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# Systematic review of preoperative n-3 fatty acids in major gastrointestinal surgery

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## ABSTRACT

**Objectives** Perioperative nutrition aims to replenish nutritional stores before surgery and reduce postoperative complications. 'Immunonutrition' (including omega-3 fatty acids) may modulate the immune system and attenuate the postoperative inflammatory response. Hitherto, immunonutrition has overwhelmingly been administered in the postoperative period—however, this may be too late to provide benefit.

**Design** A systematic literature search using MEDLINE and EMBASE for randomized controlled trials (RCTs).

**Setting** Perioperative major gastrointestinal surgery.

**Participants** Patients undergoing major gastrointestinal surgery.

**Interventions** Omega-3 fatty acid supplementation commenced in the preoperative period, with or without continuation into postoperative period.

**Main outcome measures** The effect of preoperative omega-3 fatty acids on inflammatory response and clinical outcomes.

**Results** 833 studies were identified. After applying inclusion and exclusion criteria, 12 RCTs, involving 1456 randomized patients, were included. Ten articles exclusively enrolled patients with cancer. Seven studies used a combination of EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) as the intervention and five studies used EPA alone. Eight out of 12 studies continued preoperative nutritional support into the postoperative period.

Of the nine studies reporting mortality, no difference was seen. Duration of hospitalisation ranged from 4.5 to 18 days with intervention and 3.5 to 23.5 days with control. Omega-3 fatty acids had no effect on postoperative C-reactive protein and the effect on cytokines (including tumor necrosis factor-α, interleukin (IL)-6 and IL-10) was inconsistent. Ten of the 12 studies had low risk of bias, with one study having moderate bias from allocation and blinding.

**Conclusions** There is insufficient evidence to support routine preoperative omega-3 fatty acid supplementation for major gastrointestinal surgery, even when this is continued after surgery.

**PROSPERO registration number** CRD42018108333.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immunonutrition can comprise a range of micronutrients, that may include the n-3 fatty acids—eicosapentaenoic acid and docosahexaenoic acid.
⇒ Early clinical studies suggested that postoperatively delivered immunonutrition may attenuate inflammation.
⇒ There has been no evaluation of the effect of preoperatively delivered n-3 fatty acids, independent of other components of immunonutrition.

### WHAT THIS STUDY ADDS

⇒ For patients undergoing gastrointestinal surgery, we found no benefit from the provision of preoperative n-3 fatty acids in modulating the postoperative inflammatory response.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There is insufficient evidence to support routine preoperative omega-3 fatty acid supplementation for major gastrointestinal surgery.

## INTRODUCTION

Major gastrointestinal surgery results in postoperative catabolism. The aim of preoperative nutritional intervention is to optimize nutritional stores before major surgery, to preempt and mitigate postoperative catabolism. Immunonutrition may add to this by specific immunomodulatory effects of nutrients, such as: arginine, glutamine, omega-3 (or n-3) fatty acids, and nucleotides. These may attenuate the postoperative inflammatory response. Analyses of therapeutic effects of immunonutrition are hampered by the inability to discern which nutrients (if any) provide benefit. The very long chain n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are readily incorporated into tissues leading to decreased production of proinflammatory mediators, by interference with arachidonic acid metabolism.[1] Fish oil is a rich source of DHA and EPA and early clinical studies suggested that this may attenuate inflammation.[2 3] In particular, EPA has been shown to modulate the

proinflammatory nuclear factor kappa B (NF-κB), and thereby reduce myocellular inflammation.[4 5]

The inflammatory cascade is a key mediator in the myogenic response to muscle damage. Inflammatory cytokines (such as tumor necrosis factor (TNF)-α, interleukin (IL)-6) can inhibit muscle regeneration and trigger muscle wasting.[6] The sequelae of acute inflammation are lower muscle strength and subsequent higher dependency for activities of daily living.[7]

A decade ago, two meta-analyses reported on combinations of immunonutrients given preoperatively. These demonstrated reductions in postoperative infection and length of stay but heterogeneity of trial design, and subsequent change in perioperative care (such as Enhanced Recovery After Surgery (ERAS)), makes broader interpretation challenging.[8 9] There has been no evaluation of the effect of pre-operative n-3 fatty acids, independent of other components of immunonutrition.

The purpose of this systematic review is to determine the effect of preoperative n-3 fatty acids on the inflammatory response and clinical outcomes after major gastrointestinal surgery, in the modern era.

## METHODS

A systematic review of the literature was performed according to Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) recommendations. The protocol for this systematic review was registered with the PROSPERO database. The study idea was discussed at the University of Surrey Clinical Academic Group. This included members of the public, and allowed for the perspectives and experiences of patients and the public in the research process.

### Search strategy

Electronic databases MEDLINE (1946–November 1, 2020) and EMBASE (1947–November 1, 2020) were searched. The search was restricted to English language and included three search term categories: (1) type of intervention (n-3 fatty acids), (2) timing of intervention and (3) type of surgery. Both thesaurus terms and text words (ie, words or phrases appearing in the title or abstract of the references) were identified for each concept. The search strategy is provided in online supplemental appendix figure S1. In addition, further studies were identified by snowballing and reverse snowballing.

### Inclusion and exclusion criteria

Studies were included in the review if they met the following criteria: (1) adult patients undergoing elective abdominal surgery, (2) nutritional intervention involving n-3 fatty acids, (3) preoperative commencement of the intervention (with or without continuation into the postoperative phase), (4) published in English, (5) human studies and (6) peer-reviewed journals. Studies were excluded if: (1) they involved patients undergoing chemotherapy or cardiac, bariatric, vascular, urological, gynaecological or transplant surgical procedures—in order to focus on patients undergoing gastrointestinal resections; (2) the intervention did not include a preoperative component; (3) the intervention used specialized immunonutrition products (nutritional supplements enriched with a combination of immunonutrients such as arginine, glutamine, nucleotides and antioxidants)—therefore studies incorporating products such as IMPACT were excluded to enhance homogeneity; (4) the study design was not a prospective randomized controlled trial (RCT); (5) full-text articles were not available, for example, conference abstracts only.

### Outcome measures

The primary outcome of interest was the postoperative inflammatory response, and immune function. Other outcome measures were all-cause mortality, postoperative complication rates, hospital and intensive therapy unit duration of stay, and preservation of lean body mass. We excluded studies where the primary outcome comprised cytological data, for example, cellular incorporation of fatty acids or proliferation indices, as opposed to clinical outcomes and/or the inflammatory response.

### Study selection and data extraction

Titles and abstracts of articles were screened by two independent reviewers (JG and DW). Articles that were irrelevant were excluded. Full-text articles were then screened against the inclusion and exclusion criteria. Discrepancies were resolved by discussion and consensus with a third author (MBW). Data were then extracted independently from the articles into a standardized data collection form. Study characteristics of interest included: country, year, study design, blinding, randomization method and outcome measures. The following participant characteristics were recorded if available: type of gastrointestinal surgery, number of patients, group sizes, sex, age and body mass index. In addition to data regarding relevant outcomes, intervention characteristics including timing, duration, dose of n-3 fatty acids, control formulation used, and route of administration were collected to evaluate methodological heterogeneity.

### Assessment of risk of bias

We used the Cochrane Risk of Bias Tool.[10] This employs a methodological component-based approach consisting of six items: (1) appropriate random sequence generation, (2) allocation concealment, (3) blinding, (4) incomplete outcome data, (5) selective outcome reporting, and (6) any other sources of bias. Two authors (JG and DW) independently assessed included studies for risk of bias. Any discrepancies were resolved by discussion and consensus.

## RESULTS

### Literature search

The MEDLINE and EMBASE searches resulted in 827 articles (figure 1). Six additional articles were identified from

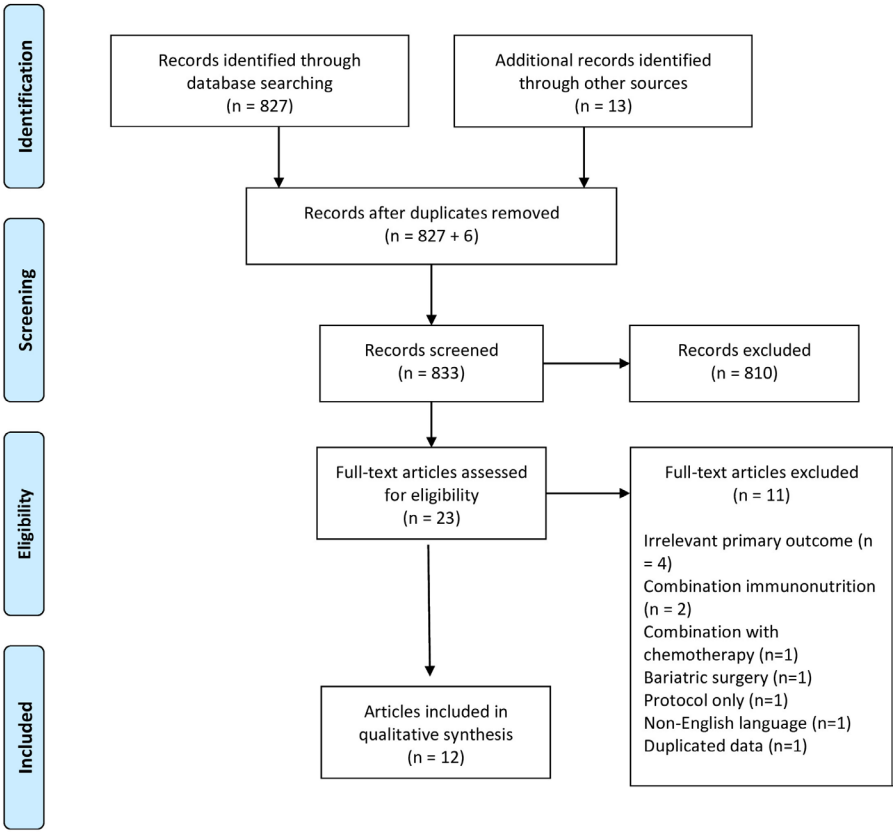


**Figure 1** PRISMA (Preferred Reporting of Systematic Reviews and Meta-Analyses) flowchart.

manual search, making a total of 833. After screening of titles and abstracts, 810 articles were excluded. The full-text articles of the remaining 23 studies were retrieved and reviewed.[11–33] Four studies were then excluded as the primary outcomes were outside the scope of interest.[18 20 25 28] Two studies were excluded because the intervention was combination immunonutrients,[27 32] one was a protocol paper,[12] one evaluated chemotherapy with omega-3,[11] one paper in Spanish language,[15] one paper included patients undergoing bariatric surgery[16] and one[23] reported on patients included in a (later) manuscript.[13]

Therefore, 12 full-text articles met selection criteria and were included.[13 14 17 19 21 22 24 26 29–31 33] Two papers reported on the same cohort of patients; of these, one paper focused on clinical outcomes[30] while the other focused on inflammatory markers.[29] We have included these two papers for evaluation of the separately reported effects.

## Study characteristics

The key characteristics of the 12 articles are shown (table 1, online supplemental appendix table S2). Nine were European studies,[17 21 22 24 26 29–31 33] one South American,[19] two from Japan.[13 14] Ten were published in the last decade[13 14 17 19 21 22 24 29–31]; the oldest in 2002.[33] In 10 papers, patients and investigators were blinded[14 17 19 21 22 24 26 29–31]; one study was open-label[13] and one lacked information of blinding.[33]

## Participants

Ten articles exclusively enrolled patients with cancer (online supplemental appendix table S2).[13 14 17 19 22 26 27 29–31] Papers by Sorensen *et al*,[29 30] and by Bakker *et al*[17] and Hossain *et al*[22] investigated patients with colorectal cancer. Two studies reported on patients with esophageal cancer.[21 26] One study enrolled patients with resectable esophageal or gastric cancer.[31] One study involved patients with gastric or colon cancer.[19] One study was of solely gastric cancer[13]; one of periampullary cancer.[14] One study involved partial liver resection—of which approximately 90% was due to the presence of tumor.[24] One study differed by including patients undergoing extended surgical interventions (over 3 hours duration) on either stomach or pancreas; therefore, this may have included patients with benign pathology.[33] Most studies involved patients either undergoing open surgery,[21 22 26 33] or mixed open and laparoscopic,[13 19 24 29 30] although these latter trials consisted mostly (~90%) of open procedures. One study was almost entirely composed of laparoscopic surgery.[17]

In total, our review includes 1456 patients randomized to trials of preoperative initiation of n-3 fatty acids before gastrointestinal surgery (online supplemental appendix table S2). After allowing for drop-outs and additional groups (comprising an intervention other than n-3), 635 patients received an intervention and 628 controls. As two papers used the same patient cohort,[29 30] numbers were

Table 1 Study characteristics

| Study | Country | Year | Blinding* | Randomization method | Category of primary outcome | Primary outcomes |
|---|---|---|---|---|---|---|
| Weiss *et al*[33] | Germany | 2002 | NR | NR | Inflammatory and immune response | IL-6 release and HLA-DR expression |
| Ryan *et al*[26] | Ireland | 2009 | Double | Statistician | Lean body mass | Body composition |
| Sultan *et al*[31] | UK | 2012 | Double | Computer generated block randomization | Postoperative clinical outcomes | Infectious complications |
| Sorensen *et al*[30] | Denmark | 2013 | Double | Sealed non-transparent envelopes | Postoperative clinical outcomes | Infectious and non-infectious complications within 30 days of surgery |
| de Miranda Torrinhas *et al*[19] | Brazil | 2013 | Double | Computer generated block randomization | Postoperative clinical outcomes | Postoperative complications |
| Sorensen *et al*[29] | Denmark | 2014 | Double | Sealed non-transparent envelopes | Inflammatory and immune response | Leukotriene levels |
| Healy *et al*[21] | Ireland | 2017 | Double | Computer generated block randomization | Lean body mass | Body composition |
| Aoyama *et al*[13] | Japan | 2019 | Open label | NR | Lean body mass | Body composition |
| Ashida *et al*[14] | Japan | 2019 | Double | NR | Inflammatory and immune response | IL-6 |
| Bakker *et al*[17] | Netherlands | 2020 | Double | Computer generated 1:1 randomization | Inflammatory and immune response | Ex-vivo LPS stimulated IL-6 |
| Hossain *et al*[22] | UK | 2020 | Double | Computer generated 1:1 randomization | Inflammatory and immune response<br>Lean body mass | Muscle protein expression of NF-kB<br>Body composition |
| Linecker *et al*[24] | Romania, Russia, Switzerland | 2020 | Double | Computer generated block randomization | Postoperative clinical outcomes | Postoperative complications |

HLA-DR: Human Leukocyte Antigen-DR isotope
*All studies were parallel design.
†
‡
IL-6, interleukin-6; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa B; NR, not reported.

counted from one paper.[30] In the control groups, mean age ranged from 60 to 71 years and in the intervention groups, 57 to 69 years. There were no significant differences in gender between groups, except in one study where the male:female ratio was greater in the intervention group.[26] Body mass index (BMI) was no different between groups in eight studies[13 14 17 21 26 29–31]; in one study median BMI was 24 kg/m$^2$ (IQR 22–27 kg/m$^2$) in intervention groups versus 25 kg/m$^2$ (IQR 23–28 kg/m$^2$) in control (p=0.042)[24]; three studies did not provide further detail on BMI.[19 22 33]

## Intervention

Seven studies used a combination of EPA and DHA (table 2).[17 19 24 29–31 33] The dose of EPA ranged from 1.25 g to ~4.0 g; DHA dose from 1.0 g/day to ~4.0 g/day. Exact doses used in parenteral and tube-delivered enteral studies were difficult to quantify, being dependent on body weight.[17 19 24] Five studies used EPA alone (2.0 to 2.2 g/day orally).[13 14 21 22 26] In one study, the enteral tube-delivered dose gradually increased after surgery, reaching a maximum during postoperative days 4–7.[31]

There was significant heterogeneity in timing, duration, and route of administration. Four studies involved solely preoperative delivery.[14 19 24 29] The remainder included extension of provision into the postoperative period. The duration of preoperative intervention ranged from 1 to 7 days. Postoperative intervention ranged from 1 to 78 days.

N-3 fatty acids were administered using an oral solution by Sorensen *et al*.[29 30] Parenteral delivery was used in four studies[17 19 24 33]; in two of these, it was exclusively in the preoperative period.[19 24] The remaining studies employed enteral delivery,[31] oral alone,[13 14 22] or using a combination of oral and tube feeding perioperatively.[21 26] All trials used a control group. Six employed an isocaloric and isonitrogenous control without n-3 fatty acids; these were all enteral studies.[21 22 26 29–31] Two groups administered ProSure (Abbott Japan, Tokyo, Japan) containing DPA plus 600 kcal.[13 14] One trial involved a parenteral lipid infusion containing n-3 fatty acids and the control was an identical lipid infusion minus n-3 fatty acids.[33] Bakker *et al*[17] and Linecker *et al*[24] each used an infusion

**Table 2** Composition of intervention and control supplements

| | Content and timing | Intervention dose | Control | Route of administration |
|---|---|---|---|---|
| Weiss *et al*[33] | EPA and DHA (Omegaven) 1 day preop and day 5 postop | Per 10 g of fat: EPA 1.25–2.82 g DHA 1.44–3.09 g | Identical perioperative nutrition infusion protocol (without n-3FA) | Parenteral (100 mL Omegaven) |
| Ryan *et al*[26] | EPA (240 mL BD Prosure) 5 days preop to day 21 postop | 2.2 g EPA | Iso-caloric iso-nitrogenous standard nutritional feed (without n-3FA) | Oral (200 mL BD) / jejunostomy (500 mL feed) |
| Sultan *et al*[31] | EPA and DHA (Oxepa) 7 days preop to day 7 postop | EPA 0.51 g per 100 mL; daily target of 675 mL preop; 3.4 g EPA and 1.4 g DHA. Variable postop to 1200 mL/day—therefore 6.12 g EPA and 2.64 DHA | Two groups:<br>1. Standard enteral nutrition (iso-caloric iso-nitrogenous).<br>2. 'Control': no preop supplementation, postop enteral nutrition—hypo-caloric and hypo-nitrogenous. | Enteral (Oxepa) |
| Sorensen *et al*[30] | EPA and DHA (Supportan 200 mL BD) 7 days preop to day 7 postop | 2.0 g EPA and 1.0 g DHA | Iso-caloric iso-nitrogenous standard nutritional feed (without n-3FA) | Oral (200 mL BD) |
| de Miranda Torrinhas *et al*[19] | EPA and DHA (Omegaven) 3 days preop | 0.2 g fat / kg BW for 6 hours daily per 10 g of fat: EPA 1.25–2.82 g; DHA 1.44–3.09 g | Parenteral lipid emulsion (MCT/LCT) rich in medium-chain triglycerides (Lipovenos 10%) | Parenteral (0.2 g fat/kg for 6 hours daily) |
| Sorensen *et al*[29] | EPA and DHA (Supportan 200 mL BD) 7 days preop | 2.0 g EPA and 1.0 g DHA | Iso-caloric iso-nitrogenous standard nutritional feed (without n-3FA) | Oral (200 mL BD) |
| Healy *et al*[21] | EPA (240 mL BD Prosure) 5 days preop to 1 month postop | 2.2 g EPA | Iso-caloric iso-nitrogenous standard nutritional feed (without n-3FA) (Lipovenos 10%) | Oral / jejunostomy (500 mL feed) |
| Aoyama *et al*[13] | EPA (Prosure) 7 days preop to 21 days postop feeding | 2.2 g/day of EPA | No preoperative supplementation | Oral |
| Ashida *et al* [14] | EPA (Prosure) 7 days preop | 2.0 g/day of EPA | Isonitrogenous standard nutrition (600 kcal/day) without EPA (Procure Z) | Oral |
| Bakker *et al*[17] | EPA and DHA (Omegaven) 1 day preop and 1 day postop | 0.2 g/kg/day (2 mL/kg infusion) | Isovolumetric 0.9% saline | Intravenous |
| Hossain *et al*[22] | 500 mg capsules of EPA (Minami Nutrition, Belgium) 5 days preop to 21 days postop | 500 mg EPA three times per day | Placebo capsules three times per day (Wassen Nutrition, UK) (EPA 500 mg, DHA 0 mg, other omega-3s 27 mg, omega-6 fatty acids 0 mg | Oral |
| Linecker *et al*[24] | EPA and DHA (Omegaven) 100 mL 1 day preop and on day of surgery | Omegaven (100 mL) contains 10 g of highly refined fish oil. Per 10 g of fat: EPA 1.25–2.82 g; DHA 1.44–3.09 g | Isovolumetric 0.9% saline | Intravenous |

.BD, two times per day; BW, body weight; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; n-3FA, omega-3 fatty acids.

of Omegaven (470 kJ per 100 mL) with saline control. The other parenteral study compared a lipid emulsion containing n-3 fatty acids against a control lipid emulsion, rich in medium-chain triglycerides.[19]

### Comparator group

All studies employed a parallel design. The trial by Sultan *et al* involved three arms, the intervention group (receiving n-3 fatty acids); an arm receiving preoperative standard enteral nutrition (Ensure Plus, Abbott Nutrition) and a control group that received no preoperative supplementation.[31]

### Outcomes

Eight papers evaluated postoperative clinical outcomes.[13 14 17 19 22 24 30 31] Five used inflammatory and immune response as primary endpoints[14 17 22 29 33] and four used preservation of lean body mass as the primary outcome.[13 21 22 29] Quantitative synthesis (meta-analysis) could not be undertaken due to heterogeneity of study designs and outcomes and number of studies capable of analysis, per outcome.

#### Postoperative inflammatory response

Ten studies included inflammatory markers.[14 17 19 21 22 26 29–31 33] Six studies reported postoperative C-reactive protein levels[17 19 21 30 31 33] (table 3), with no difference found. Seven studies measured cytokine levels during the perioperative period.[14 17 19 21 26 29 33] Results of cytokine analysis were inconsistent. For example, IL-6 levels (a proinflammatory cytokine) were significantly lower in intervention groups in two studies[19 33] but not in Bakker *et al*,[17] despite higher leukocyte membrane EPA and DHA content after each intravenous infusion. However, IL-10 (considered anti-inflammatory) was lower in the intervention groups in two studies[19 26] but with no difference in Bakker *et al*.[17] Ryan *et al* found TNFα and IL-10 levels to be lower in the EPA group.[26] Ashida *et al*[14] found no differences for serum IL-1β or TNF-α between control and intervention. Furthermore, in a larger RCT (n=191), no difference was found in: IL-6, IL-8, IL-10, IL-4, IL-17, TNF-α, interferon (IFN)-γ, transforming growth factor (TGF)-β at any postoperative time point.[21] In addition, Hossain *et al*[22] showed no difference in muscle protein expression of NF-kB, between EPA and placebo groups when adjusting for baseline values.

The effect of 7 days of oral EPA and DHA on plasma level of leukotrienes on the day of surgery was investigated by Sorensen *et al*.[29] Leukotrienes are a subgroup within a larger family of signaling molecules known as eicosanoids; other subgroups include prostaglandins and thromboxanes. Leukotriene B4 (LTB4), produced from arachidonic acid (an n-6 FA), has potent proinflammatory effects. In this large RCT of 129 patients, levels of LTB4 were significantly lower in the n-3 FA-treated group (p<0.01). This may occur by replacement of n-6 FA with n-3 FA in membranes of immunologically active cells.[29]

#### Postoperative immune cell response

Four studies reported the cellular immune response[14 19 31 33] with three evaluating HLA-DR monocyte expression—representing immune competence.[19 31 33] Parenteral n-3 fatty acids produced higher levels of monocyte HLA-DR expression in the intervention arms. This was not supported by the largest RCT involving enteral nutrition,[31] in which no difference was observed in HLA-DR expression on monocytes. Ashida *et al* found no difference in the CD4/CD8 ratio with preoperative DPA supplementation.[14] Two studies investigated leukocyte oxidative burst activity,[19 33] a cellular reaction that occurs during phagocytosis. Again, results were conflicting. Higher levels of oxidative burst were found in the intervention group with one study,[19] but not by Weiss *et al*.[33]

#### Postoperative complications

Complication data were reported as: 'any complications within 30 days of surgery', 'in-hospital postoperative complications', 'any complication' and 'infective complications'. The time frame for postoperative complications varied from the index admission to 30-day complication rate, and were evaluated using Buzby,[34] Bozzetti,[35] or Clavien-Dindo[36] criteria. Four studies identified postoperative complication rate as their primary outcome.[19 24 30 33] The remaining studies listed postoperative complication rates as secondary outcomes. Bakker *et al*[17] found significantly more patients with urinary tract infection (p=0.030), anastomotic leakage (p=0.030), and systemic inflammatory response syndrome (SIRS; p=0.036) in those treated with n-3 fatty acids. No other study showed differences in postoperative complication rates (table 3).

#### Length of hospital stay and mortality

Mean length of hospital stay (LoS) was reported in six studies and ranged from 4.5 to 18 days with intervention arm and from 3.5 to 23.5 days in controls.[17 19 22 24 31 33] Sorensen *et al* subdivided length of stay data into two categories: LoS<5 (expected) and LoS>10 days (extended).[30] In six studies, there was no difference in LoS.[17 19 22 24 30 31] However, in the smallest study (n=24), Weiss *et al* reported a shorter LoS (17.8 days with n-3 fatty acids vs 23.5 days with control; p<0.05).[33] No difference in mortality was found in all nine studies reporting this outcome.[13 14 17 24 26 29–31 33]

#### Lean body mass

Four studies reported effect on lean body mass (LBM)[13 21 22 26] (table 3), using bioelectrical impedance,[13 21 26] or dual-energy X-ray absorptiometry.[22] Hossain *et al*[22] found no difference in whole-body LBM following colorectal cancer resection, when adjusting for baseline values (mean difference 704.77 g; 95% CI −1045.6 g to −2455.13 g; p=0.42). Similarly, in Aoyama *et al*,[13] median loss of LBM was 6.74% (range −3.91% to 20.27%) in the standard-diet group and 6.89% (range −5.11% to 20.04%) with EPA, 1 month after surgery (p=0.794). Ryan *et al*, was a single-centre, proof of concept study and involved 53 patients. There was no significant increment in LBM

**Table 3** Outcomes of clinical trials

| Study | Omega-3 fatty acid levels | | | Results | | |
|---|---|---|---|---|---|---|
| | Baseline | Post-intervention | P value | Primary outcome | P value | Secondary outcomes |
| Weiss *et al*[33] | NR | NR | NR | Postoperative inflammatory and immune responses<br>▶ ↓IL-6.<br>▶ ↓Monocyte HLA-DR suppression.<br>▶ CRP / TNF-α / PCT.<br>▶ Respiratory burst activity of granulocytes. | P<0.05.<br>P<0.05.<br>*NS.*<br>*NS.* | ▶ Hospital LoS decreased with intervention (p<0.05).<br>▶ Mortality: NS.<br>▶ Postoperative complications: NS. |
| Ryan *et al*[26] | 0.3% EPA in cell membrane. | 1.7% EPA in cell membrane (POD7). | P=0.005; pre-intervention vs post-intervention status. | N-3 FA associated with preservation of lean body mass. | P<0.05. | ▶ Postoperative complications: NS.<br>▶ Mortality: NS.<br>▶ IL-6: NS.<br>▶ ↓IL-8, IL-10, TNFα in intervention group postop: p<0.05. |
| Sultan *et al*[31] | 0.05% EPA plasma FA.<br>0.18% DHA plasma FA. | 0.28% EPA plasma FA (1 day preop).<br>0.24% DHA plasma FA (1 day preop). | P=0.001; *vs* controls.<br>P=0.007; *vs* controls. | Infective complications. | *NS* | ▶ Plasma and lymphocyte n-3FA levels: increased in intervention.<br>▶ Morbidity, mortality=NS.<br>▶ Hospital LoS: p=0.701.<br>▶ ITU stay: p=0.569.<br>▶ Postop HLA-DR expression on monocytes or activated T cells: NS.<br>▶ Postop CRP: NS. |
| Sorensen *et al*[30] | NR | 2.10% EPA on day of surgery vs 0.54% (control).<br>1.61% DHA on day of surgery vs 1.31% (control). | P<0.001; intervention vs control on day of surgery. | 30-day postoperative complications (infectious and non-infectious). | *NS* | ▶ n-3FA in granulocytes (individual and total): ↑ in intervention.<br>▶ n-3FA (arachidonic acid): ↓ in intervention group.<br>▶ Hospital LoS: NS.<br>▶ ITU stay: NS.<br>▶ Re-admissions: NS.<br>▶ Mortality: NS.<br>▶ Postop CRP: NS. |
| de Miranda Torrinhas *et al*[19] | NR | NR | NR | Postoperative complications. | *NS* | ▶ ↓ Postop IL6, IL10 on POD6 in intervention : p<0.05.<br>▶ ↑ IL-10 on POD3 in intervention: p<0.05.<br>▶ ↑Leukocyte oxidative burst, neutrophil CD32 expression and HLA-DR expression on monocytes in intervention: p<0.05.<br>▶ Postop CRP, PGE2=*NS.*<br>▶ ITU stay: p=0.826.<br>▶ Hospital LoS: p=0.844. |
| Sorensen *et al*[29] | NR | 2.10% EPA on day of surgery vs 0.54% (control).<br>1.61% DHA on day of surgery vs 1.31% (control). | P<0.001; intervention vs control on day of surgery. | ▶ Decrease in LTB4 production.<br>Increase in LTB5 production.<br>▶ Increase in 5HEPE production. | P<0.05.<br>P<0.05.<br>P<0.05. | ▶ Postoperative complications: NS.<br>▶ Mortality: NS.<br>▶ Postop IL-8, IL-10, TNFα ↓ in intervention: p<0.05. |
| Healy *et al*[21] | NR | NR | NR | Lean body mass. | *NS* | ▶ Post-operative complications: NS.<br>▶ Inflammatory response: NS.<br>* *WCC, CRP, IL6, IL10, IL8, IL17, IL4, TNF, IFNg, TGFb* |
| Aoyama *et al*[13] | NR | NR | NR | Lean body mass. | *NS* | ▶ Postoperative complications: NS. |

Continued

**Table 3** Continued

| | Omega-3 fatty acid levels | | | Results | | |
|---|---|---|---|---|---|---|
| **Study** | **Baseline** | **Post-intervention** | **P value** | **Primary outcome** | **P value** | **Secondary outcomes** |
| Ashida *et al*[14] | NR | NR | EPA/AA ratios in the treatment group were higher than those in the control group on PODs 0, 1, and 4 ($p<0.01$). | Serum IL-6 on POD 0, 1, 4, 7, 14. | *NS* | ▶ Serum albumin, prealbumin, transferrin POD 0: NS.<br>▶ Serum IL-1β, TNF-α and CD4/8 T-lymphocyte balance on PODs 1, 4, 7, 14: NS.<br>▶ Incidence of postoperative infectious complications: NS. |
| Bakker *et al*[17] | EPA~0.35 mol%. DHA~1.4–1.5 mol%. | Membrane EPA higher at all time points. DHA increased after each infusion but normalised by 12 hours. | | Ex-vivo LPS-stimulated IL-6 production. | *Higher at POD1 with intervention ($p=0.014$).* | ▶ Inflammatory response (IL-6, IL-10, CRP): NS.<br>▶ Postoperative complications: NS. |
| Hossain *et al*[22] | NR | NR | NR | Muscle protein expression of NF-kB. | *NS* | ▶ Inflammatory response (WCC, temperature): NS.<br>▶ Length of stay: NS.<br>▶ Postoperative complications: NS. |
| Linecker *et al*[24] | NR | NR | NR | Postoperative complications. | *NS* | ▶ Length of stay: NS.<br>▶ ICU stay: NS.<br>▶ Surrogate laboratory parameters of safety (including ALT, AST): NS. |

*AA: arachidonic acid, ALT: alanine transaminase, AST: aspartate aminotransferase, 5HEPE: 5-hydroxyeicosapentaenoic scid, HLA-DR: Human Leukocyte Antigen-DR isotope, IFN: interferon, NS: non-significant, PCT: procalcitonin, POD: post-operative day, TGF: transforming growth factor, WCC: white cell count
CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ICU, intensive care unit; IL, interleukin; ITU, intensive therapy unit; LoS, length of stay; LPS, lipopolysaccharide; LTB4, leukotriene B4; n-3FA, omega-3 fatty acids; TNF, tumor necrosis factor.

between preoperative and day 21 postoperative with n-3 fatty acid supplementation.[26] Conversely, the control group lost 1.9±3.7 kg) (p=0.03). The same research group later published results from a larger multicenter RCT (N=191) with the primary endpoint being LBM 1 month post discharge.[21] Per-protocol analysis showed no difference in LBM. Loss of LBM was 3.7±8.7 kg (control) vs 5.6±12.1 kg (n-3 fatty acids) (p=0.355). Proof-of-concept was therefore not supported by the subsequent, larger RCT.

### Risk of bias

Selection bias: Ten of 12 papers provided adequate information for random sequence generation and allocation concealment[13 17 19 21 22 24 26 29–31] (online supplemental appendix table S3). Performance and detection bias: Ten studies were double blinded.[14 17 19 21 22 24 26 29–31] Attrition bias: Seven papers were at low risk of attrition bias.[13 19 21 22 29–31] Two studies did not provide a CONSORT (Consolidated Standards of Reporting Trials) diagram making it difficult to assess exclusions and drop-outs.[26 33] Reporting bias: Ten papers were at low risk of reporting bias.[13 17 21 22 24 26 29–31 37] Two studies used endpoints which were either not clearly defined or changed during the report.[19 33]

Overall risk of bias was generally low, with 10 papers deemed low risk in at least four domains.[13 17 19 21 22 24 26 29–31] One study was at moderately high risk of bias.[33] Regarding other sources of bias, two studies had significant differences between groups in terms of baseline characteristics.[19 26] Poor adherence in the postoperative period was an issue in two papers.[29 31] In five cases the authors received funding support or supplied with feeds ex gratia from nutritional companies that produce fish oil supplement.[17 19 26 29 30]

## DISCUSSION

This is the first systematic review to examine the specific impact of preoperative n-3 fatty acids on clinical and inflammatory outcomes in patients undergoing major gastrointestinal surgery. We found inconsistent evidence of modified biological response (inflammation, cellular immune function) but no evidence of clinical benefit.

Although systematic reviews and meta-analyses have suggested that immunonutrition can ameliorate postoperative outcomes,[37] these have usually been commenced postoperatively and involved a combination nutrition. Few have examined n-3 fatty acids specifically.

There was no reduction in postoperative complications, despite considerable variation in route of administration, duration and timing of administration, and demographics of the study population. Poor compliance may limit interpretation of trial data.[31] Ryan *et al* measured pre-intervention and post-intervention n-3 FA status and demonstrated significantly increased levels of cell membrane incorporation 7 days postoperatively,[26] signifying good protocol adherence. One RCT achieved very good compliance (96%) but nevertheless, no difference was found in total number of complications.[21]

The effect on inflammatory markers and immune response was also inconsistent across studies. This could be attributed to heterogeneity of interventions, populations, choice of markers and sampling time points. Sorensen *et al* found significantly lower levels of the proinflammatory eicosanoid LTB4, on the day of surgery.[29] However, there was no data for evolution of LTB4 levels in the postoperative course. IL-6, a key proinflammatory cytokine, was measured in six trials.[14 17 19 21 26 33] Although no difference was seen in three studies,[14 21 26] IL-6 levels were significantly lower when n-3 was administered parenterally.[19 33] Bakker *et al* found that ex vivo IL-6 after LPS stimulation was significantly higher in the n-3 Polyunsaturated fatty acid (PUFA) group at the first day after surgery (p=0.014), but not different at the second day after surgery (p=0.467).[17]

The only other cytokine to show any significant difference between groups among the enteral studies was IL-8[26] but this was no longer apparent in the subsequent, larger RCT.[21] De Miranda Torrinhas *et al* acknowledged baseline differences in IL-6 and IL-10 between groups.[19] However, they argued that this was unlikely to have had an impact on results as levels inverted by the third postoperative day.[19] Higher levels of monocyte HLA-DR expression (a measure of immune response) were seen in the two parenteral studies but not in the enteral study by Sultan *et al*.[31] Given the conflicting results between studies, no firm conclusions could be made regarding effect on inflammatory and immune response.

Malnourished patients might receive greater benefit from immunonutrition.[38 39] In Sorensen's study fewer than 20% of the sample had lost more than 5% of body weight at inclusion, therefore the proportion of well-nourished patients was high.[30] This could explain the lack of translation between effect on proinflammatory mediators and clinical outcomes. Another factor is bioavailability—dose, route and duration can all influence membrane incorporation of n-3 fatty acids. Dosage of n-3 fatty acids in the study by Weiss *et al*[33] was 1.25–2.82 g of EPA, and 1.44–3.09 g of DHA. In the study by de Miranda Torrinhas *et al*,[19] dose was body weight dependent; therefore, a 70 kg subject would receive between 1.75–3.95 g EPA and 2.02–4.33 g DHA. By comparison, the median dose of n-3 fatty acids delivered enterally was 2.2 g EPA and 1.0 g DHA. Small sample size of the parenteral studies raises the possibility of a type II statistical error.

Poor compliance may also contribute to a type II error.[31] The perioperative context in which these studies took place could also be important. Older studies are less likely to have occurred within an ERAS context. Existing ERAS protocols (without immunonutrition) reduce rates of postoperative infection.[40 41] The addition of immunonutrition to ERAS protocols may exert a relatively small additional effect.

One RCT from China has demonstrated that parenteral soybean, plus fish oil, given after gastrointestinal

cancer surgery reduced the incidence of SIRS and LoS, compared with intravenous soybean oil alone.[42] There was no significant reduction in other complications. This is the first study to demonstrate an improvement in outcomes with parenteral fish oil versus standard lipid emulsions. Of note, the infection rate in the control arms was high compared with Sorensen's and Sultan's data[30 31]—possibly explained by the absence of an ERAS protocol. Previous meta-analyses have suggested that to improve clinical outcomes, immunonutrition requires formulae containing both arginine and n-3 fatty acids.[43] There may be synergism between n-3 fatty acids and arginine.[44 45]Current European Society for Clinical Nutrition and Metabolism (ESPEN) and Aerican Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend combination immunonutrition, with both fish oil and arginine, for patients undergoing abdominal cancer surgery.[40 41]

Financial support from companies supplying n-3 fatty acids supplements introduced the possibility of external bias in most studies. There was heterogeneity involving surgical pathology and procedures. Upper gastrointestinal malignancies are more aggressive (compared with colonic cancers) with regards to impact on nutritional status and cachexia. This implies possible disparity across studies in terms of baseline nutritional status. Upper gastrointestinal resections also generate a larger postoperative stress response, particularly operations such as two-phase Ivor-Lewis procedures which involve an abdominal and thoracic phase.

The strengths of this study were the methodological quality of the review process: two investigators cross-checked data and evaluated study quality independently; in terms of the quality of the studies incorporated, the risk of bias assessment was 'reasonable'. All studies used appropriate controls to compare against the intervention. Furthermore, the majority were isocaloric and isonitrogenous.

A limitation is restriction of searches to English language publications. The presence of an ERAS pathway was not prespecified in the inclusion or exclusion criteria and neither was it specified in the reporting of the studies.

Several unanswered questions remain. Little is known about the minimum dose and duration required for incorporation preoperatively. Variance in adherence with nutritional regimes should be taken into consideration when planning studies—measurement of erythrocyte membrane incorporation of omega-3 fatty acids is possible, although required specialized equipment and is costly.

In conclusion, there is insufficient evidence to support routine preoperative n-3 fatty acid supplementation, as n-3 fatty acids did not reduce postoperative complications after major gastrointestinal surgery. The effect on inflammatory markers and immune response was inconsistent. Combination of omega-3 fatty acids with other immunonutrients may be necessary for clinical benefit.

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