; Ch ² = 2.79, df = 3 (P = 0.42); $r^2 = 0\%$ 17 (P = 0.24) 321 314 100.0% 65 61 ; Ch ² = 4.77, df = 6 (P = 0.57); $r^2 = 0\%$ | s. SO 6 35 11 37 15.9% 0.77 [0.35, 1.69] 4 11 3 11 6.3% 1.33 [0.39, 4.62] 19 103 21 101 31.5% 0.69 [0.51, 1.55] 149 149 53.7% 0.89 [0.58, 1.37] 31 35 ; Ch ² = 0.54, df = 2 (P = 0.76); $l^2 = 0\%$ 0.52 (P = 0.60) F or SO/OO 2 28 3 26 3.4% 0.62 [0.11, 3.41] 0 28 2 28 1.1% 0.20 [0.01, 3.99] 26 81 16 78 33.6% 1.56 [0.91, 2.68] 6 35 5 33 8.3% 1.13 [0.38, 3.36] 172 165 46.3% 1.32 [0.83, 2.08] 34 26 ; Ch ² = 2.79, df = 3 (P = 0.42); $l^2 = 0\%$ 17 (P = 0.24) 321 314 100.0% 1.07 [0.78, 1.46] 65 61 ; Ch ² = 4.77, df = 6 (P = 0.57); $l^2 = 0\%$ | s. SO 8 35 11 37 15.9% 0.77 [0.35, 1.69] 2002 4 11 3 11 6.3% 1.33 [0.39, 4.62] 2005 19 103 21 101 31.5% 0.69 [0.51, 1.55] 2012 149 149 53.7% 0.89 [0.58, 1.37] 31 35 ; Ch ² = 0.54, df = 2 (P = 0.76); h ² = 0% 0.52 (P = 0.60) F or SO/OO 2 28 3 26 3.4% 0.62 [0.11, 3.41] 2003 0 28 2 28 1.1% 0.20 [0.01, 3.99] 2009 26 81 16 78 33.6% 1.56 [0.91, 2.68] 2014 6 35 5 33 8.3% 1.13 [0.38, 3.36] 2019 172 165 46.3% 1.32 [0.83, 2.08] 34 26 ; Ch ² = 2.79, df = 3 (P = 0.42); h ² = 0% 17 (P = 0.24) 321 314 100.0% 1.07 [0.78, 1.46] 65 61 ; Ch ² = 4.77, df = 6 (P = 0.57); h ² = 0% 0.41 (P = 0.68) |

| | Fish Oi | I PN | Standar | 'd PN | | Risk Ratio | | Risk Ratio |
|-----------------------------------|-----------|---------------------|-----------|------------------|-------------------------|---------------------|--------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M–H, Random, 95% Cl |
| 3.3.1 Omegaven | | | | | | | | |
| Grecu 2003 | 2 | 28 | 3 | 26 | 7.2% | 0.62 [0.11, 3.41] | 2003 | |
| Nang 2009 | 0 | 28 | 2 | 28 | 2.4% | 0.20 [0.01, 3.99] | 2009 — | |
| Subtotal (95% CI) | | 56 | | 54 | 9.6% | 0.47 [0.11, 2.07] | | |
| Total events | 2 | | 5 | | | | | |
| Heterogeneity: Tau ² = | 0.00; Chř | ⁱ = 0.42 | 2, df = 1 | $(\mathbf{P}=0)$ | 51); | 0% | | |
| Test for overall effect: | - | | - | • | | | | |
| 3.3.2 Other Fish Oil e | mulsions | | | | | | | |
| Grau-Carmona 2014 | 26 | 61 | 16 | 78 | 72.5% | 1.56 [0.91, 2.68] | 2014 | + - - |
| Donoghue 2019 | 6 | 35 | 5 | 33 | 17.9% | 1.13 [0.38, 3.36] | 2019 | _ |
| Subtotal (95% CI) | | 116 | | 111 | 90.4% | 1.47 [0.91, 2.38] | | ◆ |
| Fotal events | 32 | | 21 | | | | | |
| Heterogeneity: Tau ² = | 0.00; Chř | ⁱ = 0.2) | 7, df = 1 | $(\mathbf{P}=0)$ | 60); t ² = i | 0% | | |
| Test for overall effect: | - | | - | - | | | | |
| Total (95% CI) | | 172 | | 165 | 100.0% | 1.32 [0.83, 2.08] | | • |
| Total events | 34 | | 26 | | | | | - |
| Heterogeneity: Tau ² = | 0.00; Chi | ⁱ = 2.7 | 9. df = 3 | $(\mathbf{P}=0)$ | 42); | 0% | L. | a ala da ala ana |
| Test for overall effect: | - | | - | | | | 0.0 | |
| Test for subgroup diffe | | - | | 1 /9 - 1 | ∩ 15\ P. | - 51 38 | | Favours Fish oil PN Favours Standard PN |

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

| | Omega-6 Re | - | LCT or LCT | | | Risk Ratio | | Risk Ratio |
|--|----------------------------|-------------|---------------------------|-------|--------|---------------------|------|---------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M-H, Random, 95% Cl |
| 4.1.1 SO/MCT vs. SO | | | | | | | | |
| Undgren 2001 | 4 | 9 | 5 | 11 | 6.5% | 0.98 [0.37, 2.59] | 2001 | |
| Garnacho-Montero 2002 | 11 | 35 | 13 | 37 | 14.4% | 0.89 [0.46, 1.72] | 2002 | |
| Subtotal (95% CI) | | 44 | | 48 | 20.9% | 0.92 [0.53, 1.59] | | |
| Fotal events | 15 | | 18 | | | | | |
| Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 0. | | | = 0.88); l ² • | - 0% | | | | |
| 4.1.2 SO/OO vs. SO/MCT o | r SO | | | | | | | |
| Garcia-de-Lorenzo 2005 | 4 | 11 | 3 | 11 | 4.0% | 1.33 [0.39, 4.62] | 2005 | |
| ontes-Arruda 2012 | 24 | 103 | 26 | 101 | 26.7% | 0.91 [0.56, 1.47] | 2012 | |
| Implerrez 2012 | 5 | 51 | 6 | 49 | 5.7% | 0.60 [0.21, 1.71] | 2012 | |
| Subtotal (95% CI) | | 165 | | 161 | 36.4% | 0.89 [0.59, 1.34] | | - |
| lotal events | 33 | | 37 | | | | | |
| Heterogeneity: Tau ² = 0.00; | Chl ² = 0.96, (| df = 2 (P · | = 0.62); l ² • | - 0% | | | | |
| Test for overall effect: $Z = 0$. | 57 (P = 0.57) | ł | | | | | | |
| 4.1.3 FO containing PN vs. | SO or SO/MC | T or SO/C | 00 | | | | | |
| Gultekin 2014 | 7 | 16 | 6 | 16 | 11.3% | 0.88 [0.42, 1.84] | 2014 | |
| Grau-Carmona 2014 | 32 | 61 | 22 | 76 | | 1.40 [0.90, 2.19] | 2014 | |
| Subtotal (95% CI) | | 97 | | 94 | 42.7% | 1.22 [0.80, 1.86] | | |
| Fotal events | 39 | | 30 | | | | | |
| Heterogeneity: Tau ² = 0.01; Fest for overall effect: Z = 0. | | | = 0.28); l ² • | - 13% | | | | |
| | | 306 | | 303 | 100.0% | 1.03 [0.80, 1.32] | | + |
| Total (95% CI) | | | | | | | | |
| Fotal (95% CI) Fotal events | 87 | | 85 | | | | | |

| | Experim | | Cont | | | Risk Ratio | | Risk Ratio |
|---|------------------|----------|----------|----------|----------------|--|------|---------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M–H, Random, 95% CI | Year | M-H, Random, 95% CI |
| 4.2.1 SO/MCT or SO/OO | vs. SO | | | | | | | |
| Lindgren 2001 | 4 | 9 | 5 | 11 | 6.5X | 0.98 [0.37, 2.59] | 2001 | |
| Garnacho-Montero 2002 | 11 | 35 | 13 | 37 | 14.4% | 0.89 [0.46, 1.72] | 2002 | |
| Garcia-de-Lorenzo 2005 | 4 | 11 | 3 | 11 | 4.0% | 1.33 [0.39, 4.62] | 2005 | |
| Jmplerrez 2012 | 5 | 51 | 6 | 49 | 5.7% | 0.60 [0.21, 1.71] | 2012 | |
| Pontes-Arruda 2012 | 24 | 103 | 26 | 101 | 26.7% | 0.91 [0.56, 1.47] | 2012 | |
| Subtotal (95% CI) | | 209 | | 209 | 57.3% | | | |
| Total events | 48 | | 55 | | | | | |
| Test for overall effect: Z = + 4.2.2 FO vs. SO or SO/MC Grau-Carmona 2014 | - | 0 61 | 22 | 78 | | | 2014 | |
| Gultekin 2014 Subtotal (95% CI) | 7 | 16 97 | 6 | 16 94 | 11.3× 42.7% | 0.66 [0.42, 1.64] 1.22 [0.80, 1.86] | 2014 | |
| Total events | 39 | | 30 | | | | | |
| Heterogeneity: $Tau^2 = 0.03$ Test for overall effect: $Z = 1$ | | | = 1 (P = | 0.28); | r = 13X | | | |
| Total (95% CI) | | 306 | | 303 | 100.0% | 1.03 [0.80, 1.32] | | + |
| Fotal events | 87 | | 85 | | | | | |
| leterogeneity: Tau ² = 0.00 |); $Cht^2 = 3$. | .68, df | = 6 (P = | 0.72); | l² = 0% | | | 0.1 0.2 0.5 1 2 5 1 |

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 N | Aortality | in PN | Trials U | Jsing F | ish Oils | : Subgroup Analyses | of Ome | egavei | n vs. Other Fish Oil Emulsions |
|-----------------------------------|------------|--------------------|-----------------|-------------------------|-----------------------|---------------------|--------|--------|---|
| | Fish oi | I PN | Standaı | rd PN | | Risk Ratio | | | Risk Ratio |
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | | M–H, Random, 95% CI |
| 4.3.1 Omegaven | | | | | | | | | |
| Guitekin 2014 | 7 | 16 | 8 | 16 | 29.6X | 0.66 [0.42, 1.64] | 2014 | | |
| Subtotal (95% CI) | | 16 | | 16 | 29.6% | 0.88 [0.42, 1.84] | | | |
| Total events | 7 | | 8 | | | | | | |
| Heterogeneity: Not app | plicable | | | | | | | | |
| Test for overall effect: | Z = 0.35 (| (P= 0) | 72) | | | | | | |
| 4.3.2 Other Fish Oil e | mulsions | | | | | | | | |
| Grau-Carmona 2014 | 32 | 61 | 22 | 78 | 70.4% | 1.40 [0.90, 2.19] | 2014 | | +- B |
| Subtotal (95% CI) | | 81 | | 78 | 70.4% | 1.40 [0.90, 2.19] | | | |
| Total events | 32 | | 22 | | | | | | |
| Heterogeneity: Not app | plicable | | | | | | | | |
| Test for overall effect: | Z = 1.48 (| (P= 0) | 14) | | | | | | |
| Total (95% CI) | | 97 | | 94 | 100.0% | 1.22 [0.80, 1.86] | | | - |
| Total events | 39 | | 30 | | | | | | |
| Heterogeneity: Tau ² = | 0.01; Chř | [•] = 1.1 | 5, df = 1 | $\langle \mathbf{P}=0,$ | 28); i ² = | 13% | | | 0.2 0.5 1 2 5 10 |
| Test for overall effect: | Z = 0.92 (| $(\mathbf{P}=0.)$ | 36) | | | | | 0.1 | 0.2 0.5 1 2 5 10 Favours Fish oil PN Favours Standard PN |
| Test for subgroup diffe | | - | | 1 (P = | 0.29), P | = 12.2% | | | ravours rish on rive ravours standard riv |

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

| | Fish | oil | Cont | rol | | Risk Ratio | | | Risk | Ratio | | | |
|-----------------------------------|----------|----------------------|----------|--------|-----------------------|---------------------|------|---|------------------|-----------------|-----------|----------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | | M-H, Rand | lom, 95 | % CI | | |
| 4.4.1 Omegaven | | | | | | | | | | | | | |
| Gupta 2011 | 9 | 31 | 14 | 30 | 72.5% | 0.62 [0.32, 1.22] | 2011 | | | +- | | | |
| Hall 2014 | 4 | 30 | 8 | 30 | 27.5% | 0.50 [0.17, 1.48] | 2014 | | | <u> </u> | | | |
| Subtotal (95% CI) | | 61 | | 60 | 100.0% | 0.59 [0.33, 1.04] | | | | - | | | |
| Total events | 13 | | 22 | | | | | | | | | | |
| Heterogeneity: Tau ² = | 0.00; Cl | ht ² = 0. | 11, df = | 1 (P = | 0.74); l ² | - 0% | | | | | | | |
| Test for overall effect: | Z = 1.64 | 4 (P = 0 | .07) | - | | | | | | | | | |
| 4.4.2 Other Fish Oil | emulsior | is | | | | | | | | | | | |
| Subtotal (95% CI) | | 0 | | 0 | | Not estimable | | | | | | | |
| Total events | 0 | | 0 | | | | | | | | | | |
| Heterogeneity: Not ap | plicable | | - | | | | | | | | | | |
| Test for overall effect: | • | licable | | | | | | | | | | | |
| Total (95% CI) | | 61 | | 60 | 100.0% | 0.59 [0.33, 1.04] | | | | - | | | |
| Total events | 13 | | 22 | | | | | | | | | | |
| Heterogeneity: Tau ² = | | hť ² = 0. | | 1 (P = | 0.74); ř | - 0% | L . | | | <u> </u> | | <u>+</u> | |
| Test for overall effect: | | | | • | | | 0.1 | - | | 1 2 Faularia | Contro | 5 | 10 |
| Test for subgroup diff | | - | | | | | | | Favours Fish oil | Favour | 's Contro | JI | |

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

| | Omega-6 Re | ducing | LCT or LCT | +MCT | | Risk Ratio | | Risk Ratio |
|---|-----------------|----------|---------------------------|-------|--------|---------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M–H, Random, 95% Cl |
| 5.1.2 SO/OO vs SO/MCT | or SO | | | | | | | |
| Garcia-de-Lorenzo 2005 | 6 | 11 | 6 | 11 | 11.5% | 1.00 [0.47, 2.14] | 2005 | |
| Pontes-Arruda 2012 | 28 | 103 | 23 | 101 | 21.4% | 1.19 [0.74, 1.93] | 2012 | _ |
| Umplerrez 2012 | 29 | 51 | 21 | 49 | 25.6% | | 2012 | + |
| Subtotal (95% CI) | | 165 | | 161 | 58.5% | 1.23 [0.92, 1.63] | | ◆ |
| Total events | 63 | | 50 | | | | | |
| Heterogeneity: $Tau^2 = 0.00$ Test for overall effect: $Z = 2$ | | | = 0.60); l ² - | 0% | | | | |
| 5.1.3 FO containing PN vs | . SO or SO/MC | T or SO/ | 00 | | | | | |
| Grecu 2003 | 0 | 6 | 1 | 7 | 0.9% | 0.30 [0.01, 6.29] | 2003 | |
| Friesecke 2008 | 11 | 63 | 12 | 62 | 11.6X | 0.91 [0.42, 1.93] | 2008 | |
| Wang 2009 | 6 | 28 | 9 | 28 | 9.1% | 0.67 [0.27, 1.62] | 2009 | |
| Grau-Carmona 2014 | 17 | 61 | 29 | 76 | 19.6% | | 2014 | |
| Subtotal (95% CI) | | 200 | | 195 | 41.5% | 0.65 [0.44, 0.95] | | ◆ |
| Total events | 34 | | 51 | | | | | |
| Heterogeneity: $Tau^2 = 0.00$ Test for overall effect: $Z = 1$ | | | = 0.73); l ² - | 0% | | | | |
| Total (95% CI) | | 365 | | 356 | 100.0% | 0.94 [0.70, 1.26] | | • |
| Total events | 97 | | 101 | | | | | |
| Heterogeneity: $Tau^2 = 0.05$ Test for overall effect: Z = 0 Test for subgroup difference | 0.41 (P = 0.68) | } | | | × | | | 0.01 0.1 1 10 100 Favours Omega-6 Reducing Favours LCT or LCT+MCT |

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

| | Fish oi | I PN | Standa | rd PN | | Risk Ratio | | Risk Ratio |
|---|----------|------------------|--------|-----------|----------------|--|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M–H, Random, 95% Cl |
| 5.3.1 Omegaven | | | | | | | | |
| Grecu 2003 | 0 | 6 | 1 | 7 | 1.5% | 0.30 [0.01, 6.29] | 2003 | |
| Friesecke 2008 | 11 | 63 | 12 | 82 | 25.1% | 0.91 [0.42, 1.93] | 2008 | _ |
| Wang 2009 Subtotal (95% CI) | 6 | 28 119 | 9 | 28 117 | 18.2% 44.8% | 0.67 [0.27, 1.62] 0.77 [0.44, 1.36] | | • |
| Total events | 17 | | 22 | | | | | |
| Heterogeneity: $Tau^2 = Test$ for overall effect: 5.3.2 Other Fish Oil E | Z = 0.91 | (P= 0) | - | (r = 0. | 72); (* = | ^o | | |
| | | | ~~ | | | | | _ |
| Grau-Carmona 2014 Subtotal (95% CI) | 17 | 81 81 | 29 | 76 78 | 55.2% 55.2% | | | • |
| Total events | 17 | | 29 | | | | | |
| Heterogeneity: Not app Test for overall effect: | | (P = 0.4 | 03) | | | | | |
| Total (95% CI) | | 200 | | 195 | 100.0% | 0.65 [0.44, 0.95] | | • |
| Total events | 34 | | 51 | | | | | |
| Heterogeneity: $Tau^2 =$ Test for overall effect: Test for subgroup diffe | Z = 2.23 | $(\mathbf{P}=0)$ | 03) | | | | 0. | 01 0.1 1 10 100 Favours Fish oil PN Favours Standard PN |

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

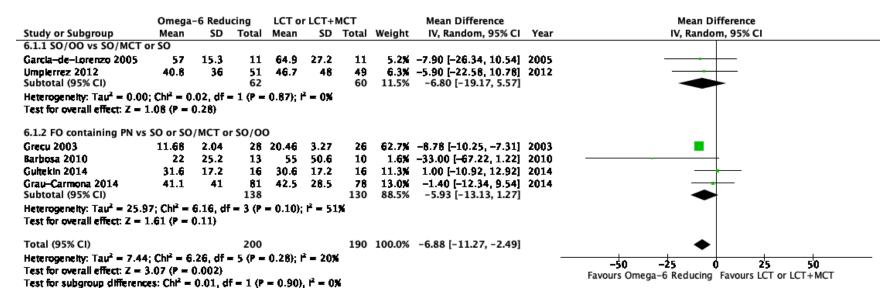


Figure 6.2 Hospital LOS in PN Trials Using Fish Oils: Subgroup Analyses of Omegaven vs. Other Fish Oil Emulsions

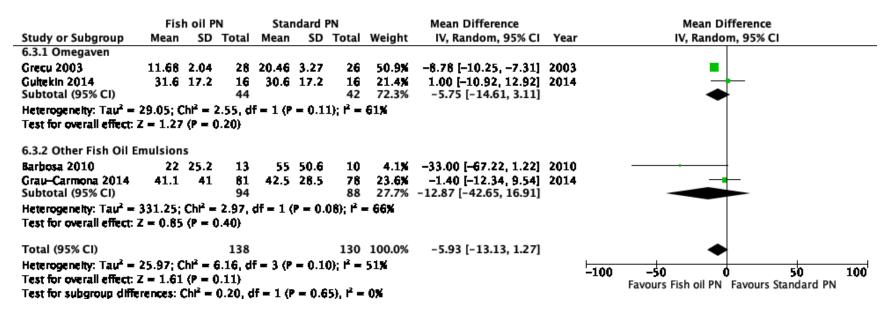


Figure 6.3 Hospital LOS in Trials Comparing Stand-Alone Fish Oil Emulsions to Standard of Care

| | F | ish Oils | | (| Control | | | Mean Difference | | Mean Difference |
|---|------|----------|-------|--------|----------|----------|--------|----------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | r IV, Random, 95% CI |
| Gupta 2011 | 19 | 13.26 | 31 | 19.3 | 16.65 | 30 | 23.6% | -0.30 [-7.87, 7.27] | 2011 | . + |
| Khor 2011 | 19.6 | 6.5 | 14 | 17.5 | 5.3 | 13 | 68.0% | 2.10 [-2.36, 6.56] | 2011 | . 📕 |
| Hall 2014 | 26.7 | 18.2 | 30 | 33.5 | 30.4 | 30 | 6.4% | -6.80 [-19.48, 5.88] | 2014 | ·+ |
| Total (95% CI) | | | 75 | | | 73 | 100.0% | 0.78 [-2.89, 4.46] | | + |
| Heterogeneity: Tau ² = Test for overall effect: | | | | = 2 (P | = (0.41) | ; ² = 0 | * | | | -100 -50 0 50 100 Favours Fish Oils Favours Control |

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

| | Omega- | -6 Redu | cing | LCT or | LCT+ | мст | | Mean Difference | | Mean Difference |
|--|--------------------------|----------|-----------|-----------|---------------------|---------------------|--------|------------------------|------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 7.1.1 SO/MCT vs SO | | | | | | | | | | |
| Undgren 2001 | 26 | 6 | 9 | 20 | 5 | 11 | 8.7% | 6.00 [1.09, 10.91] | 2001 | |
| Garnacho-Montero 2002 | 16.6 | 6.1 | 35 | 15.8 | 7 | 37 | 11.1% | 0.60 [-2.23, 3.63] | | |
| Subtotal (95% CI) | _ | | 44 | | | 48 | 19.9% | 3.03 [-2.02, 8.07] | | - |
| Heterogeneity: Tau ² = 9.1! | • | | = 1 (P = | 0.08); f | - 667 | 6 | | | | |
| Test for overall effect: Z = | 1.16 (P = 0) |).24} | | | | | | | | |
| 7.1.2 SO/OO vs SO/MCT | or SO | | | | | | | | | |
| Garcia-de-Lorenzo 2005 | 32.9 | 10.6 | 11 | 41.8 | 18.6 | 11 | 3.0% | -8.90 [-21.55, 3.75] | 2005 | |
| Umplerrez 2012 | 17 | 16 | 51 | 15.2 | 14 | 49 | 7.1% | 1.60 [-4.51, 8.11] | | |
| Subtotal (95% CI) | | | 62 | | | 60 | 10.1% | -2.09 [-12.17, 8.00] | | |
| Heterogeneity: Tau ² = 31.7 Test for overall effect: Z = | • | | ' = 1 (P | = ().14); | ۴ = 55 | × | | | | |
| 7.1.3 FO containing PN vs | s SO or SO | /MCT o | r SO/O | 0 | | | | | | |
| Grecu 2003 | 3.32 | 1.48 | 6 | 9.28 | 3.08 | 7 | 11.6% | -5.96 [-8.46, -3.46] | 2003 | |
| Friesecke 2008 | 26 | 25 | 83 | 23 | 20 | 82 | 6.5X | 5.00 [-1.90, 11.90] | 2008 | |
| Guo 2008 | 21.1 | 2.9 | 38 | 28.4 | 4.2 | 42 | 12.7% | -7.30 [-8.87, -5.73] | | |
| Barbosa 2010 | 12 | 14.4 | 13 | 13 | 12.6 | 10 | 3.6X | | | |
| Grau-Carmona 2014 | 18.9 | 15.5 | 61 | 21.8 | 20.9 | 76 | 7.6% | -2.90 [-8.64, 2.84] | - | |
| Wang 2014 | 7.75 | 1.9 | 25 | | 2.15 | 26 | 13.0% | -2.28 [-3.37, -1.19] | | - |
| Chen 2017b | 13.8 | 9.9 | 24 | 24.4 | 23.2 | 24 | - | -10.60 [-20.69, -0.51] | - | |
| Donoghue 2019 Subtatal (05% CI) | 9.5 | 7.09 | 35 307 | 10.7 | 7.6 | 33 | 10.5% | -1.20 [-4.70, 2.30] | 2019 | |
| Subtotal (95% CI) | 0. 0L12 04 | . or 18 | | | | 304 | 70.0% | -3.53 [-6.16, -0.90] | | - |
| Heterogeneity: $Tau^2 = 8.74$ Test for overall effect: Z = | - | - | - / (P | < 0.000 |)1); F i | - 62% | | | | |
| Total (95% CI) | | | 413 | | | 412 | 100.0% | -1.94 [-4.41, 0.52] | | • |
| Heterogeneity: Tau ² = 11.1 | 80: Chi ² = 6 | 65.88. a | if = 11 | (P < 0.00 | 0001): | l ² = 83 | × | | _ | |
| Test for overall effect: Z = | | | | | /1 | | - | | | -20 -10 0 10 20 |
| Test for subgroup different | | | F - 2 /P | - 0.081 | $\vec{F} = \vec{G}$ | 0.8% | | | | Favours Omega-6 Reducing Favours LCT or LCT+MCT |

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

| | Expe | erimen | tal | с | ontrol | | | Mean Difference | | Mean Difference |
|---|-----------------------|--------|---------------|---------------------------------|--------|-----------|----------------|------------------------|------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 7.2.1 SO/MCT or SO/OO | vs. SO | | | | | | | | | |
| Undgren 2001 | 26 | 6 | 9 | 20 | 5 | 11 | 8.7% | 6.00 [1.09, 10.91] | 2001 | |
| Garnacho-Montero 2002 | 16.6 | 6.1 | 35 | 15.8 | 7 | 37 | 11.1% | 0.80 [-2.23, 3.83] | 2002 | _ |
| Garcia-de-Lorenzo 2005 | 32.9 | 10.6 | 11 | 41.8 | 18.6 | 11 | 3.0% | -8.90 [-21.55, 3.75] | 2005 | · · · · · · · · · · · · · · · · · · · |
| Umplerrez 2012 Subtotal (95% CI) | 17 | 18 | 51 106 | 15.2 | 14 | 49 108 | 7.1× 30.0% | | 2012 | |
| Heterogeneity: $Tau^2 = 7.50$ |); Cht ² = | 5.98, | df = 3 | $\langle \mathbf{P}=0. \rangle$ | 11); 🖻 | - 50% | | | | |
| Test for overall effect: Z = (| 0.87 (P | = 0.38 |) | - | | | | | | |
| 7.2.2 FO vs. SO or SO/MC | T or SO | /00 | | | | | | | | |
| Grecu 2003 | 3.32 | 1.48 | 6 | 9.28 | 3.08 | 7 | 11.6% | -5.96 [-8.46, -3.46] | 2003 | _ |
| Guo 2008 | 21.1 | | 38 | 28.4 | | 42 | 12.7% | | | |
| Friesecke 2008 | 28 | 25 | 83 | 23 | 20 | 82 | 6.5% | 5.00 [-1.90, 11.90] | 2008 | |
| Barbosa 2010 | 12 | 14.4 | 13 | 13 | 12.6 | 10 | 3.6X | -1.00 [-12.06, 10.06] | 2010 | |
| Grau-Carmona 2014 | 18.9 | 15.5 | 81 | 21.8 | 20.9 | 78 | 7.8% | -2.90 [-8.64, 2.84] | 2014 | |
| Wang 2014 | 7.75 | 1.9 | 25 | 10.03 | 2.15 | 28 | 13.0% | -2.28 [-3.37, -1.19] | 2014 | + |
| Chen 2017b | 13.8 | 9.9 | 24 | 24.4 | 23.2 | 24 | 4.1% | -10.60 [-20.69, -0.51] | 2017 | ← |
| Donoghue 2019 Subtotal (95% CI) | 9.5 | 7.09 | 35 307 | 10.7 | 7.6 | 33 304 | 10.5% 70.0% | | 2019 | |
| Heterogeneity: $Tau^2 = 8.76$ Test for overall effect: $Z = 3$ | | | | 7 (P < (| 0000. | 1); | 82% | | | |
| Total (95% CI) | | | 413 | | | 412 | 100.0% | -1.94 [-4.41, 0.52] | | - |
| Heterogeneity: $Tau^2 = 11.6$ Test for overall effect: Z = 2 Test for subgroup difference | 1.55 (P | = 0.12 | 18, df = } | | | 001); ř | - 83 % | | | -20 -10 0 10 20 Favours Experimental Favours Control |

| Figure 7.3. ICU L | OS in l | PN T | rials 1 | Using | Fish | Oils: | Subgro | up Analyses of Om | egaven | vs. Other Fish Oil Emulsions |
|---|----------|--------------------|---------|-----------|------------------|----------------------|--------------------|------------------------|--------|---|
| 2 | Fis | h oil P | 'N | Sta | ndard | PN | U | Mean Difference | e | Mean Difference |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 7.3.1 Omegaven | | | | | | | | | | |
| Grecu 2003 | 3.32 | 1.48 | 8 | 9.28 | 3.08 | 7 | 17.4% | -5.96 [-8.46, -3.46] | 2003 | |
| Friesecke 2008 | 28 | 25 | | | | | 8.5% | | | |
| Wang 2014 | 7.75 | 1.9 | 25 | 10.03 | 2.15 | 28 | | | 2014 | + |
| Chen 2017b | 13.8 | 9.9 | 24 | | 23.2 | | 5.1% | -10.60 [-20.69, -0.51] | 2017 | e |
| Subtotal (95% CI) | | | 140 | | | 141 | 50.9% | | | ◆ |
| Heterogeneity: Tau ² = Test for overall effect: | - | | - | lf = 3 (f | P = 0.0 |)03); f ² | - 79% | | | |
| 7.3.2 Other Fish Oil I | Emulsior | ıs | | | | | | | | |
| Guo 2008 | 21.1 | 2.9 | 38 | 28.4 | 4.2 | 42 | 19.2% | -7.30 [-8.87, -5.73] | 2008 | + |
| Barbosa 2010 | 12 | 14.4 | 13 | 13 | 12.6 | 10 | 4.4% | -1.00 [-12.06, 10.06] | 2010 | |
| Grau-Carmona 2014 | 18.9 | 15.5 | 81 | 21.8 | 20.9 | 78 | 10.4% | -2.90 [-8.64, 2.84] | 2014 | |
| Donoghue 2019 | 9.5 | 7.09 | 35 | 10.7 | 7.6 | 33 | 15.1% | -1.20 [-4.70, 2.30] | 2019 | _ |
| Subtotal (95% CI) | | | 167 | | | 163 | 49.1% | -3.81 [-7.96, 0.34] | | ◆ |
| Heterogeneity: Tau ² = | 11.51; (| Cht ² = | 11.77, | df = 3 | $(\mathbf{P}=0)$ | .008); (| ² = 75% | | | |
| Test for overall effect: | Z = 1.80 |) (P = 1 | 0.07) | | | | | | | |
| Total (95% CI) | | | 307 | | | 304 | 100.0% | -3.53 [-6.16, -0.90] | | • |
| Heterogeneity: Tau ² = Test for overall effect: | Z = 2.63 | 3 (P = | 0.009) | - | | _ | | | | -20 -10 0 10 20 Favours Fish oil PN Favours Standard PN |
| Test for subgroup diffe | erences: | Çnr = | 0.05,0 | pr = 1 (| r = Q.I | 02), F • | - V/I | | | |

7.2 LOULOG :-- DN T-:-- La Llain - Eish Oile, Gash **T**2

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| | Fis | sh Oil: | s | 0 | Control | | | Mean Difference | | Mean Difference |
|--|-------|---------|-------|----------|---------|------------------|--------|----------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| Khor 2011 | 10.3 | 7.4 | 14 | 8.4 | 5.7 | 13 | 18.6% | 1.90 [-3.06, 6.86] | 2011 | |
| Zhao 2011 | 6 | 2.02 | 56 | 10.97 | 2.02 | 60 | 46.9% | -2.97 [-3.71, -2.23] | 2011 | |
| Gupta 2011 | 15.27 | 9.54 | 31 | 13.7 | 11.56 | 30 | 17.0% | 1.57 [-3.76, 6.90] | 2011 | |
| Hall 2014 | 6.6 | 7.7 | 30 | 12.3 | 12.4 | 30 | 17.4% | -3.50 [-8.72, 1.72] | 2014 | |
| Total (95% CI) | | | 131 | | | 133 | 100.0% | -1.38 [-4.11, 1.34] | | |
| Heterogeneity: Tau ² - Test for overall effect | | | | f = 3 (P | = 0.10) | ; i ² = 5 | 2% | | ŀ | -10 -5 0 5 10 Favours Fish Oils Favours Control |

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

| | Omega | a-6 Redu | icing | LCT o | r LCT+ | мст | | Mean Difference | | Mean Difference |
|---------------------------------------|--------------------------|------------|----------|---------|-----------|-------|--------|-----------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 8.1.1 SO/MCT vs. SO | | | | | | | | | | |
| Nijveldt 1998 | 13.6 | 2.9 | 12 | 17.4 | 3 | 6 | 9.2% | -3.60 [-6.25, -0.95] | 1998 | |
| ovinelli 2007 | 10.6 | 3 | 7 | 13.4 | 3.5 | 7 | 6.2% | -2.80 [-6.21, 0.61] | 2007 | |
| Subtotal (95% CI) | | | 19 | | | 15 | 15.5% | -3.30 [-5.39, -1.21] | | ◆ |
| Heterogeneity: Tau ² = 0.0 | 00; Chř = 0 |).13, df • | = 1 (P = | 0.72); | ř = 0% | | | | | |
| Test for overall effect: Z = | | | | | | | | | | |
| 8.1.2 SO/OO vs. SO/MC | T or SO | | | | | | | | | |
| Garcia-de-Lorenzo 2005 | 11 | 11.94 | 11 | 13 | 16.25 | 11 | 0.6% | -2.00 [-13.92, 9.92] | 2005 | |
| Subtotal (95% CI) | | | 11 | | | 11 | 0.6% | -2.00 [-13.92, 9.92] | | |
| Heterogeneity: Not applic | able | | | | | | | | | |
| Test for overall effect: Z = | - 0.33 (P = | 0.74) | | | | | | | | |
| 8.1.3 FO containing PN v | vs. SO or SO | O/MCT o | or SO/O | 0 | | | | | | |
| Grecu 2003 | 2.83 | 1.62 | 6 | 5.23 | 2.6 | 7 | 10.9% | -2.40 [-4.76, -0.04] | 2003 | |
| Friesecke 2008 | 22.8 | 22.9 | 63 | 20.5 | 19 | 82 | 2.0% | 2.30 [-4.12, 8.72] | 2008 | |
| Barbosa 2010 | 10 | 14.4 | 13 | 11 | 12.64 | 10 | 0.7% | -1.00 [-12.07, 10.07] | 2010 | |
| Grau-Carmona 2014 | 8.4 | 6.6 | 67 | 9.2 | 6.9 | 64 | 11.2% | -0.60 [-3.11, 1.51] | 2014 | |
| Wang 2014 | 2.43 | 1.06 | 25 | 2.94 | 1.37 | 28 | 29.3% | -0.51 [-1.17, 0.15] | 2014 | - |
| Donoghue 2019 | 1.24 | 0.83 | 35 | 0.88 | 1.63 | 33 | 29.8% | 0.36 [-0.26, 0.98] | | |
| Subtotal (95% CI) | | | 231 | | | 224 | 83.9% | -0.31 [-1.07, 0.45] | | ♦ |
| Heterogeneity: Tau ² = 0.2 | 27; Chi ² = 6 | 8.13, df • | = 5 (P = | 0.15); | r² = 397 | 6 | | | | |
| Test for overall effect: Z = | = 0.80 (P = | 0.42) | | | | | | | | |
| Total (95% CI) | | | 261 | | | 250 | 100.0% | -0.87 [-1.82, 0.07] | | ◆ |
| Heterogeneity: Tau ² = 0.6 | | | f = 8 (P | = 0.03) | ; i² = 52 | 27 | | | ŀ | -20 -10 0 10 |
| Test for overall effect: Z = | = 1.82 (P = | 0.07) | | | | | | | | Favours Omega-6 Reducing Favours LCT or LCT+MCT |
| Test for subgroup differen | | | f = 2 (P | = 0.03 |), 🖞 = 7 | 1.3× | | | | ravours onlega-o reducing ravours cer of certmer |

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

| | Exp | eriment | tal | | Control | | | Mean Difference | | Mean Difference |
|------------------------------|-----------------------|---------|----------|--------------------------|-----------------------|---------|--------|-----------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 8.2.1 SO/MCT or SO/OO | vs. SO | | | | | | | | | |
| Nijvekit 1998 | 13.8 | 2.9 | 12 | 17.4 | 3 | 8 | 9.2% | -3.60 [-6.25, -0.95] | 1998 | _ |
| Garcia-de-Lorenzo 2005 | 11 | 11.94 | 11 | 13 | 16.25 | 11 | 0.6% | -2.00 [-13.92, 9.92] | 2005 | |
| iovinelli 2007 | 10.6 | 3 | 7 | 13.4 | 3.5 | 7 | 6.2% | -2.80 [-6.21, 0.61] | 2007 | + |
| Subtotal (95% CI) | | | 30 | | | 26 | 16.1% | -3.26 [-5.32, -1.20] | | • |
| Heterogeneity: $Tau^2 = 0.0$ | 0; Chl ² = | 0.18, 0 | if = 2 (| P = 0.9 | 92); | 0% | | | | |
| Test for overall effect: Z = | | | | | | | | | | |
| 8.2.2 FO vs. SO or SO/M | CT or SO | /00 | | | | | | | | |
| Grecu 2003 | 2.83 | 1.62 | 6 | 5.23 | 2.8 | 7 | 10.9% | -2.40 [-4.76, -0.04] | 2003 | |
| Friesecke 2008 | 22.8 | 22.9 | 83 | 20.5 | 19 | 62 | 2.0% | 2.30 [-4.12, 8.72] | 2008 | |
| Barbosa 2010 | 10 | 14.4 | 13 | 11 | 12.64 | 10 | 0.7% | -1.00 [-12.07, 10.07] | 2010 | |
| Wang 2014 | 2.43 | 1.06 | 25 | 2.94 | 1.37 | 28 | 29.3% | -0.51 [-1.17, 0.15] | 2014 | - |
| Grau-Carmona 2014 | 8.4 | 6.6 | 67 | 9.2 | 6.9 | 64 | 11.2% | -0.80 [-3.11, 1.51] | 2014 | |
| Donoghue 2019 | 1.24 | 0.83 | 35 | 0.66 | 1.63 | 33 | 29.6% | 0.36 [-0.26, 0.98] | 2019 | + |
| Subtotal (95% CI) | | | 231 | | | 224 | 83.9% | -0.31 [-1.07, 0.45] | | • |
| Heterogeneity: $Tau^2 = 0.2$ | 7; Chi ² = | 8.13, 4 | if = 5 (| P = 0.1 | l5); i ² = | 39X | | | | |
| Test for overall effect: Z = | 0.80 (P | = 0.42) | | | | | | | | |
| Total (95% CI) | | | 261 | | | 250 | 100.0% | -0.87 [-1.82, 0.07] | | • |
| Heterogeneity: $Tau^2 = 0.6$ | 8; Chl ² = | 16.70, | df = 8 | $\langle \mathbf{P} = 0$ | .03); P | = 52% | | | | -20 -10 0 10 2 |
| Test for overall effect: Z = | 1.82 (P | = 0.07) | | | - | | | | | -20 -10 0 10 2 Favours Experimental Favours Control |
| Test for subgroup differen | | | | l (P = 0 | .009). (| ² = 85. | 6% | | | ravours experimental ravours control |

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

| | Fis | h oil P | 'N | Sta | ndard P | 'n | | Mean Difference | | Mean Difference | |
|-----------------------------------|----------|---------|---------|-----------------|--------------------|----------------------|--------|-----------------------|------|---|----|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | ar IV, Random, 95% CI | |
| 8.3.1 Omegaven | | | | | | | | | | | |
| Grecu 2003 | 2.83 | 1.62 | 6 | 5.23 | 2.8 | 7 | 6.6% | -2.40 [-4.76, -0.04] | 2003 | 3 | |
| Friesecke 2008 | 22.8 | 22.9 | 83 | 20.5 | 19 | 82 | 1.4% | 2.30 [-4.12, 8.72] | 2008 | 8 | |
| Wang 2014 | 2.43 | 1.06 | 25 | 2.94 | 1.37 | 28 | 39.5X | -0.51 [-1.17, 0.15] | 2014 | 4 🗧 | |
| Subtotal (95% CI) | | | 116 | | | 117 | 49.7% | -0.87 [-2.37, 0.63] | | ◆ | |
| Heterogeneity: Tau ² = | 0.75; C | hř = 3 | .09, df | = 2 (P | = 0.21) | ; i² = 3 | 5X | | | | |
| Test for overall effect: | Z = 1.14 | 4 (P = | 0.26) | - | | | | | | | |
| 8.3.2 Other Fish Oil E | mulsior | ıs | | | | | | | | | |
| Barbosa 2010 | 10 | 14.4 | 13 | 11 | 12.64 | 10 | 0.5% | -1.00 [-12.07, 10.07] | 2010 | 0 | |
| Grau-Carmona 2014 | 6.4 | 6.6 | 67 | 9.2 | 6.9 | 64 | 9.1% | -0.60 [-3.11, 1.51] | 2014 | 4 | |
| Donoghue 2019 | 1.24 | 0.83 | 35 | 0.88 | 1.63 | 33 | 40.8% | | | 9 🛉 | |
| Subtotal (95% CI) | | | 115 | | | 107 | 50.3% | 0.28 [-0.32, 0.88] | | ◆ | |
| Heterogeneity: Tau ² = | - | | - | = 2 (P | = 0.62) | ; | × | | | | |
| Test for overall effect: | Z = 0.91 | 1 (P = | 0.36) | | | | | | | | |
| Total (95% CI) | | | 231 | | | 224 | 100.0% | -0.31 [-1.07, 0.45] | | • | |
| Heterogeneity: Tau ² = | 0.27; C | hť = 6 | .13, df | = 5 (P | = 0.15) | : I ² = 3 | 9% | | | | ~~ |
| Test for overall effect: | | | | • | - , | | | | | -20 -10 0 10 Favours Fish oil PN Favours Standard PN | 20 |
| Test for subgroup diffe | | - | - | df = 1 <i>6</i> | $\mathbf{P} = 0 1$ | 6) ř. | AR 5% | | | ravours rish oli PN Favours Standard PN | |

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

| 0 | Fi | sh Oils | 5 | (| Control | | | Mean Difference | | | Mean Diff | ference | | |
|--|-------|---------|-------|--------------|---------|-------|--------|---------------------|------|-----------------|-----------------------|-------------------|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | | IV, Random | i, 95% Cl | | |
| Gupta 2011 | 13.39 | 8.3 | 31 | 11.3 | 10.44 | 30 | 83.4% | 2.09 [-2.65, 6.83] | 2011 | | | | | |
| Khor 2011 | 13 | 10.1 | 9 | 11. 6 | 9.5 | 5 | 16.6X | 1.40 [-9.22, 12.02] | 2011 | | | | _ | |
| Total (95% CI) | | | 40 | | | 35 | 100.0% | 1.98 [-2.36, 6.31] | | | | | | |
| Heterogeneity: Tau ² - Test for overall effect | | | | | - 0.91 |); | 0% | | | -20 -1 Favou | 0 0 rs Fish Oils F | 10 Favours Cor | | Ŋ |

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