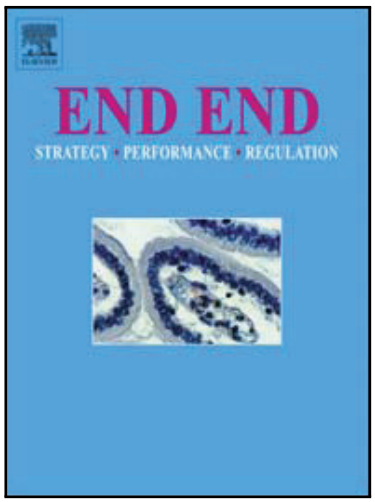

Current Evidence on Omega-3 Fatty Acids in Enteral Nutrition in the Critically ill – a systematic review and meta-analysis

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Highlights

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- Enteral fish oil confers anti-inflammatory and immunomodulatory effects.
- No evidence for improved mortality from enteral fish oil supplementation among critically ill patients was found.
- ICU length of stay and duration of ventilation was significantly shorter with fish oil, however results were based on heterogeneous studies.
- Reduced mortality in ARDS patients was found, however studies had low methodological quality.
- Enteral fish oil supplementation cannot be recommended for critically ill patients.
- Further research should focus on the relation between the individual critically ill patients' immune response, the administration of fish oil and clinical outcomes.

Current Evidence on Omega-3 Fatty Acids in Enteral Nutrition in the Critically ill – a systematic review and meta-analysis

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Introduction

As fish oil exerts anti-inflammatory and immunomodulatory properties which may be beneficial for critically ill patients, multiple RCTs and meta-analysis have been performed. However, controversy remains as to whether fish oil enriched enteral nutrition can improve clinical outcomes in adult critically ill patients in intensive care units.

Methods

A systematic literature search was conducted. The primary outcome was 28-day mortality. Secondary outcomes were ICU and hospital mortality, ICU and hospital length of stay, ventilation duration and infectious complications. Predefined subgroup and sensitivity analyses were performed.

Results

Twenty-four trials, enrolling 3574 patients, met the inclusion criteria. The assessment of risk of bias showed that most of included studies were of moderate quality. The overall results revealed no significant effects of enteral fish oil supplementation on 28-day, ICU or hospital mortality. However, ICU LOS and ventilation duration were significantly reduced in patients receiving fish oil supplementation. Furthermore, subgroup analysis revealed a significant reduction in 28-day mortality, ICU LOS and ventilation duration in ARDS patients but not in other subgroups. When comparing high with low quality trials, significant reductions in 28-day mortality and ventilation duration in low but not high quality trials were observed. Regarding ICU LOS a significant reduction was observed in high quality trials whereas only a trend was observed in low quality trials.

No significant effects on hospital LOS or infectious complications were observed in overall or subgroup analyses.

Conclusions

Enteral fish oil supplementation cannot be recommended for critically ill patients as strong scientific evidence for improved clinical benefits could not be found. There is a signal of mortality benefit in ARDS patients, however results are based on low quality studies. Further research should focus on the relation between the individual critically ill patients' immune response, the administration of fish oil and clinical outcomes.

Introduction

Fish oil (FO) has gained great interest as dominant source of ω-3 polyunsaturated fatty acids (PUFAs), more specifically eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3). It has been suggested that EPA and DHA may attenuate the production of pro-inflammatory lipid mediators and cytokines, modulate the activity of nuclear receptors and expression of nuclear transcription factors (factor-kappa B, NF-κB; peroxisome proliferator-activated receptor γ, PPAR-γ; intracellular adhesion molecule 1, ICAM-1) and act as precursors of resolvins which in turn attenuate inflammation [1, 2]. Thus, FO exerts anti-inflammatory and immunomodulatory properties [3, 4], that may potentially confer improved clinical outcomes of critical illness.

Over the past 30 years, several randomized controlled trials have been performed addressing the clinical effects of fish-oil supplementation among critically ill patients. Conflicting results have been reported, ranging from clinical benefit to possible harm. Recently, several meta-analysis have been performed regarding fish-oil containing nutrition in critically ill patients. The effects of enteral fish-oil containing formulas in ARDS patients was studied in two recent meta-analysis [5, 6]. In both, no significant effects on mortality or ventilator free days and ICU free days were found. Manzanares and coworkers recently studied effects of intravenous fish-oil lipid emulsions in critically ill patients [7]. In a meta-analysis of 10 randomized controlled trials (RCTs) no effect on overall mortality was found, however a significant reduction in infections was observed. Furthermore, a recent meta-analysis of 17 RCTs by Lu and colleagues on parenteral and enteral fish oil supplementation in critically ill patients with sepsis showed significant reductions in ICU length of stay (LOS) and duration of mechanical ventilation. No effects on mortality were observed [8]. The value of peri-operative fish-oil supplementation was studied by Langlois and coworkers in a meta-analysis of 19 RCTs on cardiac surgery patients [9]. A significant reduction in hospital LOS as well was the occurrence of postoperative atrial fibrillation was found. However, no effects on ICU LOS, mortality or duration of ventilation were observed.

Fish oil supplementation has also been addressed in international guidelines. The ESPEN guidelines suggest a benefit of fish oil lipid emulsions in ARDS, but have not been updated since 2009 [10]. The more recent ASPEN guidelines withhold to recommend fish oil due to conflicting data [11]. The Canadian Clinical Practice Guidelines advise consideration of enteral formulas containing fish oils in patients with ARDS/ALI as associations with its use and reduction in 28-day mortality were found [12].

The purpose of the current study was to provide an up-to-date systematic review and meta-analysis of all RCTs of fish-oil containing enteral nutrition addressing relevant clinical outcomes in critically ill patients.

Methods

Search Strategy and Study Identification

A systematic review was conducted to identify all relevant randomized clinical trials published before January 2018 in MEDLINE, Embase, CINAHL and the Cochrane Central Register of Controlled Trials. We used the following medical subject headings or keywords "fish oils", "docosahexaenoic", "eicosapentaenoic", "omega-3", "lipid emulsions", "intensive care", "critical illness", "critically ill", "enteral nutrition" and "randomized". In addition, citations of the selected RCTs were checked in Web of Science and references of the selected RCTs were manually searched for additional original studies. The search was restricted to English articles only and abstracts from scientific meetings were not accepted for inclusion into this systematic review.

Study Selection Criteria/Eligibility criteria

Only trials meeting the following characteristics were included:

1. *Study design:* randomized clinical, parallel group, controlled trials (RCTs).
2. *Study population*: critically ill adult patients (>95% of patients >18 years of age).
3. *Intervention*: Enteral supplementation of fish oil (ω-3 fatty acids) or fish oil containing enteral nutrition compared with a control or placebo intervention.
4. *Study outcomes* must have included one of the following: mortality, ICU or hospital length of stay (LOS), duration of mechanical ventilation and infectious complications.

Those trials performed in elective surgery patients or only reporting biochemical, metabolic, immunologic or nutritional outcomes were excluded.

Two authors (WK and VP) independently performed methodological quality assessment of the studies. The risk of bias was assessed by using a data abstraction form with a scoring system from 0 to 14 scoring the components recommended by the Cochrane Collaboration including: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data (including ITT analysis); selective reporting; and other sources of bias [13]. Scores of 9-14 were regarded as high quality (Level I) and 0-8 as low quality (Level II). Any disagreement was resolved by consensus.

Data synthesis

The primary outcome of the systematic review was 28-day mortality. Separately, we analyzed data reported as ICU or hospital mortality. When mortality was unspecified, data were not included in data analysis. Secondary outcomes included infections, ventilation duration and ICU and hospital LOS. We used definitions of infections as defined by the authors in their original articles. Critically ill patients were defined as patients admitted to an ICU who had an urgent or life-threatening complication (high baseline mortality rate ≥5%) to distinguish them from patients with elective surgery who were also cared for in some ICUs, but had a low baseline mortality rate (<5%).

We combined data from all trials to estimate the pooled risk ratio (RR) with 95% confidence interval (CI) for mortality and infectious complications and overall weighted mean difference (WMD) with 95% CI for LOS and duration of ventilation. When studies reported only medians with interquartile ranges, these were converted to means and standard deviations according to the Cochrane guidelines. Pooled RRs were calculated using the Mantel-Haenszel test, and WMDs were estimated using the inverse variance approach. The random-effects model of DerSimonian and Laird was used to estimate variances for the Mantel-Haenszel and inverse variance estimations. All data analysis was conducted using Review Manager (RevMan) 5.3 software [14]. Whenever possible, studies were aggregated on an intention-to-treat basis. Statistical heterogeneity was measured and quantified using the I^2 test and the Mantel–Haenszel χ^2 test. Statistical heterogeneity was predefined at I^2 >50 % or p<0.05. Sensitivity analysis was used to assess the sources of heterogeneity. Publication bias was assessed for all analyses after visual inspection of funnel plots. We considered p<0.05 to be statistically significant and p<0.10 as the indicator of a trend.

Subgroup analysis

A predefined subgroup analysis was performed to investigate whether there were difference in treatment effect among patients with sepsis, ARDS or trauma. Additionally, we compared older (< 2010) and newer studies on treatment effects. We also assessed the effect of trial quality on outcome, as trials with lower quality may demonstrate a greater treatment effect than those with higher quality.

Results

Study identification and selection

The literature search identified 58 potentially eligible trials [15-72]. We excluded 34 trials for the following reasons: (1) patients not considered to be adult critically ill patients (n=6) [39-44]; (2) no clinical outcomes meeting inclusion criteria (n=2)[45,46]; (3) parenteral fish oil administration (n=8) [47-54]; (4) duplicate studies,

reviews of published trials or subgroups of included studies (n=4)[55-58]; (5) published as abstracts (n=8) [59-66]; (6) papers published in a language other than English(n=6) [67-72], (Figure 1).

Finally, 24 RCTs, with a total number of 3574 patients, met the inclusion criteria and were included in this systematic review [15-38]. In total, 1787 patients were treated with enteral FO supplementation and 1787 patients with a control feed. The results were based on data derived from the included studies, depicted in Table 1 and 2. We reached 100% agreement for inclusion of the trials. The mean methodological score was 8.5 (range, 3 to 13). Details of methodological quality are shown in Figure 2.

Meta-Analyses of Primary Outcome

Overall effect on 28-day Mortality

After aggregation of the data from 13 RCTs [17,18,20,21,23,24,27-30,32,33,38] evaluating 28-day mortality, no significant reductions in case fatality was found (RR 0.92, 95% CI 0.79 – 1.08; p=0.31; Figure 3). Statistical heterogeneity was not significant (I^2 = 2%, p = 0.43).

Secondary outcomes

Overall effect on ICU and Hospital Mortality

Five and seven RCTs reported the effects of fish oil supplementation on ICU [15,19,24,37,38] and hospital [15,16,18,24,34,36,38]mortality respectively. We pooled the data and found no significant effect on ICU mortality (RR 0.96, 95%CI 0.78–1.18; p=0.69; see figure 1 in [73]) or hospital mortality (RR 1.08, 95%CI 0.95–1.23; p=0.23; see figure 2 in [73]). Heterogeneity was non-significant (I^2=27%, p=0.24 for ICU mortality and I^2 =0%, p=0.43 for hospital mortality).

Overall effect on ICU length of stay

ICU length of stay was reported in 21 RCTs [15,16-30,32-35,37,38]. A significant reduction in ICU length of stay favouring fish oil supplementation (MD -2.23, 95%CI -3.34, -1.12; p<0.0001; Figure 4) was observed. However, heterogeneity was significant (I^2=78%, p<0.0001).

Overall effect on hospital length of stay

Four trials reported hospital LOS [15,18,23,38]. We pooled these data and found no significant effect of fish oil

supplementation on hospital LOS (MD -0.52, 95%CI -4.51, 3.48; p=0.80 and heterogeneity was significant (I^2 = 56%, p=0.08).

Overall effect on ventilation duration

Aggregation of the data of 19 RCTs [15,18-27,29,30,32-34,36-38] reporting the effects of fish oil supplementation on ventilation duration showed a significant reduction in ventilation duration favouring fish oil (MD -2.08, 95%CI -3.30, -0.85; p=0.0009, Figure 5). However, heterogeneity was significant (I^2 =87%, p<0.0001).

Overall effect on infectious complications

After aggregation of data from 11 RCTs [19-22,,24, 26, 27, 32, 34, 36, 38] regarding overall infectious complications no significant effects of fish oil were found (RR 0.96, 95%CI 0.81–1.13; p=0.60). Heterogeneity was significant (I^2 =53%, p=0.03). We also pooled data of several specific infectious complications: ventilator associated pneumonia (9 RCTs), bacteraemia (11 RCTs), urinary tract infections (8 RCTs) and catheter related infections (5 RCTs). However, no significant effect of fish oil was found in any of these analyses.

Risk of Publication Bias in Included Trials

Upon visual inspection of funnel plots no indications for publication bias were found.

Sensitivity Analysis

We conducted sensitivity analyses to investigate the effects of intention to treat analysis (vs per protocol analysis), different enteral nutrition formulas and outcome measures reported as medians and IQRs. No significant effects were observed.

Subgroup analyses

Of the 13 RCTs that investigated the effects of enteral fish oil supplementation on 28-day mortality, 7 were performed in ARDS patients[17,18,20,28,29,32,33], 2 in sepsis patients [21,30], 1 in trauma patients [23] and 3 in heterogeneous groups of ICU patients [24,27,38]. Although the overall treatment effect was not significant, aggregation of the data from the 7 trials performed in ARDS patients did show a significant reduction in 28-day mortality, favouring fish oil supplementation (RR 0.69, 95%CI 0.54–0.89, p=0.004, Figure 3). In the other subgroups no significant effects were found. Moreover, ICU LOS and ventilation duration were also significantly reduced in ARDS patients but not in the other subgroups (Figure 4 and 5). No significant

differences between subgroups were found regarding ICU mortality, hospital mortality, hospital LOS and infectious complications.

Old versus new studies

Nine of the 13 RCTs investigating the effects of enteral fish oil supplementation on 28-day mortality were published between 2010 and 2015 [17,20,21,23,27,28,30,32,38]. No significant differences in 28-day mortality were observed when these were compared with the four studies published between 1999 and 2009 (p=0.16, see figure 3 in [73]) [18,24,29,33]. No significant differences between old and new studies were found regarding ICU mortality, hospital mortality, hospital LOS and infectious complications.

Effect of study quality on outcomes

While low quality trials did show a decrease in 28-day mortality with fish oil supplementation (RR 0.77, 95% CI 0.61 – 0.96, p=0.02), high quality trials did not (RR 1.07, 95% CI 0.88 – 1.30, p=0.51, see figure 4 in [73]). In addition, duration of ventilation was significantly shorter in fish oil supplemented patients in low quality trials (p=0.03), but not in high quality trials (p=0.05). Furthermore, in high quality trials ICU LOS was significantly reduced (p=0.002) in fish oil supplementation while this effect was non-significant in low quality trials (p=0.07). No differences were observed between Level 1 and 2 trials regarding ICU and hospital mortality and infectious complications. Hospital LOS was only reported in high quality trials.

Post-hoc analysis of adverse events and tolerability

In order to evaluate the risk-to-benefit ratio of omega-3 supplementation we performed a post-hoc analysis of adverse events and tolerability. Adverse events are systematically reported in 5 studies. No difference was observed between adverse events in patients with and without omega-3 supplementation (RR 1.04, 95% CI 0.96-1.13, p=0.34), see figure 5 in [73]. Tolerability of omega-3 was assessed by incidence of nausea/vomiting, dyspepsia, high GRV, aspiration, diarrhea, constipation, abdominal distention, ileus, pancreatitis, calories delivered, tube replacement rates, achievement of feeding target, triglyceride levels, prokinetics use and overall GI complications (see table 3 in [73]). No significant differences were observed between groups.

Discussion

We systematically reviewed 24 eligible RCTs evaluating the effects of enteral fish oil supplementation in ICU patients [15-38]. The overall results showed no effects on 28-day, ICU or hospital mortality, but length of ICU stay and ventilation duration were significantly reduced by enteral fish oil supplementation. However, upon inspection of the results retrieved from our subgroup analysis, the significance of these findings seems largely due to the benefits found in the ARDS subgroup (*i.e.* decrease in 28-day mortality, ICU LOS and duration of ventilation). These results should be interpreted with caution as 6 out of 7 ARDS studies were of low methodological quality [17,20,28,29,32,33].

Three recent meta-analysis evaluated the effects of enteral fish oil supplementation specifically in ARDS patients [5,6,74]. No effects on mortality were found and either none or a small reduction in ICU LOS and ventilation duration were reported. In addition, Manzanares et al. recently published the results of a systematic review of parenterally administered fish oil in critically ill patients [7]. They concluded that although no significant effects on mortality were found, fish oil containing lipid emulsions may be associated with a reduction in infections and also could be associated with a reduction in duration of ventilation and hospital LOS. It is however difficult to compare parenteral with enteral administration as the bioavailability of enteral administered fish oil is hard to predict especially in critically ill patients in whom pharmacokinetics are changing during the course of the illness. Moreover, pharmacodynamics including local effects of enteral fish oil on gut immunity may be important, however this assumption is purely speculative. Contemplating the results of recent meta-analysis, including our own, it remains unclear whether fish oil supplementation is beneficial. A closer look at the individual clinical trials shows even larger differences in clinical outcomes. These conflicting results may be, at least partially, explained by two factors. Study populations were heterogeneous and ranged from general ICU patients to specific groups like elective surgical patients admitted to the ICU, severe trauma patients and patients with sepsis or ARDS. Furthermore, study designs are variable demonstrated by differences in method of administration (*i.e.* parenteral vs enteral, continuous vs bolus, FO as a component of nutrition vs a separate supplement), amount and composition of the (par)enteral nutrition studied as well as the composition of the control feeds.

However, we should also investigate the possibility of a (patho)physiological explanation as for why studies find conflicting results. Dysregulation of the immune response in critical illness has long been the target of development of new therapeutic interventions. The anti-inflammatory and immunomodulatory effects of fish oil have been established in multiple studies. Downregulation of pro-inflammatory mediators (i.e. cytokines and adhesion molecules) as well as a decrease in the cellular immune response have been widely reported [75-87]. Moreover, a meta-analysis by Pradelli et al showed that the amount of fish oil supplemented in clinical trials led to a significant increase in EPA and DHA plasma levels, which was associated with a significant reduction in IL-6 and a shift in the generation of leukotrienes indicating an anti-inflammatory response in vivo [88]. These findings are important as they suggest that bioavailability of enteral fish oil and the induction of an anti-inflammatory effect are not a problem. The consequently reported immunological response to fish oil supplementation may however be the key to the differences in clinical outcomes found in individual trials [75-87]. The (patho)physiological immunological response to critical illness is different between individual patients and over time, ranging from an extensive hyperinflammatory response to severe immunosuppression. The persistent inflammatory immunosuppressed catabolic syndrome as described by Hotchkiss et al. and Rosenthal et al. suggests diverging immunological phenotypes of multiple organ failure including early deaths due to overwhelming inflammation and late deaths due to both intractable inflammation-induced organ injury or persistent immunosuppression and recurrent infections [89,90]. Whereas the anti-inflammatory effects of fish oil may be beneficial during hyperinflammation it may also be potentially harmful in case of pathophysiological immunosuppression. This may for instance explain why in a post-hoc analysis of the Metaplus trial increases of plasma (EPA+DHA)/LCP-ratios from baseline to day 4 were associated with increased adjusted mortality risk at 6 months independent of baseline levels in the predefined subgroup of medical patients. The exposure of the fish oil supplementation in this study was long (median 12 days) and may have aggravated an immunosuppressed phenotype [38].

Additionally, it may be further illustrated by the differences in clinical outcome effects between old and new studies. Although not significantly different, a marked trend towards better mortality outcome was observed in earlier studies, while no effect was seen in recent studies. When calculating the placebo group mortality large differences were found (32.9% in studies < 2010, 19.6% in studies > 2010). This may suggest that the

anti-inflammatory effects are of most benefit to the sickest patients but may be harmful in less severely ill critically ill patients.

Strengths and Limitations

A large number of RCTs were included in this meta-analysis, providing a large number of patients which strengthens the results. However, the studies included have several methodological differences which may influence the outcomes. These include differences in control feeds used, additional immunomodulatory contents (i.e. antioxidants and arginine/glutamine), dose and timing of fish oil supplementation. Furthermore, we only subtracted data reported in the original papers but were unable to contact the authors to complete missing data. Moreover, the effects of omega-3 supplementation may depend on baseline EPA and DHA levels and on EPA and DHA levels reached. However, only 6 of 24 studies reported plasma levels. As they were reported in different manners it was not possible to analyse them systematically. EPA and DHA levels are reported in Table 1 in [73].

Conclusions

Based on the results of this meta-analysis enteral fish oil supplementation cannot be recommended for critically ill patients as strong scientific evidence for improved clinical benefits could not be found. There is a signal of mortality benefit in ARDS patients, however results are based on low quality studies. Therefore, enteral fish oil feeds may be considered in patients with ARDS. Further research should focus on the relation between the individual critically ill patients' immune response, the administration of fish oil and clinical outcomes.

Conflict of Interest Statement and Funding sources

Arthur van Zanten reported that he has received honoraria for advisory board meetings, lectures, and travel expenses from Abbott, Baxter, BBraun, Beacon, Danone-Nutricia, Fresenius Kabi, Lyric and Nestle - Novartis. Inclusion fees for patients in nutrition trials were paid to the local ICU research foundation. The remaining authors have disclosed that they do not have any conflicts of interest.

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Table 1: Randomized Clinical Trials evaluating enteral fish oil supplementation in ICU patients.

Study	Population	Intervention	Mortality		Length of stay		Duration of ventilation	
Atkinson 1998	ICU patients N = 390	**Intervention:** EN supplemented with L-arginine, RNA and EPA/DHA 1.7g/L vs **Control:** Isocaloric isonitrogenous EN identical in vitamin & trace element profiles.	**ICU** 80/197 **HOS** 95/197	**ICU** 74/193 **HOS** 85/193	**ICU** 6 (0-103) **HOS** 12 (0-187)	**ICU** 6 (0-282) **HOS** 13 (0-289)	4 (0-101)	4 (0-204)
Bower 1995	ICU patients with SIRS/Sepsis N = 326	**Intervention:** EN supplemented with L-arginine, RNA and EPA/DHA 1.7g/L vs **Control**: isonitrogenous EN with similar protein-fat-carbohydrate distribution and vitamin/trace element profile.	**HOS** 23/147	**HOS** 10/132	**HOS** 21	**HOS** 26	NR	NR
Elamin 2012	ICU patients with ARDS N = 22	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** isocaloric isonitrogenous EN identical in protein-fat-carbohydrate distribution and vitamin/ trace element profiles.	**28-day** 0/9	**28-day** 1/8	**ICU** 12.8	**ICU** 17.5	6.7	8.2
Gadek 1999	ICU patients with ARDS N = 146	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** Isocaloric, isonitrogenous EN identical in protein-fat-carbohydrate distribution	**HOS** 11/70	**HOS** 19/76	**ICU** 11 ± 0.9 **HOS** 27.9 ± 2.1	**ICU** 14.8 ± 1.3 **HOS** 31.1 ± 2.4	9.6 ± 0.9	13.2 ± 1.4
Galban 2000	ICU patients with sepsis N = 181	**Intervention:** EN supplemented with L-arginine, RNA and EPA/DHA 1.7g/L vs **Control:** High caloric EN with similar protein-fat-carbohydrate distribution.	**ICU** 17/89	**ICU** 28/87	**ICU** 18.2 ± 12.6	**ICU** 16.6 ± 12.91	12.4 ± 10.4	12.2 ± 10.3
Grau-Carmona 2011	ICU patients with sepsis and ARDS N = 160	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** low fat, high carbohydrate EN	**28-day** 11/61	**28-day** 11/71	**ICU** 16 (11-25)	**ICU** 18 (10-30)	10 (6-14)	9 (6-18)
Hosny 2013	ICU patients with sepsis N = 75	**Intervention:** EN (unspecified) supplemented with DHA+EPA 3dd 3g, Vit C 1000mg/d, Vit E 800IU/d, selenium 100 ug/d vs **Intervention:** EN (unspecified)	**28-day** 8/25 11/25	**28-day** 10/25	**ICU** 11.6 ± 6.1 13.6 ± 4.1	**ICU** 13.9 ± 4.2	6.7 ± 3.83 8.4 ± 4.63	10.9 ± 6.3

		supplemented with DHA+EPA 3dd 1g, Vit C 1000mg/d, Vit E 800IU/d, selenium 100 ug/d vs **Control:** EN (unspecified) without supplements.						
Jakob 2017	ICU patients N = 90	**Intervention:** High protein, low carbohydarate EN with high omega-3 FA 3.6g/L vs **Control:** Low protein, high carbohydrate EN with low omega-3 FA 2.9g/L.	NR	NR	**ICU** 7.0 (5.3-8.7) **HOS** 31.0 (27.0-35.0)	**ICU** 10.0 (6.6-13.4) **HOS** 36.0 (29.9-42.1)	6.2 (4.8-7.7)	7.0 (4.7-9.3)
Kagan 2015	ICU patients with severe trauma N = 120	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** high fat, low carbohydrate EN, isocaloric and similar in protein and macronutrient composition.	**28-day** 8/62	**28-day** 5/58	**ICU** 19.5 ± 15.3 **HOS** 33.1 ± 25.7	**ICU** 16.4 ± 11.3 **HOS** 27.1 ± 17.3	NR	NR
Kieft 2005	ICU patients N = 597	**Intervention:** EN supplemented with arginine, glutamine and EPA 0.8g/L/DHA 0.3g/L vs **Control:** isocaloric control EN	**28-day** 93/302 **ICU** 84/302 **HOS** 114/302	**28-day** 82/295 **ICU** 78/295 **HOS** 106/295	**ICU** 7.0 (4.0-14.0) **HOS** 20.0 (10.0-35.0)	**ICU** 8.0 (5.0-16.0) **HOS** 20.0 (10.0-34.0)	6.0 (3.0-12.0)	6.0 (3.0-12.0)
Kudsk 1996	ICU patients with emergency celiotomy N = 35	**Intervention:** high protein EN with arginine, glutamine and omega-3 1.1 g/L vs **Control:** isocaloric, isonitrogenous EN	**5-day** 1/17	**5-day** 1/18	**ICU** 5.8 ± 1.8 **HOS** 18.3 ± 2.8	**ICU** 9.5 ± 2.3 **HOS** 32.6 ± 6.6	2.4 ± 1.3	5.4 ± 2.0
Mendez 1997	ICU patients with severe trauma N = 59	**Intervention:** EN with arginine and 40% canola oil (omega-3) **Control:** isocaloric, isonitrogenous EN with soy and corn oil	**?** 1/22	**?** 1/21	**ICU** 18.9 ± 20.7	**ICU** 11.1 ± 6.7	?	?
Mesejo 2015	Mechanically ventilated ICU patients with hyperglycemia N = 157	**Intervention:** high protein EN with modified maltodextrin and EPA/DHA 0.68g/L **Control:** high caloric standard maltodextrin EN **Control: i**socaloric modified maltodextrin EN	**28-day** 11/52 **6-month** 16/52	**28-day** 10/53 13/52 **6-month** 20/53 18/52	**ICU** 13 (9-20) **HOS** 27 (18-50)	**ICU** 12 (7-21) 11.5 (7.5-18) **HOS** 25 (17-51) 30.5 (14-46.5)	7 (4-13)	6 (2-11) 6 (3-12)
Parish 2014	ICU patients with ARDS N = 58	**Intervention:** EN (unspecified) + omega-3 soft gels 720mg 3dd **Control:** same EN (unspecified) without soft gels	**28-day** 7/29	**28-day** 9/29	**ICU** 15 ± 3.5	**ICU** 15.6 ± 4.3	**VFD** 6.6 ± 2	**VFD** 6 ± 2.5

Pontes-Arruda 2006	ICU patients with ALI and severe sepsis or septic shock N = 165	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** Isocaloric and isonitrougenous EN	**28-day** 26/83	**28-day** 38/82	**ICU-free days** 10.8 ± 1.1	**ICU-free days** 4.6 ± 0.9	**VFD** 13.4 ± 1.2	**VFD** 5.8 ± 1.0
Pontes-Arruda 2011	ICU patients with sepsis N = 115	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** isocaloric, isonitrogenous, low fat, high carbohydrate EN	**28-day** 15/57	**28-day** 16/58	**ICU** 7 (4-12) **ICU-free days** 21.1 ± 4.7 **HOS** 9 (6-14) **HOS-free days** 19.5 ± 7.8	**ICU** 13 (9-18) **ICU-free days** 14.7 ± 5.1 **HOS** 19 (13-24) **HOS-free days** 10.3 ± 8.6	7 (4-12)	15 (8-21)
Rice 2011	ICU patients with ALI N = 272	**Intervention:** EN (unspecified) + supplement with omega-3 FA & AOX **Control:** same EN (unspecified) + isocaloric isovolemic carbohydrate rich controls supplement	**60-day** 38/143	**60-day** 21/129	**ICU-free days** 14.0 ± 10.5	**ICU-free days** 16.7 ± 9.5	**VFD** 14.0 ± 11.1	**VFD** 17.2 ± 10.2
Shirai 2015	ICU patients with sepsis induced ARDS N = 46	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** Low caloric, low protein, high carbohydrate EN	**28-day** 3/23	**28-day** 3/23	**ICU** 15 (11-24) **ICU-free days** 13 (0-17)	**ICU** 24 (20-30) **ICU-free days** 4 (0-8)	14 (10-17) **VFD** 14 (11-18)	17 (12-24) **VFD** 11 (3-16)
Singer 2006	ICU patients with ARDS or ALI N = 100	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** isocaloric, isonitrogenous control with similar protein-fat-carbohydrate distribution.	**28-day** 13/46	**28-day** 28/49	**ICU** 13.5 ± 11.8	**ICU** 15.6 ± 11.8	12.1 ± 11.3	14.7 ± 12
Stapelton 2011	ICU patients with ALI N = 90	**Intervention:** EN (unspecified) + 9.75g EPA/d + 6.75g DHA/d **Control:** same EN (unspecified) + saline 0.9% enterally in similar amount	**HOS** 9/41	**HOS** 10/49	**?**	**?**	**?**	**?**
Thiella 2012	ICU patients with pressure ulcers N = 40	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** low-fat, high carbohydrate EN	NR	NR	**ICU** 26.1 ± 14.2	**ICU** 21.1 ± 9.1	NR	NR
Tihista 2017	ICU patients with burns > 15% requiring mechanical	**Intervention:** Low-fat EN (unspecified) of which 50% of the fat was replaced by fish-oil	**HOS** 15/53	**HOS** 13/53	**HOS** 52 (29-78)	**HOS** 51 (36-72)	14 (10-28)	18 (11-32)

	ventilation N = 106	**Control:** Low-fat EN (unspecified) without fish-oil						
Weimann 1998	ICU patients with severe trauma N = 32	**Intervention**: EN supplemented with L-arginine, RNA and EPA/DHA 1.7g/L vs **Control:** Isonitrogenous isocaloric EN	**ICU** 2/16	**ICU** 4/13	**ICU** 31.4 ± 23.1 **HOS** 70.2 ± 52.9	**ICU** 47.4 ± 32.8 **HOS** 58.1 ± 30.1	21.4 ± 10.8	27.8 ± 14.6
Van Zanten 2014	ICU patients requiring mechanical ventilation N = 301	**Intervention:** high protein, high fat EN with glutamine, MCT, antioxidants and EPA+DHA 5.0g/L **Control:** isocaloric high protein, low fat EN	**28-day** 31/152 **ICU** 30/152 **HOS** 38/152 **6-months** 53/152	**28-day** 25/149 **ICU** 29/149 **HOS** 33/149 **6-months** 42/149	**ICU** 18 (12-29) **HOS** 30 (21-44)	**ICU** 18 (10-34) **HOS** 30 (20-49)	9 (5-15)	8 (5-15)

Table 2: Infectious complications in randomized clinical trials evaluating fish oil supplementation in ICU patients.

Study	Population	Infections		VAP		Bacteremia		UTI		CRI		Intra-abdominal	
Atkinson 1998	ICU patients N = 390	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bower 1995	ICU patients with SIRS/Sepsis N = 326	0.74 ± 0.97*	0.98 ± 1.27*	NR	NR	9/147	17/132	24/147	30/132	NR	NR	NR	NR
Elamin 2012	ICU patients with ARDS N = 22	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gadek 1999	ICU patients with ARDS N = 146	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Galban 2000	ICU patients with sepsis N = 181	46/89	68/87	11/89	11/87	7/89	19/87	11/89	11/87	10/89	11/89	NR	NR
Grau-Carmona 2011	ICU patients with sepsis N = 160	32/61	34/71	24/61	26/71	6/61	6/71	2/61	5/71	10/61	13/71	4/61	3/71
Hosny 2013	ICU patients with sepsis N = 75	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jakob 2017	ICU patients N = 90	19/46	19/44	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kagan 2015	ICU patients with severe trauma N = 120	NR	NR	25/62	22/58	14/62	3/62	NR	NR	NR	NR	NR	NR
Kieft 2005	ICU patients N = 597	130/302	123/295	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kudsk 1996	ICU patients with emergency celiotomy N = 35	NR	NR	0/16	2/17	1/16	4/17	2/16	6/17	NR	NR	1/16	6/17
Mendez 1997	ICU patients with severe trauma N = 59	19/22	12/21	16/22	11/21	6/22	7/21	3/22	4/21	NR	NR	NR	NR
Mesejo 2015	Mechanically ventilated	8/52	23/53	8/460**	10/392**	3/52	1/53	1/52	1/53	1/52	1/53	NR	NR

	ICU patients with hyperglycemia		23/52		6/424**		3/52		1/52		2/52		
	N = 157												
Parish 2014	ICU patients with ARDS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	N = 58												
Pontes-Arruda 2006	ICU patients with ALI and severe sepsis or septic shock	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	N = 165												
Pontes-Arruda 2011	ICU patients with sepsis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	N = 115												
Rice 2011	ICU patients with ALI	NR	NR	10/143	10/129	16/143	14/129	NR	NR	NR	NR	NR	NR
	N = 272												
Shirai 2015	ICU patients with sepsis induced ARDS	10/23	12/23	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	N = 46												
Singer 2006	ICU patients with ARDS or ALI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	N = 100												
Stapelton 2011	ICU patients with ALI	1/41	1/49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	N = 90												
Thiella 2012	ICU patients with pressure ulcers	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	N = 40												
Tihista 2017	ICU patients with burns > 15% requiring mechanical ventilation	NR	NR	15/53	20/53	7/53	7/53	NR	NR	2/53	6/53	NR	NR
	N = 106												
Weimann 1998	ICU patients with severe trauma	NR	NR	10/16	6/13	1/16	1/13	2/16	1/13	9/16	6/13	NR	NR
	N = 32												
Van Zanten 2014	ICU patients requiring mechanical ventilation	80/152	78/149	56/152	59/149	15/152	12/149	15/152	15/149	NR	NR	NR	NR

N = 301

Figure Legends

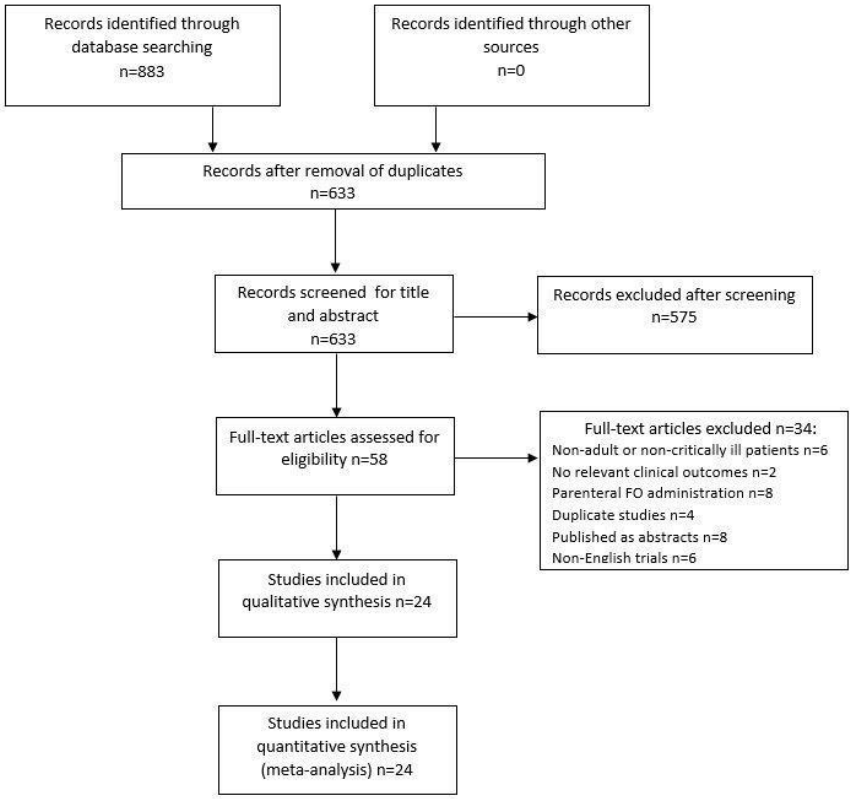

Figure 1: Flowchart.

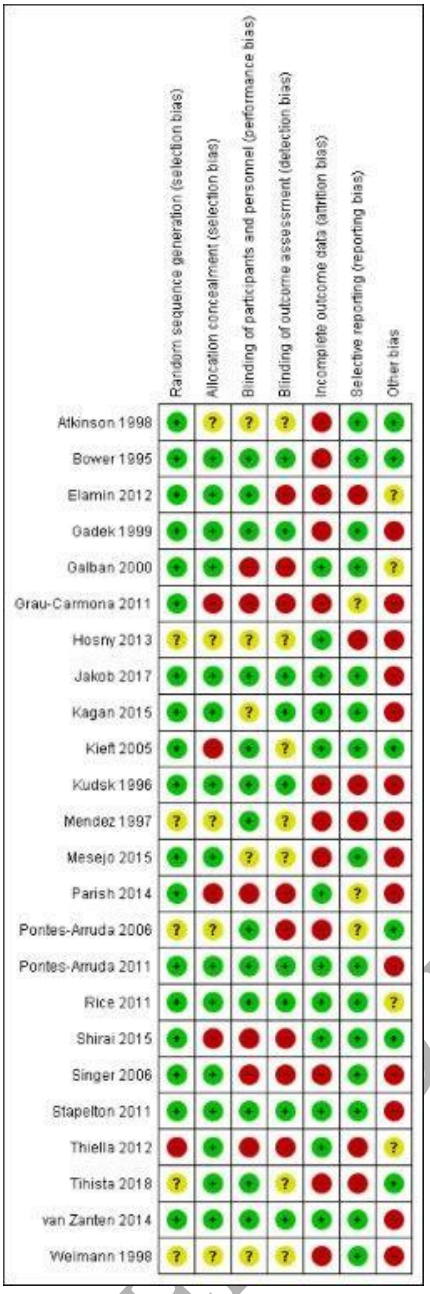

Figure 2a: Risk of bias summary of RCTs included in meta-analysis.

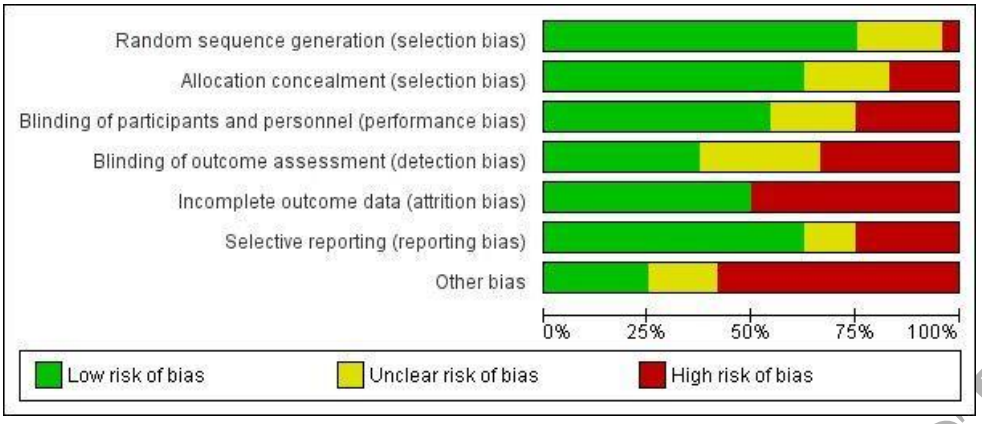

Figure 2b: Risk of bias graph of RCTs included in meta-analysis.

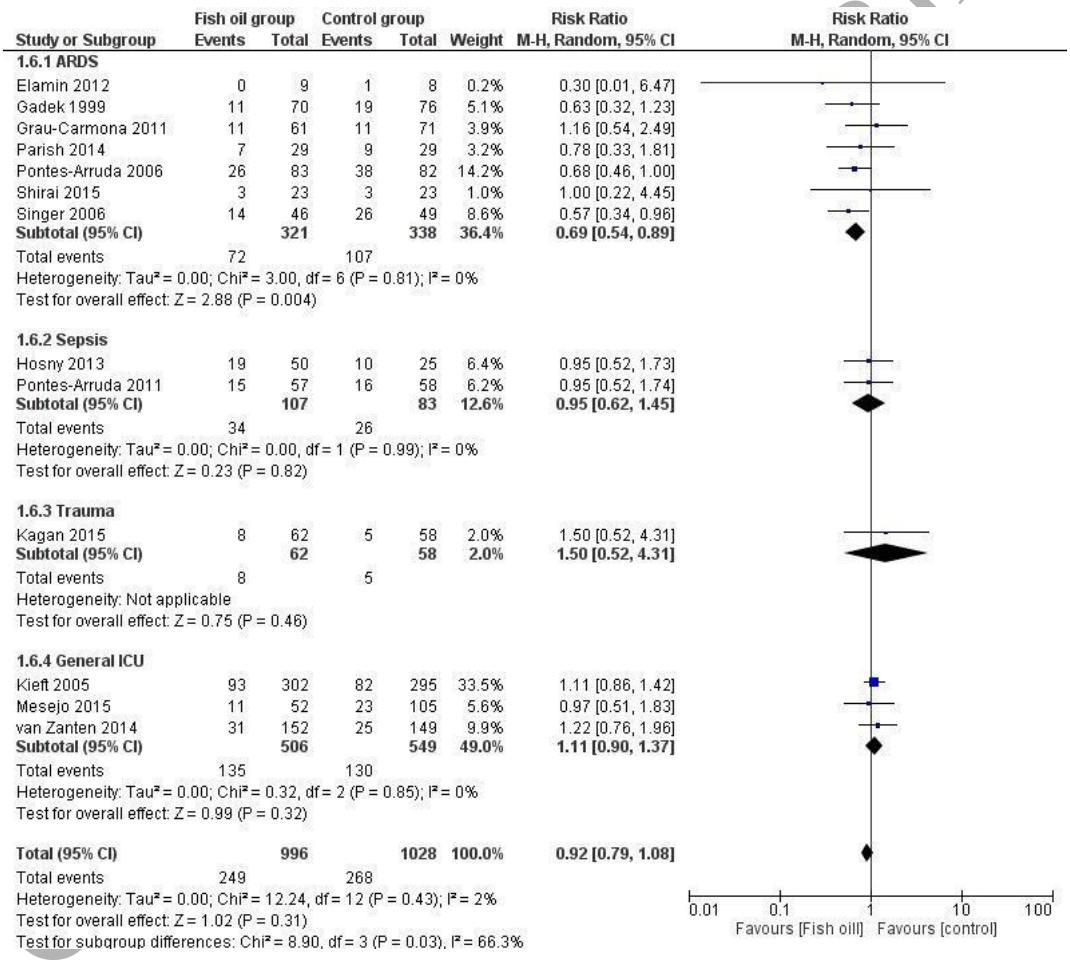

Figure 3: The effects of fish oil supplementation on 28-day mortality in different ICU populations.

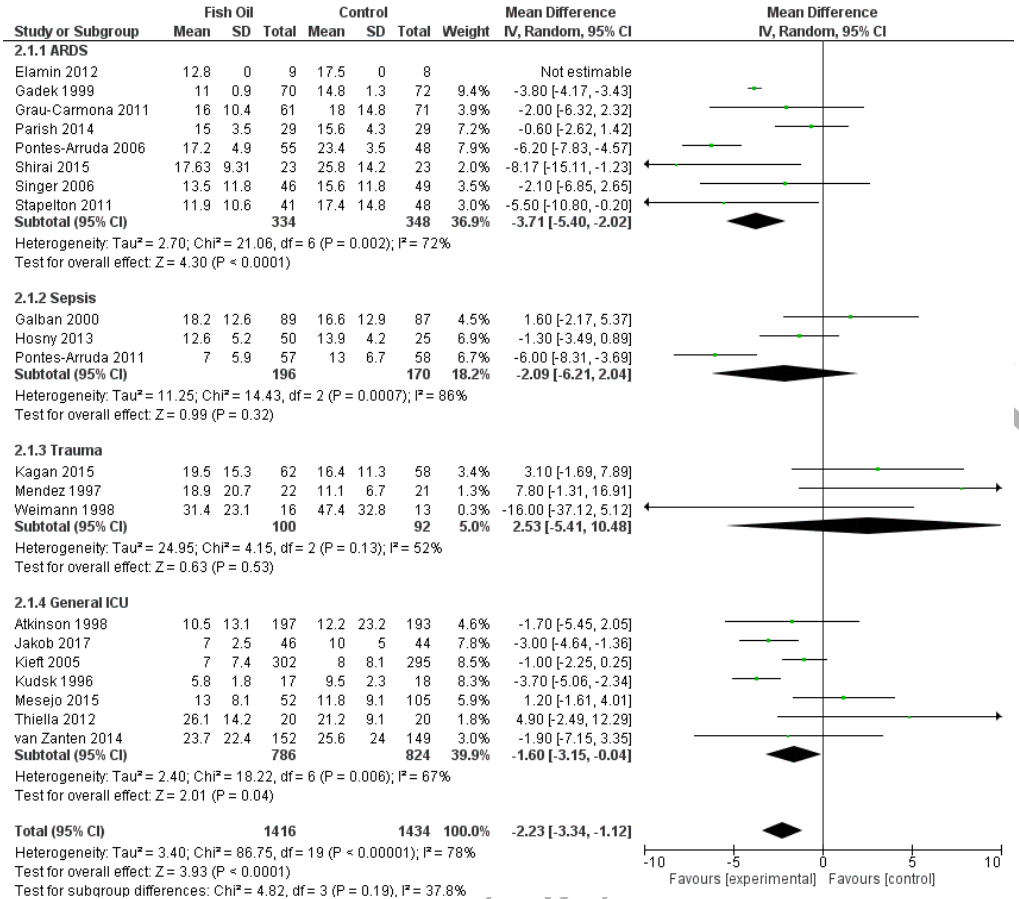

Figure 4: The effects of fish oil supplementation on ICU length of stay in different ICU populations.

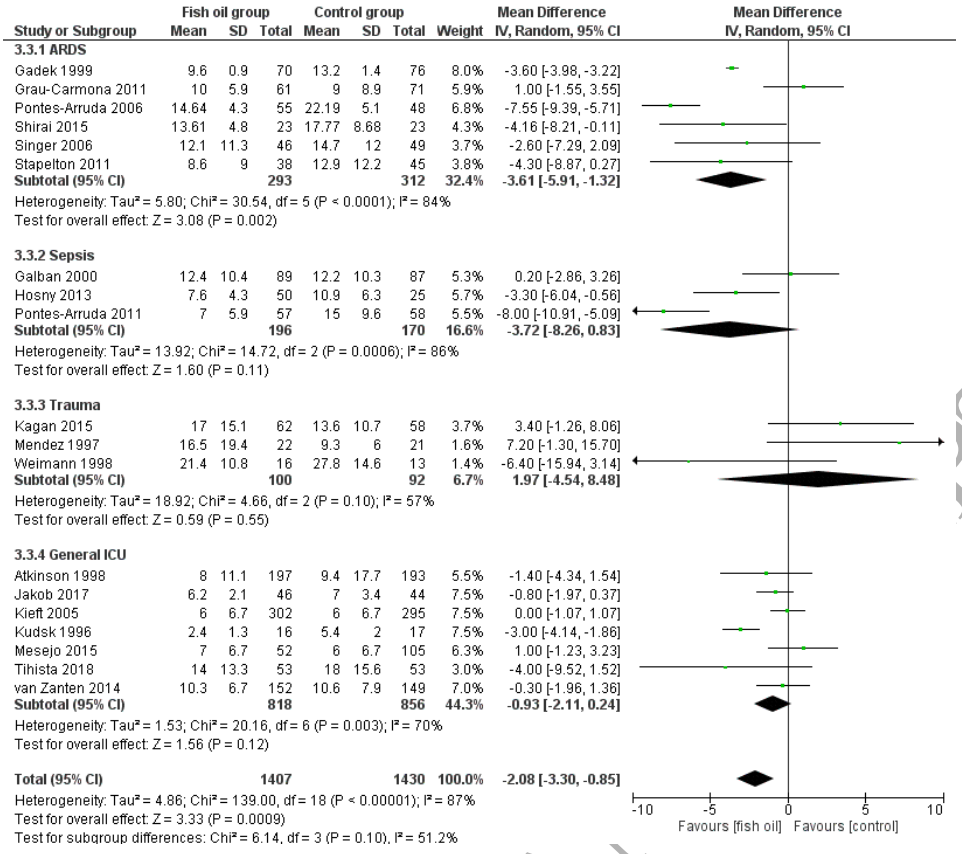

Figure 5: The effects of fish oil supplementation on ventilation duration in different ICU populations.