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Review article

Current evidence on ω-3 fatty acids in enteral nutrition in the critically ill: A systematic review and meta-analysis

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ABSTRACT

Fish oil exerts anti-inflammatory and immunomodulatory properties that may be beneficial for critically ill patients, thus multiple randomized controlled trials and meta-analyses 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 (ICUs). The aim of this study was to provide an up-to-date systematic review and meta-analysis of all randomized controlled trials of fish oil–containing enteral nutrition addressing relevant clinical outcomes in critically ill patients.

A systematic literature search was conducted. The primary outcome was 28-d mortality. Secondary outcomes were ICU and hospital mortality, ICU and hospital length of stay (LOS), ventilation duration, and infectious complications. Predefined subgroup and sensitivity analyses were performed. Twenty-four trials, enrolling 3574 patients, met the inclusion criteria. The assessment of risk for 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-d, 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-d mortality, ICU LOS, and ventilation duration in patients with acute respiratory distress syndrome but not in other subgroups. When comparing high- and low-quality trials, significant reductions in 28-d mortality and ventilation duration in low-quality trials only 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.

Enteral fish oil supplementation cannot be recommended for critically ill patients, as strong scientific evidence for improved clinical benefits was not found. There is a signal of mortality benefit in patients with acute respiratory distress syndrome; 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, more specifically eicosapentaenoic acid (EPA; 20:5 ω-3) and docosahexaenoic acid (DHA; 22:6 ω-3). It has been suggested that EPA and DHA may attenuate the production of proinflammatory lipid mediators and cytokines, modulate the activity of nuclear receptors and expression of nuclear transcription factors (nuclear factor-kappa B, peroxisome proliferator-activated receptor-γ, and intracellular adhesion molecule-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 y, several randomized controlled trials (RCTs) have addressed the clinical effects of FO supplementation among critically ill patients. Conflicting results have been reported,

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ranging from a clinical benefit to possible harm. Recently, several meta-analysis have been performed regarding FO-containing nutrition in critically ill patients. The effects of enteral FO-containing formulas in patients with acute respiratory distress syndrome (ARDS) was studied in two recent meta-analysis [5,6]. In both, no significant effects on mortality or ventilator-free days and intensive care unit (ICU)-free days were found. Manzanares et al. recently studied effects of intravenous FO lipid emulsions in critically ill patients [7]. In a meta-analysis of 10 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 et al. on parenteral and enteral FO 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 perioperative FO supplementation was studied by Langlois et al. 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.

FO supplementation has been addressed in international guidelines. Guidelines from the European Society of Clinical Nutrition and Metabolism suggest a benefit of FO lipid emulsions in patients with ARDS, but have not been updated since 2009 [10]. The more recent guidelines from the American Society for Parenteral and Enteral Nutrition withhold recommendations for FO because of the conflicting data [11]. The Canadian Clinical Practice Guidelines advise consideration of enteral formulas containing FOs in patients with ARDS/acute lung injury as associations were found with its use and reduction in 28-d mortality [12].

The purpose of the present study was to provide an up-to-date systematic review and meta-analysis of all RCTs of FO-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 RCTs 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 and eligibility criteria

Only trials meeting the following characteristics were included:

1. Study design: Randomized clinical, parallel group, controlled trials.
2. Study population: Critically ill adult patients (>95% of patients >18 y of age).
3. Intervention: Enteral supplementation of FO (ω-3 fatty acids) or FO-containing EN compared with a control or placebo intervention.
4. Study outcomes must have included one of the following: mortality, ICU or hospital LOS, duration of mechanical ventilation, and infectious complications.

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

Two authors (W.K. and V.P.) independently performed methodological quality assessment of the studies. The risk for 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 intention-to-treat [ITT] analysis), and selective reporting [13]. Scores of 9 to 14 were regarded as high quality (level I) and 0 to 8 as low quality (level II). Any disagreement was resolved by consensus.

Data synthesis

The primary outcome of the systematic review was 28-d 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 also were 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 with 95% CI for LOS and duration of ventilation. When studies reported only medians with interquartile ranges (IQRs), these were converted to means and SDs according to the Cochrane guidelines. Pooled RRs were calculated using the Mantel–Haenszel test, and weighted mean differences 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 5.3 software [14]. Whenever possible, studies were aggregated on an ITT 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. $P < 0.05$ was considered statistically significant and $P < 0.10$ was the indicator of a trend.

Subgroup analysis

A predefined subgroup analysis was performed to investigate whether there were differences in treatment effect among patients with sepsis, ARDS, or trauma. In addition, we compared older (before 2010) and newer studies on treatment effects. We also assessed the effect of trial quality on outcome, as lower-quality trials may demonstrate a greater treatment effect than those of 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 were not considered to be adult critically ill patients (n = 6) [39–44].
2. No clinical outcomes met inclusion criteria (n = 2) [45,46];
3. Parenteral FO administration was included (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]; and
6. Papers were published in a language other than English (n = 6) [67–72] (Fig. 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 all, 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, 3–13). Details of methodological quality are shown in Figure 2.

Meta-analyses of primary outcome

Overall effect on 28-d mortality

After aggregation of the data from 13 RCTs [17,18,20,21,23,24,27–30,32,33,38] evaluating 28-d mortality, no significant

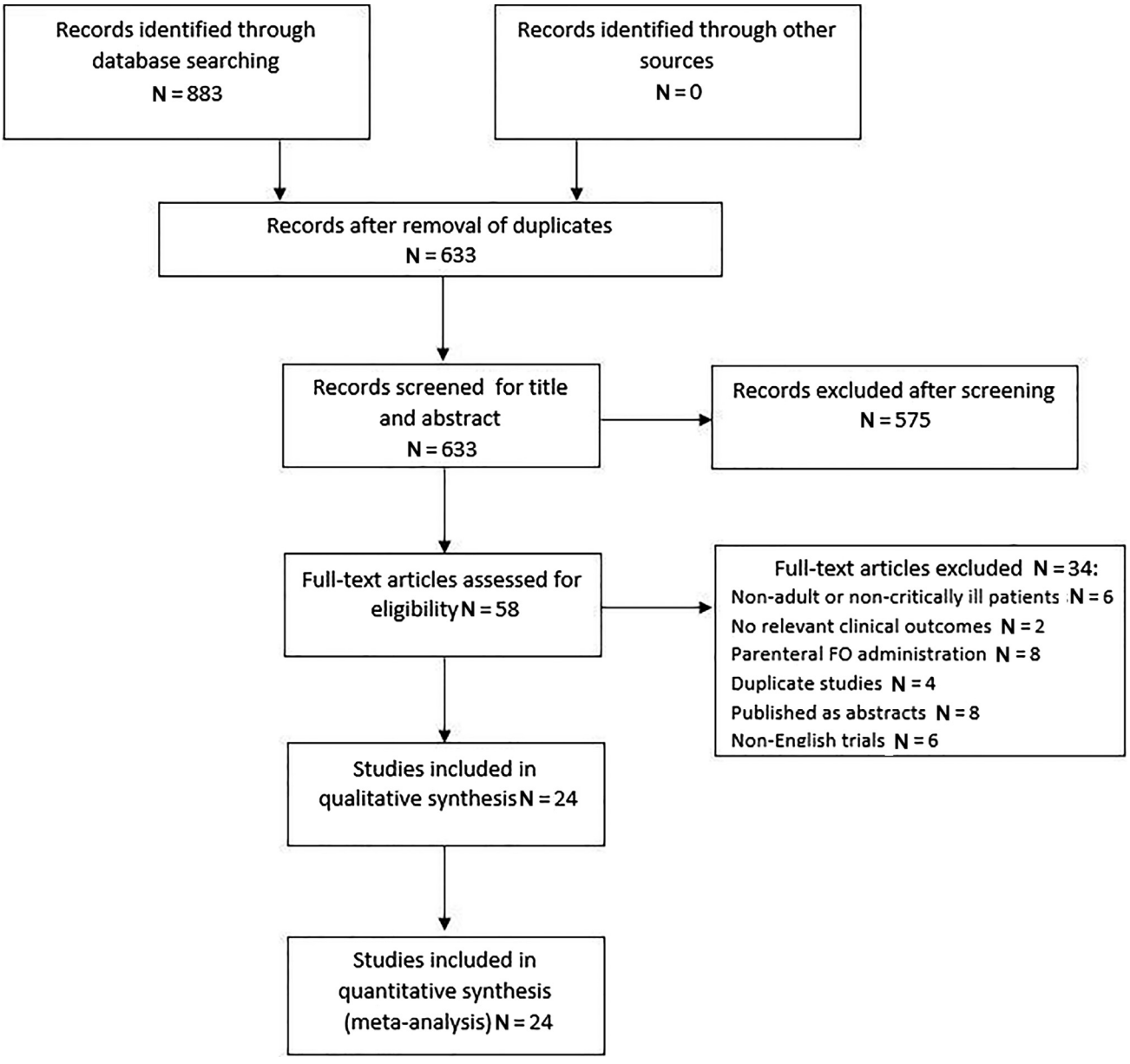

Fig. 1. Flowchart. FO, fish oil.

reductions in case fatality was found (RR, 0.92; 95% CI, 0.79–1.08; $P = 0.31$; Fig. 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 FO 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 Fig. 2 in Koekkoek et al. [73]) or hospital mortality (RR, 1.08; 95% CI, 0.95–1.23; $P = 0.23$; see Fig. 2 in Koekkoek et al. [73]). Heterogeneity was nonsignificant ($I^2 = 27\%$, $P = 0.24$ for ICU mortality and $I^2 = 0\%$, $P = 0.43$ for hospital mortality).

Overall effect on ICU LOS

ICU LOS was reported in 21 RCTs [15,16–30,32–35,37,38]. A significant reduction in ICU LOS favoring FO supplementation (MD −2.23; 95% CI −3.34 to −1.12; $P < 0.0001$; Fig. 4) was observed. However, heterogeneity was significant ($I^2 = 78\%$, $P < 0.0001$).

Overall effect on hospital LOS

Four trials reported hospital LOS [15,18,23,38]. We pooled these data and found no significant effect of FO supplementation on hospital LOS (MD −0.52; 95% CI −4.51 to 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 FO supplementation on ventilation duration showed a significant reduction favoring fish oil

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	**Group A:** EN (unspecified) supplemented with DHA+EPA 3dd 3g, Vit C 1000mg/d, Vit E 800IU/d, selenium 100 ug/d vs **Group B:** EN (unspecified) supplemented with DHA+EPA 3dd 1g, Vit C 1000mg/d, Vit E 800IU/d, selenium 100 ug/d vs **Group C (control):** EN (unspecified) without supplements.	**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
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 1:** high caloric standard maltodextrin EN **Control 2: 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)

(*continued on next page*)

Table 1 (*Continued*)

Study	Population	Intervention	Mortality		Length of stay		Duration of ventilation	
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 ventilation N = 106	**Intervention:** Low-fat EN (unspecified) of which 50% of the fat was replaced by fish-oill **Control:** Low-fat EN (unspecified) without fish-oi	**HOS** 15/53	**HOS** 13/53	**HOS** 52 (29–78)	**HOS** 51 (36–72)	14 (10–28)	18 (11–32)
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)

AF, advanced formula; ALI, acute lung injury; AOX, antioxidant; ARDS, acute respiratory depression syndrome; DHA, docosahexaenoic acid; EN, enteral nutrition; EPA, eicosapentaenoic acid; FA, fatty acid; GLA, γ-linolenic acid; HN, high nitrogen; HOS, hospital; ICU, intensive care unit; LOS, length of stay; MCT, medium-chain triglyceride; NR, no response; SIRS, systemic inflammatory response syndrome; VFD, ventilator-free day; Vit, vitamin.

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

Study	Population	Infections		VAP		Bacteremia		UTI		CRI		Intraabdominal	
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 ICU patients with hyperglycemia N = 157	8/52	23/53 23/52	8/460†	10/392† 6/424†	3/52	1/53 3/52	1/52	1/53 1/52	1/52	1/53 2/52	NR	NR
Parish 2014	ICU patients with ARDS N = 58	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pontes-Arruda 2006	ICU patients with ALI and severe sepsis or septic shock N = 165	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pontes-Arruda 2011	ICU patients with sepsis N = 115	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rice 2011	ICU patients with ALI N = 272	NR	NR	10/143	10/129	16/143	14/129	NR	NR	NR	NR	NR	NR
Shirai 2015	ICU patients with sepsis-induced ARDS N = 46	10/23	12/23	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Singer 2006	ICU patients with ARDS or ALI N = 100	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stapelton 2011	ICU patients with ALI N = 90	1/41	1/49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Thiella 2012	ICU patients with pressure ulcers N = 40	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tihista 2017	ICU patients with burns >15% requiring mechanical ventilation N = 106	NR	NR	15/53	20/53	7/53	7/53	NR	NR	2/53	6/53	NR	NR
Weimann 1998	ICU patients with severe trauma N = 32	NR	NR	10/16	6/13	1/16	1/13	2/16	1/13	9/16	6/13	NR	NR
Van Zanten 2014	ICU patients requiring mechanical ventilation N = 301	80/152	78/149	56/152	59/149	15/152	12/149	15/152	15/149	NR	NR	NR	NR

ALI, acute lung injury; ARDS, acute respiratory depression syndrome; CRI, catheter-related infection; ICU, intensive care unit; NR, no response; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infection; VAP, ventilator-associated pneumonia
*Infections per patient.
†VAP per ventilation day.

(MD −2.08, 95% CI, −3.30 to −0.85; $P = 0.0009$; Fig. 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 FO 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 FO was found in any of these analyses.

Risk for 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 ITT analysis (versus 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 FO supplementation on 28-d mortality, 7 were performed in patients with ARDS [17,18,20,28,29,32,33], 2 in patients with sepsis [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 trials performed in patients with ARDS did show a significant reduction in 28-d mortality, favoring FO supplementation (RR, 0.69; 95% CI, 0.54–0.89; $P = 0.004$; Fig. 3). No significant effects were found in the other subgroups. Moreover, ICU LOS and ventilation duration also were significantly reduced in patients with ARDS but not in the other subgroups (Figs. 4 and 5). No significant differences between subgroups were found regarding ICU mortality, hospital mortality, hospital LOS, and infectious complications.

Old versus new studies

Of the 13 RCTs investigating the effects of enteral FO supplementation on 28-d mortality, 9 were published between 2010 and 2015 [17,20,21,23,27,28,30,32,38]. No significant differences in 28-d mortality were observed when these were compared with the four studies published between 1999 and 2009 ($P = 0.16$; see Fig. 3 in Koekkoek et al. [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

Although low-quality trials did show a decrease in 28-d mortality with FO 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 Fig. 4 in Koekkoek et al. [73]). In addition, duration of ventilation was significantly shorter in patients supplemented with FO 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 FO supplementation; whereas 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

To evaluate the risk–benefit ratio of ω-3 supplementation, we performed a post hoc analysis of adverse events (AEs) and tolerability. AEs were systematically reported in five studies. No

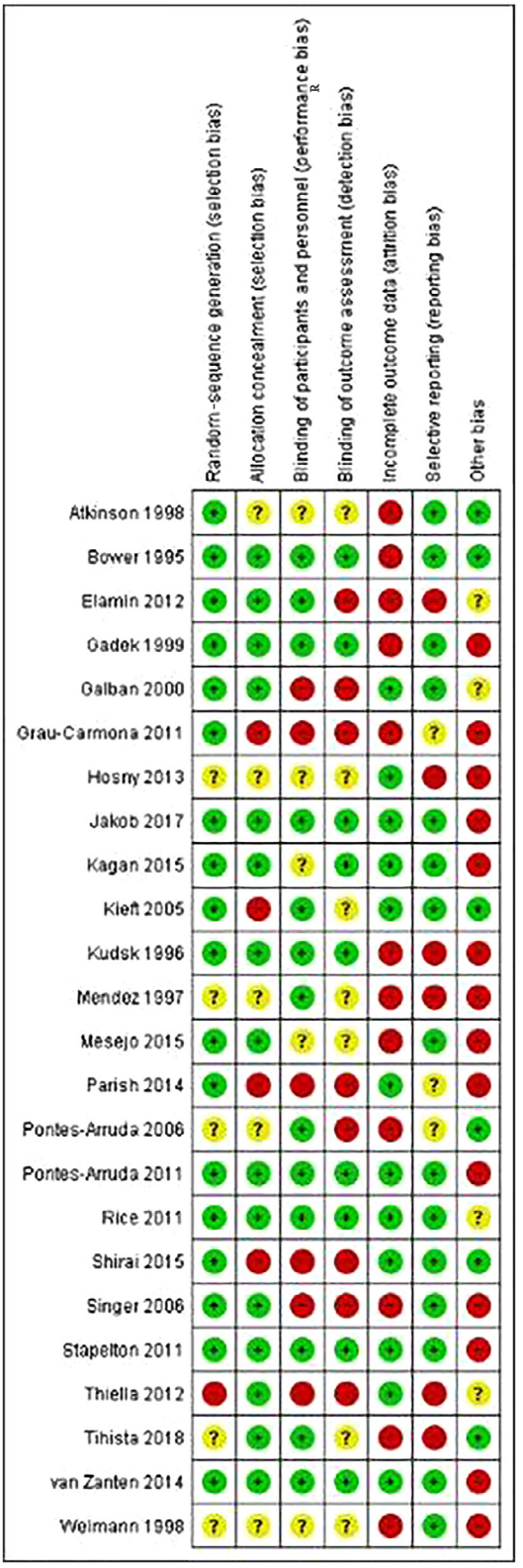

Fig. 2. (A) Risk for bias summary of RCTs included in meta-analysis. (B) Risk for bias graph of RCTs included in meta-analysis. RCT, randomized controlled trials.

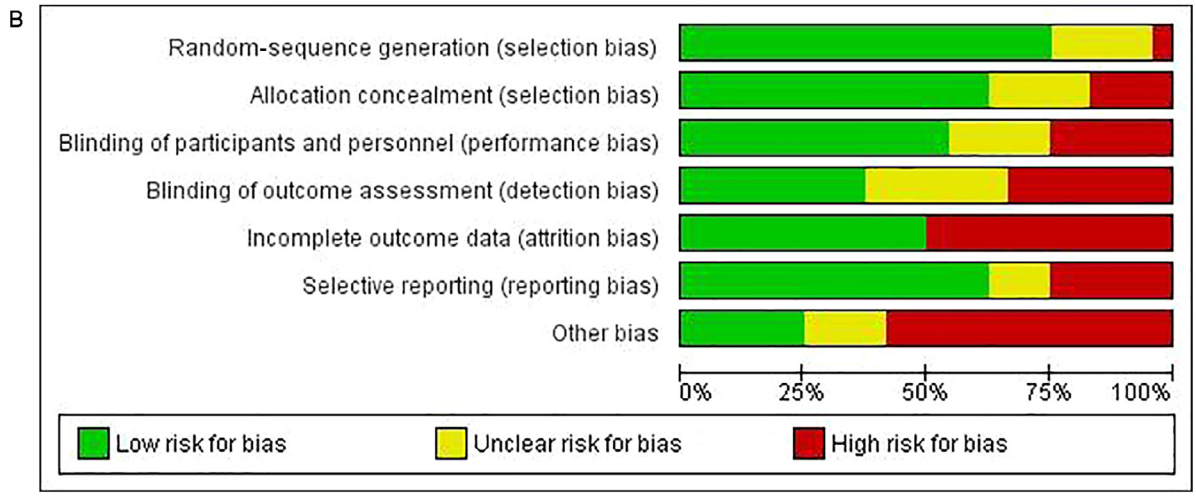

Fig. 2 Continued.

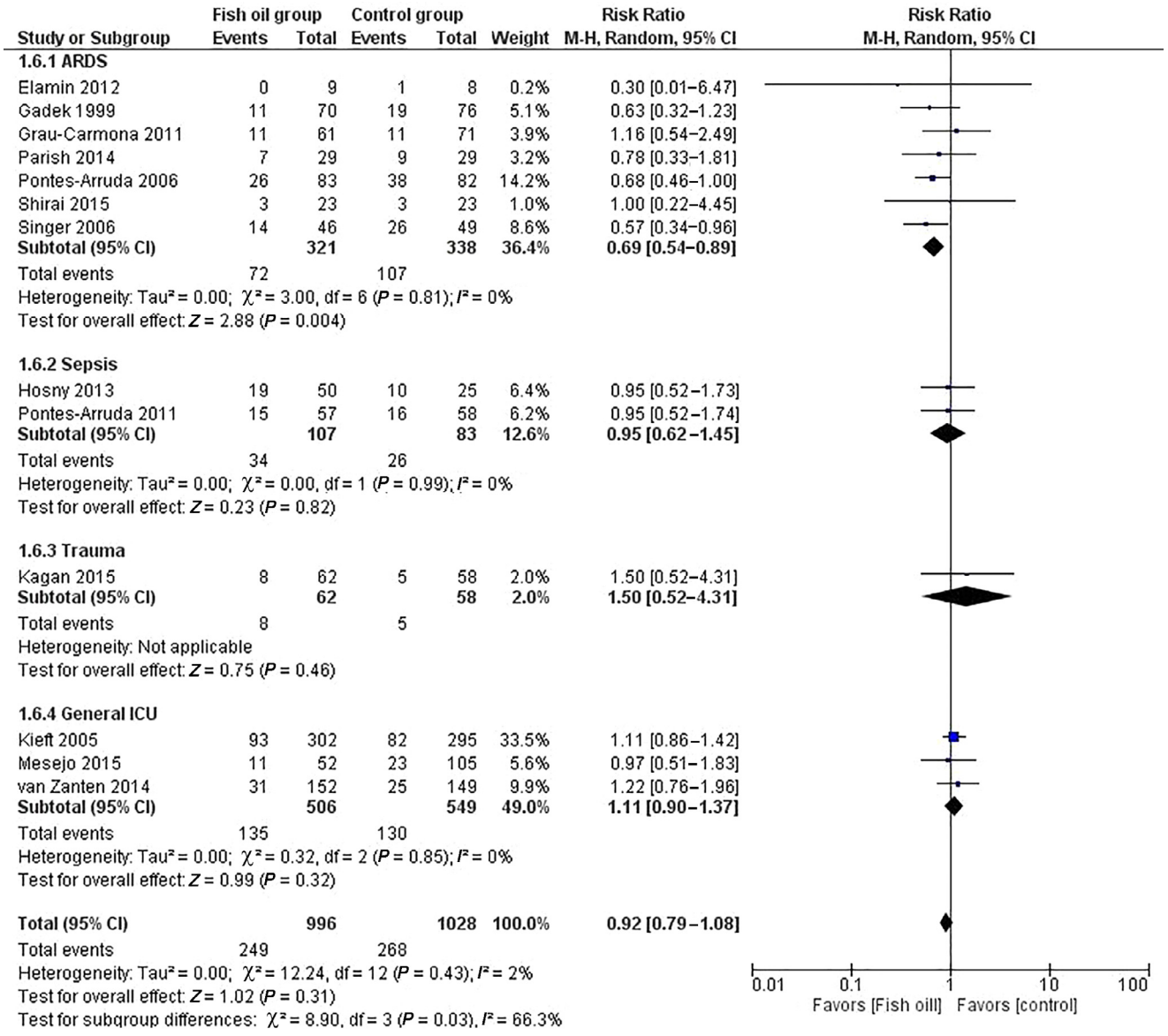

Fig. 3. Effects of fish oil supplementation on 28-d mortality in different intensive care unit populations. ARDS, acute respiratory depression syndrome; ICU, intensive care unit.

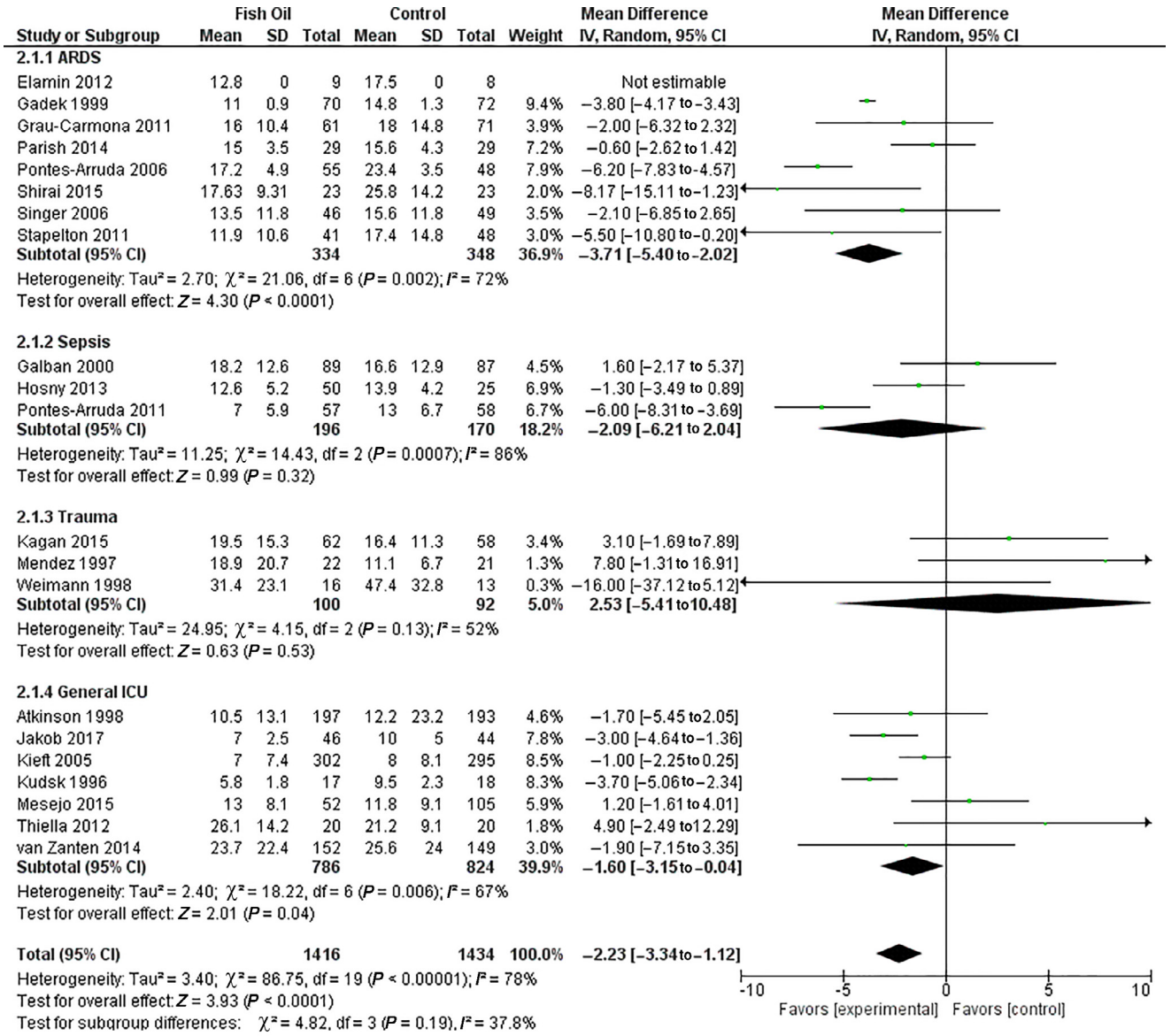

Fig. 4. The effects of fish oil supplementation on ICU length of stay in different ICU populations. ARDS, acute respiratory depression syndrome; ICU, intensive care unit.

difference was observed between AEs in patients with and without ω-3 supplementation (RR, 1.04; 95% CI, 0.96–1.13; $P = 0.34$; see Fig. 5 in Koekkoek et al. [73]). Tolerability of ω-3 was assessed by incidence of nausea and vomiting, dyspepsia, high gastric residual volume, aspiration, diarrhea, constipation, abdominal distention, ileus, pancreatitis, calories delivered, tube replacement rates, achievement of feeding target, triacylglycerol levels, prokinetics use, and overall gastrointestinal complications (see Table 3 in Koekkoek et al. [73]). No significant differences were observed between groups.

Discussion

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

Three recent meta-analysis evaluated the effects of enteral FO supplementation specifically in patients with ARDS [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 FO in critically ill patients [7]. They concluded that although no significant effects on mortality were found, FO-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 FO 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

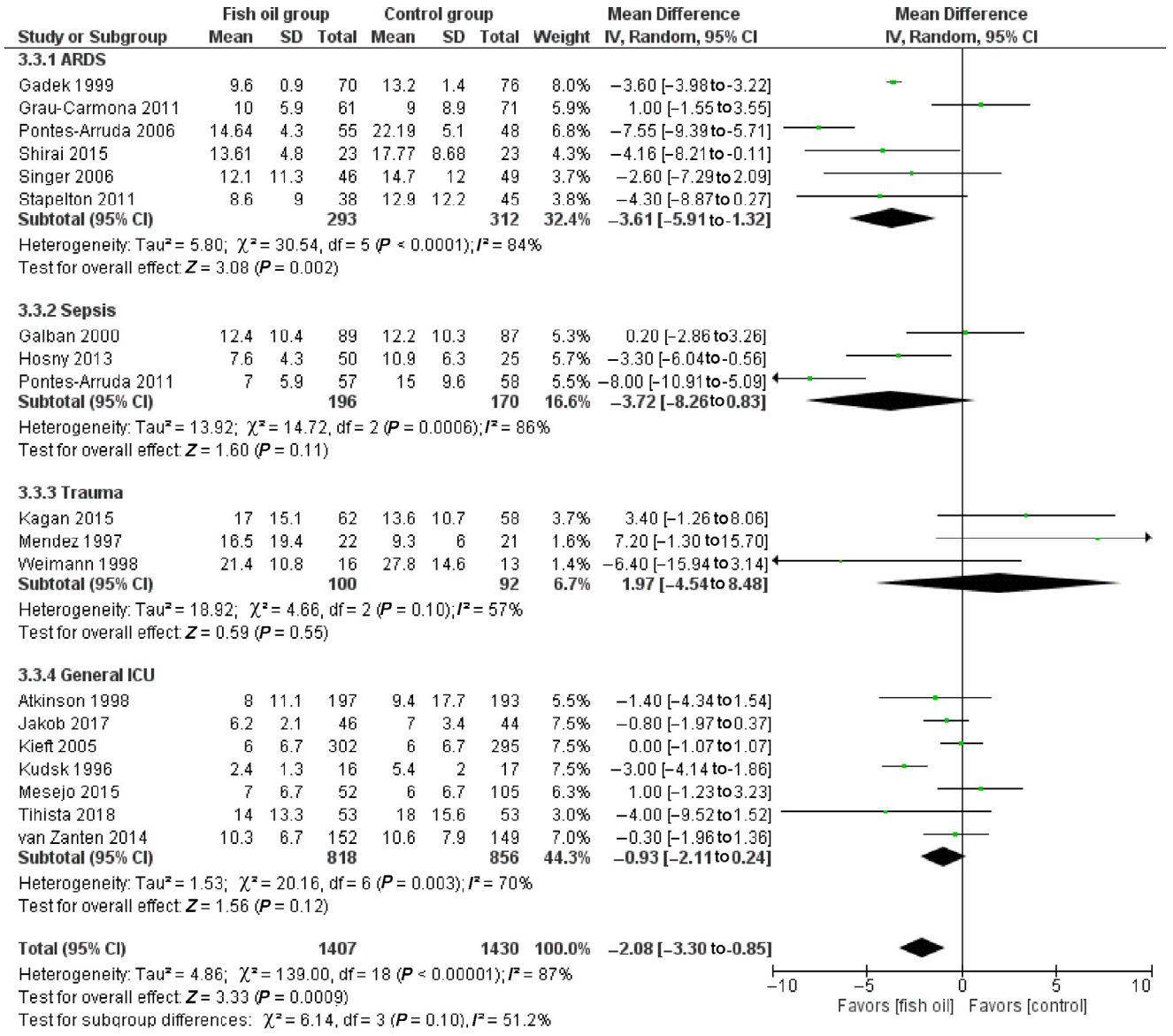

Fig. 5. The effects of fish oil supplementation on ventilation duration in different intensive care unit populations. ARDS, acute respiratory depression syndrome; ICU, intensive care unit.

FO 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 FO 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 versus enteral, continuous versus bolus, FO as a component of nutrition versus a separate supplement), amount and composition of the (par)enteral nutrition studied, and 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 FO have been established in multiple studies. Downregulation of proinflammatory 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 FO supplemented in clinical trials led to a significant increase in EPA and DHA plasma levels, which was associated with a significant reduction in interleukin-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 FO and the induction of an anti-inflammatory effect are not a problem. The consequently reported immunologic response to FO supplementation may, however, be the key to the differences in clinical outcomes found in individual trials [75–87]. The (patho) physiological immunologic 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 immunologic 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]. Although the antiinflammatory effects of FO supplementation may be beneficial during hyperinflammation, it also may be potentially harmful in case of pathophysiological immunosuppression. This may explain why in a post hoc analysis of the Metaplus trial, increases of plasma (EPA +DHA)/long-chain polyunsaturated fatty acid ratios from baseline to day 4 were associated with increased adjusted mortality risk at 6 mo, independent of baseline levels in the predefined subgroup of medical patients. The exposure of the FO supplementation in this study was long (median 12 d) and may have aggravated an immunosuppressed phenotype [38].

In addition, it may be further illustrated by the differences in clinical outcome effects between old and new studies. Although not significantly different, a marked trend toward better mortality outcome was observed in earlier studies, whereas no effect was seen in recent studies. When calculating the placebo group mortality, large differences were found (32.9% in studies before 2010, 19.6% in studies after 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 that may influence the outcomes. These include differences in control feeds used, additional immunomodulatory contents (i.e., antioxidants and arginine or glutamine), and dose and timing of FO 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 ω-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. Because they were reported in different manners it was not possible to analyze them systematically. EPA and DHA levels are reported in Table 1 in Koekkoek et al. [73].

Conclusions

Based on the results of this meta-analysis, enteral FO 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 patients with ARDS; however, results are based on low-quality studies. Therefore, enteral FO feeds may be considered in patients with ARDS. Further research should focus on the relation between the individual critically ill patient's immune response, the administration of FO, and clinical outcomes.

Supplementary materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.nut.2018.07.013.

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