Long-term effects of increasing omega-3, omega-6 and total polyunsaturated fats on inflammatory bowel disease and markers of inflammation: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Sarah M. Ajabnoor[1,2*], Gabrielle Thorpe[3**], Asmaa Abdelhamid[1**], and Lee Hooper[1**]

[1] *Norwich Medical School, University of East Anglia, Norwich Research Park, UK.*

[2] *Clinical Nutrition Department, Faculty of Applied Medical Sciences, Jeddah, King Abdulaziz University, Saudi Arabia*

[3] *School of Health Sciences, University of East Anglia, Norwich Research Park, UK.*

[*] *Corresponding author: Sarah M. Ajabnoor, Clinical Nutrition Department, Faculty of Applied Medical Sciences, King Abdulaziz University, P.O. Box 80324, Jeddah, 21589, Kingdome of Saudi Arabia, smajabnoor@kau.edu.sa, ORCID ID: 0000-0003-0996-1484.*

[**] *Gabrielle Thorpe ORCID ID: 0000-0002-0639-4229, Asmaa Abdelhamid ORCID ID: 0000-0002-9897-5433, Lee Hooper ORCID ID: 0000-0002-7904-3331.*

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Abstract

Background & Aims: Effects of long-chain omega-3 (LCn3) and omega-6 fatty acids on prevention and treatment of inflammatory bowel diseases (IBD, including Crohn's Disease, CD and ulcerative colitis, UC), and inflammation are unclear. We systematically reviewed long-term effects of omega-3, omega-6 and total polyunsaturated fats (PUFA) on IBD diagnosis, relapse, severity, pharmacotherapy, quality of life and key inflammatory markers.

Methods: We searched Medline, Embase, Cochrane CENTRAL, and trials registries, including RCTs in adults with or without IBD comparing higher with lower omega-3, omega-6 and/or total PUFA intake for ≥24 weeks that assessed IBD-specific outcomes or inflammatory biomarkers.

Results: We included 83 RCTs (41,751 participants), of which 13 recruited participants with IBD. Increasing LCn3 may reduce risk of IBD relapse (RR 0.85, 95% CI 0.72 to 1.01) and IBD worsening (RR 0.85, 95% CI 0.71 to 1.03), and reduce erythrocyte sedimentation rate (ESR, SMD -0.23, 95% CI -0.44 to -0.01), but may increase IBD diagnosis risk (RR 1.10, 95% CI 0.63 to 1.92), and faecal calprotectin, a specific inflammatory marker for IBD (MD 16.1μg/g, 95% CI -37.6 to 69.8, all low-quality evidence). Outcomes for alpha-linolenic acid, omega-6 and total PUFA were sparse, but suggested little or no effect where data were available.

Conclusion: This is the most comprehensive meta-analysis of RCTs investigating long-term effects of omega-3, omega-6 and total PUFA on IBD and inflammatory markers. Our findings suggest that supplementation with PUFAs has little or no effect on prevention or treatment of IBD and provides little support for modification of long-term inflammatory status.

Keywords: Inflammatory bowel diseases; Dietary fats, unsaturated; Fatty acids, omega-3; Fatty acids, omega-6; Alpha-linolenic acid; meta-analysis

Introduction

Crohn's Disease (CD) and ulcerative colitis (UC), collectively 'inflammatory bowel disease' (IBD), are inflammatory conditions of the gastrointestinal tract. While CD and UC share relapsing-remitting progression and chronic mucosal inflammation, they are distinct in clinical presentation and outcomes. Precise aetiologies of CD and UC are unclear, although environmental, gut microbiome, immune response and genetic factors predispose individuals to IBD [1]. A recent systematic review suggests that IBD prevalence is over 0.3% in North America, Oceania and many European countries, with lower but rising incidence in newly industrialised African, Asian, and South American countries [2]. IBD is expensive to individuals and healthcare systems, and has serious impacts on quality of life [3, 4]. The primary goal in clinical management of UC and CD is to induce and maintain remission [5]. Secondary goals include minimising IBD's psychosocial impact, physical distress and depressive symptoms associated with relapse [6]. Reducing need for pharmacological maintenance (including corticosteroids, immune-suppressants and immunomodulatory medications) may be helpful as these drugs are associated with significant adverse events [7].

Polyunsaturated fatty acids (PUFAs) include omega-3 and omega-6 fatty acids. Long-chain omega-3 fatty acids (LCn3) include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish; while alpha-linolenic acid (ALA) is found in some plant oils (including flaxseed, some nuts and rapeseed/canola). Many plant oils are rich in omega-6 fats, particularly linoleic acid (LA). LCn3 are thought to reduce various physiological aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression, leucocyte–endothelial adhesive interactions, prostaglandin and leukotriene production from omega-6 and production of pro-inflammatory cytokines [8]. Omega-6 (LA) has been correlated with pro-inflammatory effects, and its derivative arachidonic acid (AA) is a precursor for key pro-inflammatory mediators [8, 9]. Earlier case-controlled studies have reported a high levels of AA in mucosal tissues of IBD patients. While data from animal studies shown that the intake of AA have increased the severity of the inflammation in IBD [10]. Thus, LCn3 and ALA may

help maintain remission, prevent or delay diagnosis of IBD, and reduce markers of inflammation, while LA and AA omega-6 fats are considered relatively pro-inflammatory.

Inflammation is generally assessed in clinical practice and research by measuring biomarkers. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are used to measure systemic inflammation and are non-specific indicators for IBD [11]. CRP levels correlate better than ESR with IBD clinical activity, are measured more frequently in clinical situations and are less affected by aging [11, 12]. Faecal calprotectin is a promising site-specific biomarker, released within the intestinal mucosa during inflammation, and recommended to support differential diagnosis between IBD and non-IBD gastrointestinal inflammation [5]. Inflammatory cytokines (including interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α)) and adhesion molecules (such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1)) are increased in the intestinal mucosa during inflammation and may have a role in disease pathogenesis [13, 14]. Although plasma IL-6 and CRP correlate with IBD incidence pre-clinically, and may indicate early disease status of IBD [15], they are non-specific markers of inflammation and so are potentially affected by additional variables.

Additionally, increasing dietary PUFA inevitably alters the overall balance of nutrient intake and may favourably affect gut microbiota [16]. Despite strong theoretical mechanisms for utility of LCn3 and negative effects of omega-6 on IBD, the research evidence is contradictory. We aimed to systematically review effects of PUFA (LCn3, ALA, omega-6, total PUFA) on remission and relapse rates, pharmaceutical use, disease severity and incidence, and quality of life as well as key inflammatory markers in long-term trials. We were also interested in how effects varied by UC and CD, intervention type, baseline severity, dose, duration and nutrients displaced by increased PUFA.

Methods

This review is part of a series by the Polyunsaturated Fats and Health (PUFAH) group commissioned by the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health to inform and contribute to development of WHO recommendations. We collated a large set of long-term trials of PUFAs and examined them for relevant, often unpublished, outcomes [17]. The full set of reviews assesses effects of PUFA on cardiovascular disease, cancers, inflammatory bowel disease, neurocognitive outcomes and depression [17-24]. This systematic review is registered on PROSPERO [25]. Methods for the set of PUFAH reviews were based on Cochrane and GRADE, using Review Manager 5.3 and GradePRO software [26-29], reported according to PRISMA guidelines [30]. Detailed methodology for the set of reviews, the trials database and flow diagram are described elsewhere [17], review methodology is briefly presented here.

Inclusion criteria

We included published and unpublished randomised controlled trials (RCTs) comparing higher with lower omega-3, omega-6 and/or total PUFA intake for ≥24 weeks and assessed our primary outcomes. Participants were adults (aged ≥18 years) with or without a diagnosis of IBD, but trials of pregnant or acutely ill participants (with current cancer, undergoing transplantation, with acquired immune deficiency syndrome (AIDS) or human immunodeficiency virus (HIV), on haemodialysis, with IgA glomerulonephritis or any renal problem) were excluded. Eligible interventions could be dietary advice; supplementation (taken orally as oil, foods or capsules); or diet provided. Multifactorial interventions were excluded.

Primary outcomes included rates of induced IBD relapse (or remission), IBD severity or worsening and inflammatory markers (CRP, ESR, IL-6 and faecal calprotectin) in studies of people with existing IBD. In other trials primary outcomes included IBD diagnoses and inflammatory

markers. Secondary outcomes, assessed in included trials were: corticosteroid, immunosuppressant, and immuno-modulator use, measures of quality of life, other inflammatory marker levels and adiposity measures.

Methods for identification of studies

We searched Cochrane CENTRAL, Medline and Embase to 27th April 2017, ClinicalTrials.com and the World Health Organization International Clinical Trials Registry Platform to September 2016, and reassessed all ongoing trials in July 2019. We checked included trials of relevant systematic reviews, and wrote to authors of included studies for additional studies and trial data [17], creating a database of trials that randomised participants to increased omega-3, omega-6 or total PUFA compared to lower omega-3, omega-6 or total PUFA and assessed effects for ≥24 weeks (reflecting metabolic studies suggesting 6 months is the minimum duration of supplementation required to ensure equilibration of LCn3 into most body compartments) [31]. From this database, studies were chosen for this review that had assessed at least one primary review outcome (even when not fully reported).

Study inclusion, data extraction and risk of bias were assessed independently in duplicate. We assessed Cochrane risk of bias tool domains [32] as well as risk from compliance problems and attention bias [17]. We considered dietary advice trials to be at low summary risk of bias where we judged randomisation, allocation concealment and blinding of outcome assessors adequate, and supplement trials to be at low summary risk of bias where we judged randomisation, allocation concealment, blinding of participants, personnel and outcome assessors adequate (all other trials were considered at moderate or high risk of bias).

Data synthesis

Our primary analyses assessed effects of total PUFA, omega-6, LCn3 and ALA separately using random-effects meta-analysis as dietary interventions are naturally heterogeneous [33]. Treatment/control differences in outcomes were combined across studies using relative risks (RR) or mean differences (MD), measures using different units were converted to a single unit. Data on change from baseline in each arm with standard deviations were used for continuous outcomes where available, otherwise endpoint data were used [33]. As remission is the reverse of relapse we assessed these outcomes together, using relapse as the outcome. We ran sensitivity analyses for all primary outcomes using fixed-effect meta-analysis, limiting to studies at low summary risk of bias and at low risk of bias from compliance. Further sensitivity analysis (limiting analyses to trials randomising ≥100 participants), subgrouping and funnel plots were carried out where there were at least ten trials in a meta-analysis. We noted where data were measured but not fully reported to assess potential publication bias, and partially reported data were displayed in forest plots to allow assessment of consistency with meta-analysis results. Heterogeneity was assessed using I^2 and considered important where over 50% [34].

Effect sizes were interpreted as agreed with WHO NUGAG and pre-specified for this set of reviews [17]. In conjunction with Cochrane methodology we used the best estimate of effect size (rather than statistical significance) to assess whether effects occurred [17, 26]. RR <0.92 or >1.08 was considered a relevant clinical effect (RR 0.92 to 1.08 was considered "little or no effect"), while mean difference between arms of ≥10% of baseline was required for a relevant clinical effect for continuous measures. Outcome data were interpreted using GRADE assessment, drafted by LH then discussed and agreed with WHO NUGAG [17]. Where GRADE suggested data of very low-quality we did not interpret effect sizes. Where data were of low-quality we used the term "may", moderate-quality evidence warranted "probably" in describing effect sizes.

Subgroup analysis

We subgrouped on the basis of intervention type, PUFA dose, trial duration, replacement, age, sex, baseline IBD severity, diagnosis of UC or CD, baseline levels of inflammatory markers and baseline medication use (corticosteroid, immunosuppressant or immuno-modulatory therapies). We were not able to subgroup by baseline PUFA intakes or change in omega-3/omega-6 ratio (as we had planned) as these data were rarely provided.

Results

Description of studies

Brief characteristics, risk of bias assessments and references of included IBD studies are outlined in Table 1, of trials providing data on IBD diagnosis in Table 2, and included trials providing data on inflammatory markers in Table 3, while characteristics of all included studies are detailed in Additional Table 1. Further additional tables, forest plots, funnel plots and details of all sensitivity analyses and subgroups are also found in the Additional Materials.

We included 83 RCTs that measured at least one of our primary outcomes. These 83 RCTs (84 comparison groups) randomised 41,751 participants. Eleven RCTs were assessed as at low summary risk of bias, Additional Figure 1 [35-45]. Forty four trials were conducted in Europe, 18 in North America; 4 in South America; 12 in Asia; 2 in Australia, and three across several continents. Thirteen studies specifically recruited participants with IBD (7 with UC [46-52], 6 with CD [37, 42, 53-55]), 26 had CVD or raised lipids at baseline, 10 had diabetes, metabolic syndrome or raised insulin levels, 11 had rheumatoid arthritis, 4 were overweight or obese, 5 were healthy adults, the remainder other conditions (2 lupus, 2 cognitive problems, 1 dry eyes, 1 mobility problems, 3 non-alcoholic steatohepatitis, 1 various, 1 other arthritis, 1 periodontitis, 1 raised breast density, 1 multiple sclerosis). Seventy trials assessed effects of LCn3, six effects of ALA, and three effects of omega-3 (it was unclear whether LCn3, ALA or both). Seven trials assessed effects of omega-6 compared to something other than omega-3, and two assessed effects of total PUFA (several trials compared more than two relevant arms).

Effects of LCn3 in people with existing IBD

Increasing LCn3 may reduce the risk of IBD relapse (low quality evidence, downgraded once each for imprecision and publication bias). GRADE assessment of certainty of evidence on effects of increasing LCn3 on IBD and inflammatory outcomes are detailed in Additional Table 2. Six trials

provided data on relapse in CD, four in UC. Meta-analysis suggests reduction in relapse rates of IBD in those taking more LCn3 (RR 0.85, 95% CI 0.72 to 1.01, I^2 30%, 521 relapses in 1196 participants, Figure 1), and this was maintained (and statistically significant) in fixed effects analysis, when retaining only trials at low summary risk of bias, trials at low risk from compliance problems and in larger trials (see Additional Table 3). The funnel plot suggests that some small studies with increased rates of relapse in the intervention group may be missing (Additional Figure 2), but similarity in effect of fixed and random effects meta-analyses indicates this was not important. Data were mainly from CD trials, and subgrouping suggested there was no statistically significant difference in effect between CD and UC subgroups (Figure 1). There were no differences in effect when subgrouping by intervention type (though most studies were of supplementary capsules), dose, duration, age, sex, medications taken or baseline IBD status, but there was a greater effect in the subgroup where LCn3 replaced saturated fats than other replacements (p=0.02, Additional Table 3).

Increasing LCn3 may reduce the risk of IBD worsening (low quality evidence, downgraded once for risk of bias, once for imprecision). Two trials provided data on risk of worsening of CD, none on UC. This limited data set suggested that LCn3 reduced risk of worsening CD (RR 0.85, 95% CI 0.71 to 1.03, I^2 0%, 271 participants disease worsened in 748 participants [54]). This did not alter with fixed effects analysis, but neither study was at low summary risk of bias, or at low risk of compliance problems (Additional Table 4). The effect of increasing LCn3 on IBD severity was unclear as the evidence was of very low quality (downgraded once for risk of bias, twice for imprecision). Data on disease severity were more limited than those for worsening, and included UC severity score, stool frequency, stool consistency and rectal bleeding (one trial each of 18 or 20 participants, only stool consistency included SDs to enable use in meta-analysis or assessment of statistical significance, Figure 2 [48, 56]). Neither study was at low summary risk of bias.

Effects of LCn3 on IBD diagnoses

Low quality evidence suggests that increasing LCn3 may increase the risk of developing IBD (downgraded twice for imprecision). We found limited data on diagnoses of colitis in two large trials (RR 1.10, 95% CI 0.63 to 1.92, I^2 0%, 49 diagnoses in 16,015 participants, Figure 3 [36, 39]). The suggestion of increased risk in those taking LCn3 did not alter with fixed effects analysis, limiting to trials at low summary risk of bias, low risk of compliance problems, or study size (Additional Table 5).

Effects of LCn3 on inflammatory biomarkers in people with and without IBD

Higher levels of inflammatory biomarkers equate to more inflammation. The effect of increasing LCn3 on CRP was unclear as the evidence was of very low quality (downgraded once each for inconsistency, imprecision and publication bias). Thirty-nine trials assessed effects of LCn3 on CRP over at least 6 months, thirteen reporting CRP, twenty-six high sensitivity CRP (hs-CRP), but only 26 provided enough data to be included in meta-analysis. No included studies specifically recruited people with IBD at baseline. As there were not statistically significant differences between CRP and hs-CRP subgroups, we pooled the results of both in all analyses. Baseline CRP ranged from <1 to under 10mg/L with a single trial having a baseline of 18 mg/L [57]. As the data were very different in different trials we assumed this reflected differing analysis methods so ran the analyses using standardised mean difference (SMD). This suggested little or no effect of increasing LCn3 on CRP (SMD -0.09, 95% CI -0.21 to 0.03, I^2 68%, in 15,278 participants, Figure 4). Translating this back into mg/L using the AlphaOmega trial (the trial taking most weight in the meta-analysis [58]) suggested a less than 10% fall in CRP with LCn3. This lack of effect did not alter in sensitivity analyses by summary risk of bias, compliance or study size, but fixed effects analysis suggested a clinically insignificant but statistically significant effect (SMD -0.06, 95% CI -0.12 to -0.01, I^2 68%, in 15,278 participants, Additional Table 6). The funnel plot suggested that some studies with lower CRP in the LCn3 arm may be missing, if these studies were added back they would suggest a greater

298 reduction by LCn3 of CRP (Additional Figure 3). There were no important differences between
299 subgroups by intervention type, dose, duration, replacement, age, sex, medication used or baseline
300 disease status (Figure 5 & Additional Table 6).

301 Moderate quality evidence suggests that increasing LCn3 probably reduces ESR (downgraded
302 once for imprecision). Seven trials assessed effects on ESR in the long-term, of which 6 were combined
303 using SMD, suggesting a statistically significant reduction in those taking more LCn3 (SMD -0.23,
304 95% CI -0.44 to -0.01, I^2 0%, in 368 participants, Additional Table 7). The effect remained statistically
305 significant in fixed effects analysis and limiting to trials at low summary risk of bias (MD -
306 14.00mm/hour, 95% CI -25.33 to -2.67, 1 trial [37]) but the statistical significance was lost when
307 limiting by compliance. The single trial at low summary risk of bias was the single trial that included
308 people with IBD, reporting the effect of 2.7g/d LCn3 taken as a supplementary capsule over 12 months
309 on ESR in 78 participants with CD at baseline. It suggested statistically significant reduction in ESR
310 with higher LCn3 intake (MD -14.0mm/hour, 95% CI -25.3 to -2.7)[37]. No funnel plot, further
311 sensitivity analyses or subgrouping was carried out as there were so few trials. As there was no
312 difference in effect size whether random or fixed-effects analyses were carried out there was unlikely
313 to be important small study bias.

314 The effect of increasing LCn3 on IL-6 was unclear as the evidence was of very low quality
315 (downgraded once each for risk of bias, inconsistency and imprecision). Twenty-two trials assessed
316 effects on IL-6 over at least 6 months, of which 18 were combined using SMD in random effects meta-
317 analysis (SMD -0.35, 95% CI -0.62 to -0.07, I^2 83%, in 2234 participants, Figure 6). The suggestion
318 of reduction in IL-6 was highly heterogeneous, and the funnel plot was not interpretable (Additional
319 Figure 4), but effects using fixed and random-effects analyses were very similar so small study bias is
320 unlikely. The statistically significant reduction in IL-6 in those with higher LCn3 intake was also seen
321 in the sensitivity analyses using fixed effects and studies at low risk from compliance problems, but
322 statistical significance was lost when analyses were limited to trials at low summary risk of bias and

larger trials (Additional Table 8). There was no clinically or statistically significant effect in the single trial in people with existing IBD (32 participants with UC, MD 0.07pg/ml, 95% CI -0.15 to 0.29)[46]. There were no differences between subgroups for intervention type, LCn3 dose, duration, replacement, age or baseline health conditions, but there was a suggestion of greater effects in men. There were also suggestions of different effects in different age groups, but there were no clear progressions so this was probably spurious.

Increasing LCn3 may increase faecal calprotectin (low quality evidence, downgraded twice for imprecision). One trial reported faecal calprotectin, in only 34 participants with UC at baseline, suggesting a non-statistically significant increase with higher LCn3 (MD 16.1 μg/g, 95% CI -37.6 to 69.8, 34 participants[46]). This single trial was at low summary risk of bias and low risk from compliance problems.

Effects of LCn3 on TNF-α, ICAM-1 and VCAM-1 were collated as secondary outcomes (Table 3, Additional Table 9), and GRADE was not assessed. None of the trials in people with existing IBD reported any of these markers. Eighteen trials reported effects of LCn3 on TNF-α in pg/ml, of which 14 could be included in meta-analysis. The forest plot suggested that LCn3 reduced TNF-α (SMD -0.45, 95% CI -0.81 to -0.09, I^2 86%, 1774 participants, Additional Figure 5), but none of these trials were at low summary risk of bias and the funnel plot was not interpretable (Additional Figure 6). Five trials reported ICAM-1 in ng/ml of which three could be included in meta-analysis, suggesting no effect of LCn3 on ICAM-1 in the longer term (SMD 0.04, 95% CI -0.43 to 0.50, I^2 74%, 639 participants, not shown). Meta-analysis of the three of four trials reporting effects of LCn3 on VCAM-1 suggested no effect (SMD -0.18, 95% CI -0.87 to 0.51, I^2 88%, 388 participants, Additional Table 9).

Effects of LCn3 on other secondary outcomes, medication use and quality of life

Medication use was rarely reported, but one trial provided data on percentage of baseline non-steroidal anti-inflammatory drug (NSAID) use, suggesting that NSAID use was lower with higher LCn3 (MD -43.5%, 95% CI -71.4 to -15.6, 64 participants [59]). This single trial was not at low summary risk of bias. Similarly, a single trial reported quality of life, assessed using the Health Activity questionnaire (HAQ), suggesting similar levels of quality of life with higher and lower LCn3 intake (MD -0.02, 95% CI -0.12 to 0.08, 130 participants, the trial was not at low summary risk of bias [60]). Details of effects of LCn3 on measures of adiposity are systematically reviewed (as primary outcomes) in a sister review, so not discussed here [18].

Effects of ALA

The GRADE table on effects of increasing ALA on primary outcomes is Additional Table 10. We found no data on effects of increasing ALA on people with IBD on remission or relapse, severity, worsening, or medication use, on inflammatory markers, or in diagnosis of IBD in people without IBD at baseline. Four trials (in people without existing IBD but with CVD risk factors) assessed effects of increasing ALA intake (up to 2 g/day) for 12 to 40 months on CRP. Baseline CRP was 1.8 to 4.9 mg/L (mean 3.8 mg/L). Meta-analysis and GRADE suggested high quality evidence of little or no effect (SMD -0.00, 95% CI -0.08 to 0.07, I^2 0%, 2715 participants, Additional Figure 7, MD -0.00mg/L, 95% CI -0.16 to 0.16, I^2 0%). This did not alter in fixed effects analysis, limiting to the three trials at low summary risk of bias, or at low risk of compliance problems (Additional Table 11). Two of the three trials assessing effects of ALA on IL-6 were included in meta-analysis, suggesting low quality evidence of little or no effect (SMD -0.04, 95% CI -0.33 to 0.24, I^2 0%, 186 participants, neither trial at low summary risk of bias, Additional Figure 8, MD -0.28pg/ml, 95% CI -1.09 to 0.53, I^2 0%, quality of evidence downgraded for once for imprecision, once for risk of bias). Effects did not differ by fixed or random-effects analysis, Additional Table 12. Two trials reported on TNF-α, suggesting little effect of increasing ALA (SMD -0.18, 95% CI -0.51 to 0.14, I^2 0%, 146 participants, Additional Figure 9),

372 which did not differ in the single trial at low summary risk of bias. No trials reported on effects of
373 ALA on ESR, faecal calprotectin, ICAM-1 or VCAM-1 or other secondary outcomes.
374
375 **Effects of omega-6**
376 The GRADE table for omega-6 is Additional Table 13. We found no data on effects of
377 increasing omega-6 on people with IBD on worsening or medication use, or inflammatory markers, or
378 in diagnosis of IBD in people without IBD at baseline. The effects of increasing omega-6 on IBD
379 relapse and severity were unclear as the evidence for both were of very low quality. Limited
380 information was provided on relapse (2 of 20 people with UC relapsed, RR 0.54, 95% CI 0.04 to 7.36)
381 and severity by a single trial of 20 people, providing data suggesting slightly greater but non-
382 statistically significant stool solidity (MD -0.30, 95% CI -0.73 to 0.13, on a scale of 0 to 2, with 0
383 being solid and 2 watery, 20 participants [48]). Data from the same study on stool frequency and rectal
384 bleeding did not include measures of variance, so statistical significance was not clear.
385 Low quality evidence suggests that increasing omega-6 may have little or no effect on CRP
386 (downgraded once each for risk of bias and imprecision). Meta-analysis of two of three trials assessing
387 effects of omega-6 on CRP suggested little or no effect (SMD 0.09, 95% CI -0.17 to 0.35, I^2 0%, 228
388 participants, MD 0.19mg/L, 95% CI -0.28 to 0.66, neither trial was at low summary risk of bias, the
389 third trial provided no data on variance. Effects did not differ when using fixed instead of random-
390 effects meta-analysis, Additional Table 14. The effect of increasing omega-6 on ESR is unclear as the
391 evidence is of very low quality (downgraded once for risk of bias, twice for imprecision). One of three
392 trials assessing effects of omega-6 on ESR provided a measure of variance suggesting no effect (MD
393 4.00mm/hour, 95% CI -10.55 to 18.55, 75 participants without baseline IBD, not at low summary risk
394 of bias, Additional Table 15). We found no studies assessing effects of omega-6 on IL-6, faecal
395 calprotectin, ICAM-1, VCAM-1 or other secondary outcomes. A single trial assessed effects of
396 omega-6 on TNF-α (MD -0.40, 95% CI -0.95 to 0.15, 38 participants, not at low summary risk of bias).

Effects of total PUFA

We found no studies assessing effects of total PUFA on IBD relapse, worsening, severity, medication use or inflammatory markers in people with IBD or on IBD diagnosis in people without IBD at baseline, see GRADE table, Additional Table 16. Long-term effects of increasing total PUFA on CRP are unclear as the evidence is of very low quality. Three of five trials assessing effects of increasing total PUFA intake (up to 27.6 g/day for a duration of 6 to 56 months) on CRP could be included in meta-analysis, suggesting no effect of total PUFA on CRP (SMD 0.25, 95% CI -0.10 to 0.60, I^2 50%, 385 participants, Figure 7, Additional Table 17). The single trial assessing ESR did not provide any measure of variance. Increasing total PUFA may have little or no effect on IL-6, low quality evidence (downgraded once each for risk of bias and imprecision). Two trials reporting effects of total PUFA on IL-6 suggested no effect (SMD -0.09, 95% CI -0.24 to 0.07, I^2 0%, 611 participants without IBD, neither trial was at low summary risk of bias, MD -0.08 pg/ml, 95% CI -0.18 to 0.02, Figure 6, Additional Table 18). No trials assessed effects of total PUFA on faecal calprotectin or secondary outcomes.

Discussion

This is the most comprehensive meta-analysis of RCTs investigating long-term effects of omega-3, omega-6 and total PUFA on treatment and prevention of IBD and on inflammatory markers in people with and without IBD at baseline. We systematically reviewed the effects of omega-3, omega-6 and total PUFA on IBD outcomes, including 83 RCTs (41,751 participants), of which 13 recruited people with IBD and 11 were at low summary risk of bias. Low quality evidence suggested increasing LCn3 may reduce the risk of IBD relapse and worsening, and reduce ESR, but increase the risk of IBD diagnosis and increase faecal calprotectin. Only one included trial (of LCn3) assessed effects on faecal calprotectin, limiting our ability to draw conclusions on the effect of omega-3, omega-6 and PUFAs on this important biomarker. Evidence on effects of increasing ALA, omega-6 and total PUFA were sparse, but increasing ALA has little or no effect on CRP and may have little effect on IL-6. Increasing omega-6 may have little or no effect on CRP and increasing total PUFA may have little or no effect on IL-6. Evidence for other primary outcomes was of very low quality or absent. Data on inflammatory markers was often not useable in meta-analysis due to missing variance data or not being reported numerically despite being measured, so there is considerable inherent risk of small study bias. Evidence for effects of PUFA on inflammatory markers in people with existing IBD is very limited.

We were interested in how effects varied by UC and CD, intervention type, baseline severity, dose, duration and nutrients displaced by increased PUFA. For trials with participants with existing IBD, the duration of intervention ranged from 6 to 24 months, and LCn3 doses were from 1.12 to 4.5 g EPA/day plus 0.73 to 2.4 g DHA/day. Where there were enough data to subgroup effects rarely varied according to these variables, which may be due to limited data or to lack of effect of these variables.

Our findings on effects of increasing LCn3 appear contradictory, suggesting reduction in IBD relapse, reduced risk of IBD worsening but increased the risk of developing IBD. A recent systematic

review of observational studies reflects this dissonance suggesting significant negative correlations between fish consumption and CD incidence, and between LCn3 intake and UC risk, but no associations between total dietary omega-3 or ALA intake and IBD incidence [61]. The Nurses' Health Study suggested that energy-adjusted intake of omega-6 or omega-3 was not associated with risk of UC or CD but there was a (non-statistically significant) suggestion of a negative association between LCn3 intake and UC risk [62]. On the other hand, a systematic review of trials found that LCn3 supplements were probably ineffective for maintaining remission in CD [63]. Despite strong theoretical mechanisms for utility of LCn3 and negative effects of omega-6 on IBD and the inflammatory process [8], current evidence is contradictory. The trials included in this systematic review assessed effects of increasing LCn3 primarily through consumption of fish oil supplements. A diet high in oily fish would increase LCn3 intake, but also iodine, protein, selenium etc so may have different effects. Overall, this lack of clarity is reflected in the lack of guidelines on LCn3 supplementation in IBD management [5, 64-68], though the European Society of Parenteral and Enteral Nutrition (ESPEN) specifically advises that a diet high in LCn3 and low in omega-6 is preventative of IBD (based on individual observational studies), but against LCn3 supplementation for maintenance of remission [69].

As we were interested in the mechanism of any effects of PUFAs via inflammatory processes on IBD, we took the novel step of also assessing effects of omega-3, omega-6 or PUFAs on inflammatory biomarkers. Clear effects on inflammatory biomarkers could support assertions of anti- or pro-inflammatory mechanisms of action and support effects on IBD outcomes. To underpin effects on IBD we would expect to find that increasing LCn3 and ALA would reduce CRP, ESR, IL-6 and faecal calprotectin, while increasing omega-6 and total PUFA (including all omega-3 and omega-6 fatty acids) would increase these markers. These effects were not seen in our included long-term trials, except that increasing LCn3 appears to reduce ESR (in people with and without IBD) but increases

462 faecal calprotectin, a specific marker for IBD, in people with IBD. This provides little or no evidence
463 to support pro- or anti-inflammatory effects of increasing LCn3, ALA, omega-6 or total PUFA intakes.

464 Despite measurement in 39 trials the evidence of long-term effects of LCn3 on CRP was of
465 very low quality, so effects were unclear, highlighting a need for standardisation of measurement (CRP
466 vs hs-CRP) and reporting. As CRP and ESR are identified as having a role in monitoring disease
467 activity and response to treatment [5, 64, 67], and correlate with IBD diagnosis [70], their lack of
468 response to omega-3 or omega-6 fats in this review undermines the effect of omega-3 and omega-6
469 fats both on inflammation and on IBD. As faecal calprotectin is a specific and sensitive inflammatory
470 biomarker for IBD diagnosis, progression and severity [5, 64, 65, 70, 71] effects of omega-3 and
471 omega-6 on faecal calprotectin are particularly important. However, only one included trial (of LCn3)
472 assessed effects on faecal calprotectin, limiting our ability to draw conclusions on the effect of omega-
473 3, omega-6 and PUFAs on this important biomarker.

474 Most included studies measured IBD diagnosis, severity or progression or inflammatory
475 biomarkers. Measuring medication use and quality of life in people with IBD are equally as important
476 in measuring the impact of IBD on patients, and identifying and measuring outcomes that are important
477 to patients is the gold standard of high quality clinical research [72]. However, these outcomes were
478 rarely measured or reported, suggesting that this message has not been adequately received by those
479 conducting IBD research, and supporting the need for a core outcome set in IBD research that captures
480 clinically relevant and patient-centred metrics [73].

481

Conclusion

Despite rigorous searching for relevant trials, data are sparse on long-term effects of ALA, omega-6 and total PUFA on clinical outcomes in IBD, prevention of IBD, and on inflammatory markers in people with and without IBD. Methodologically only 11 of 83 included trials were at low summary risk of bias, none of the seven trials in people with existing UC, and two of the six trials of people with existing CD. Future trials of effects of fatty acids on IBD, and on inflammatory markers, need to be of high methodological quality, using strong randomisation, allocation concealment, masking of participants and outcome assessors, so that results are less susceptible to inherent bias. As effects of LCn3 on IBD outcomes are contradictory, interpretation of results is difficult. Currently, combined findings from clinical and biomarker outcomes suggest little or no effect of LCn3 on IBD or inflammation.

There is a pressing need for high quality, well designed research using a core outcome set to assess effects of interventions, particularly effects of increasing omega-3 and omega-6 fats, on IBD diagnosis, progression, inflammatory biomarkers (particularly faecal calprotectin), medication use, and quality of life. Additionally, existing trials of omega-3 and omega-6 interventions would ideally report IBD diagnoses to allow assessment of preventive effects.

500 **Table 1.** Brief characteristics of the 13 trials that assessed effects of PUFA on people with existing
501 IBD (for full details see Additional Table 1).

502

Study name & references	Participants	Intervention & comparison, duration, dose	Summary risk of bias
Almallah 1998 [47, 56]	Individuals with ulcerative colitis with only distal disease (Europe)	n3 EPA+DHA vs n6 LA, 6 months, 3.2g/d EPA + 2.4g/d DHA	Moderate to high
Belluzzi 1996 [37]	Individuals with established diagnosis of CD in clinical remission (Europe)	n3 EPA+DHA vs mixed fat, 12 months, 1.8g/d EPA + 0.9g/d DHA	Low
Belluzzi 1997 [53]	Individuals with CD in remission 1 month after ileal resection (Europe)	n3 EPA+DHA vs mixed fat), 12 months, 1.8g/d EPA + 0.9g/d DHA	Moderate to high
EPIC-1 2008 [54]	Adults with quiescent CD and CDAI score <150 (Europe, North America & Asia)	n3 EPA vs mixed fats, 52 weeks, 2.2g/d EPA + 0.8g/d DHA	Moderate or high
EPIC-2 2008 [54]	Adults with a confirmed CD and CDAI score <150 and responding to steroid induction therapy (Europe, North America & Asia)	n3 EPA+DHA vs mixed fats, 58 weeks, 2.2g/d EPA, 0.8g/d DHA	Moderate or high
FISHGASTRO - Pot 2009 [46, 74, 75]	Adults with colorectal polyps, inactive UC or no macroscopic signs of disease, given colonoscopy (Europe)	high n3 fish diet vs low n3 fish diet vs low fish diet, 6 months, 1.4g/d or 0.26g/d EPA+DHA	Moderate to high
Greenfield 1993 [48]	People with stable UC for >1 year and on <10mg prednisolone/day (Europe)	n3 EPA vs n6 GLA vs MUFA, 6 months, 1.12g/d EPA & 0.73g/d DHA	Moderate to high
Hawthorne 1992 [49]	People with established UC with ≥2 relapses in past 3 years (Europe)	n3 EPA vs MUFA, 12 months, 4.5g/d EPA + 1.08g/d DHA	Moderate or high
Loeschke 1996 [50]	People with UC in remission (Europe)	n3 EPA+DHA vs n6 LA, 24 months, 5.1g/d EPA+DHA	Moderate or high
Lorenz-Meyer 1996 [42]	People with CD in remission (but with a recent relapse) (Europe)	n3 EPA+DHA vs n6 LA, 12 months, 3.3g/d EPA + 1.8g/d DHA	Low
Mantzaris 1996 [51]	People with UC in clinical, endoscopic & histological remission (Europe)	n3 EPA+DHA Vs MUFA, 12 months, 3.2g/d EPA & 2.1g/d DHA	Moderate to high
Mate 1991 [55]	People with CD in remission (Europe)	n3 EPA+DHA vs nil, 24 months, dose unclear	Moderate or high
Varghese 2000 [52]	People with active extensive UC (Europe)	n3 vs n6, 6 months, 5.6mg/d (sic) n3 (unclear whether ALA or LCn3)	Moderate to high

503

504 **Footnotes**

505 ALA = alpha-linolenic acid

506 CD = Crohn's disease

CDAI = Crohn’s disease activity index
DHA = docosahexaenoic acid
EPA = eicosapentaenoic acid or icosapentaenoic acid
GLA = gamma linolenic acid
LA = linoleic acid
LCn3 = long-chain omega 3
MUFA = mono-unsaturated fatty acids
n3 = omega 3
n6 = omega 6
UC = Ulcerative colitis

Table 2. Characteristics of included studies with data on prevention of IBD, including risk of bias and references

Study name & references	Participants	Intervention & comparison, duration, dose	Summary risk of bias
ASCEND 2012 [36, 76]	People with DM, without apparent vascular disease	n-3 EPA + DHA vs MUFA, median 7.4 years, 460mg/d EPA + 380mg/d DHA	Low
DREAM Asbell 2018 [39, 77]	Adults with dry eye	LCn3 vs MUFA, 12 months, 2g EPA + 1g DHA/d	Low

Footnotes

DHA = docosahexaenoic acid
DM = diabetes mellitus
EPA = eicosapentaenoic acid or icosapentaenoic acid
LCn3 = long-chain omega 3

532 Table 3. Characteristics of included studies reporting markers of inflammation, including risk of bias
533 and references
534

Study name & references	Participants	Intervention & comparison, duration, dose	Summary risk of bias
AFFORD 2014 [78, 79]	People with symptomatic paroxysmal or persistent AF	n3 EPA+DHA vs n6, 12 months, 1.6g/d EPA + 0.8g/d DHA	Moderate or high
AlphaOmega - ALA [35, 80]	60-80 year olds with previous MI	n3 ALA vs MUFA, 40 months, ALA 2g/d	Low
AlphaOmega - EPA+DHA [35, 80]	60-80 year olds with previous MI	n3 EPA+DHA vs MUFA, 40 months, EPA+DHA 0.4g/d	Low
Araujo 2014 [81]	People with RA	n3 vs unclear control, 6 months, dose unclear	Moderate to high
Balfego 2016 [82]	Drug-naive patients with type 2 DM	n3 EPA+DHA vs mixed fats, 6 months, dose unclear	Moderate or high
Belch 1988 [83]	People with classical or definite RA	n6 GLA vs n6 GLA + n3 EPA vs nil, 12 months, EPA 0.24g/d + GLA 0.45g/d	Moderate to high
Belluzzi 1996 [37]	Individuals with established diagnosis of CD in clinical remission	n3 EPA+DHA vs mixed fat, 12 months, 1.8g/d EPA + 0.9g/d DHA	Low
Berbert 2005 [57]	People with RA	n3 EPA+DHA vs n6 LA, 24 weeks, 1.8g/d EPA & 1.2g/d DHA	Moderate or high
Bo 2017 [84]	Older adults with mild cognitive impairment	n3 EPA+DHA vs MUFA), 6 months, 480 mg/d DHA and 720 mg/d EPA	Moderate or high
Brox 2001 [85]	Subjects with moderate hypercholesterolaemia	n3 EPA+DHA from cod liver vs n3 EPA+DHA from seal oil vs nil, 14 months, seal oil 1.1g/d EPA + 1.5/d DHA, Cod liver oil 1.5g/d EPA + 1.8g/d DHA	Moderate or high
Brzeski 1991 [86]	People with rheumatoid arthritis and upper GI lesions due to NSAID intake	n6 GLA vs MUFA), 6 months, 0.54g/d GLA	Moderate to high
Clark 2016 [38]	Adults with impaired glucose metabolism or type 2 diabetes mellitus	n3 EPA+DHA vs n6 LA, 9 months, 3.9g/d EPA+DHA	Low
Darghosian 2015 [87]	People with paroxysmal or persistent AF	n3 EPA+DHA vs n6 LA, 6 months, 1.86g/d EPA & 1.5g/d DHA	Moderate or high
de Luis 2016 [88]	Generally healthy individuals with obesity	n3 DHA vs MUFA, 6 months, 500mg/d DHA then 250mg/d	Moderate or high
Derosa 2009 [89]	Adults with combined dyslipidaemia	n3 EPA+DHA vs non-fat placebo, 6 months, 1.13g/d EPA + 1.88g/d DHA	Moderate or high
Derosa 2011 [90]	Adults with combined lipidaemia	n3 EPA+DHA vs non-fat placebo, 6 months, 1.2g/d EPA + 1.35g/d DHA	Moderate or high
Deslypere 1992 [91-93]	Healthy monks	n3 EPA+DHA (3 different doses) vs MUFA, 12 months, 1.12g/d; 2.24g/d or 3.37g/d EPA + DHA	Moderate or high
DO IT - Einvik 2010 [94-99]	Elderly men with long standing dyslipidaemia or hypertension	n3 DHA+EPA vs n6 LA, 36 months, 0.84g/d EPA + 0.48g/d DHA	Moderate or high

Ebrahimi 2009 [100]	People with metabolic syndrome	n3 EPA+DHA vs nil, 6 months, 180mg/d EPA, 120mg/d DHA	Moderate or high
ELIA - Takaki 2011 [101]	People with CAD and dyslipidaemia on statins	n3 EPA vs nil, 11 months, 1.8g/d EPA	Moderate or high
ENRGISE 2016 [102-104]	People aged 70+ years with walking or stair-climbing difficulty	LCn-3 vs PUFA, 12 months, 0.8g/d EPA plus 0.4g/d DHA	Moderate to high
EPE-A 2014 [105]	People with non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD)	n3 EPA, low dose vs high dose vs unclear placebo, 12 months, 2.7g/d or 1.8g/d EPA+DHA	Moderate or high
EPIC-1 2008 [54]	Adults with quiescent CD and CDAI score <150	n3 EPA vs mixed fats, 52 weeks, 2.2g/d EPA + 0.8g/d DHA	Moderate or high
EPIC-2 2008 [54]	Adults with a confirmed CD and CDAI score <150 and responding to steroid induction therapy	n3 EPA+DHA vs mixed fats, 58 weeks, 2.2g/d EPA, 0.8g/d DHA	Moderate or high
EPOCH 2011 [40, 106]	Healthy older adults with no cognitive impairment	n3 EPA+DHA vs MUFA, 18 months, 1.72g/d DHA and 0.60g/d EPA	Low
Eschen 2010 [107]	People with chronic heart failure	n3 EPA+DHA vs MUFA, 6 months, 0.9g/d EPA+DHA	Moderate or high
Finnegan 2003 [108, 109]	People with hyperlipidaemia	n3 EPA+DHA vs n3 ALA vs n6 LA, 6 months, 1.7g/d or 0.8g/d EPA+DHA, 9.5g/d or 4.5g/d ALA	Moderate or high
FISHGASTRO - Pot 2009 [46, 74, 75]	Adults visiting the hospital for colonoscopy with colorectal polyps, inactive UC or no macroscopic signs of disease	high n3 fish diet vs low n3 fish diet vs low fish diet, 6 months, 1.4g/d or 0.26g/d EPA+DHA	Moderate to high
FLAX-PAD 2013 [41, 110-113]	People with peripheral artery disease	n3 ALA vs mixed fat, 12 months, unclear ALA dose	Low
Kanorsky 2007 [114]	People with persistent atrial fibrillation	n3 vs nil, 12 months, dose and type unclear	Moderate to high
Krebs 2006 [115]	Overweight hyperinsulinaemic women	n3 EPA+DHA vs n6 LA, 6 months, 1.3g EPA+ 2.9g DHA	Moderate or high
Kremer 1995 [116]	People with definite or classic active RA	n3 EPA+DHA vs n6 LA), 6 or 7 months, 130mg/kg/d EPA + DHA	Moderate or high
Kristensen 2016 [117]	People with psoriatic arthritis	LCn3 vs MUFA, 6 months, 1.5g/d EPA, 1.5g/d DHA	Moderate to high
Kumar 2008 [118]	People with RA	n6 GLA vs MUFA, 9 months, 1.32g/d GLA	Moderate to high
Lalia 2015 [119]	Insulin resistant adults	n3 EPA+DHA vs MUFA, 6 months, 2.7g/d EPA+ 1.2g/d DHA	Moderate or high
Lau 1993 [59]	People with definite or classical RA requiring NSAIDs	n3 EPA+DHA vs nil), 12 months, 1.71g EPA + 1.14g DHA	Moderate to high
Leventhal 1993 [120]	People with RA and active synovitis	n6 GLA vs mixed fats including LA, 24 weeks, 1.4g/d GLA	Moderate to high
Leventhal 1994 [121]	People with RA and active synovitis	n6 GLA & n3 ALA vs n6 LA, 24 weeks, 2g/d GLA	Moderate to high

Li 2015 [122]	People diagnosed with pathological non-alcoholic steatohepatitis (NASH)	n3 EPA+DHA vs nil, 6 months, dose unclear	Moderate or high
MARGARIN - Bemelmans 2002 [43, 123]	Hypercholesterolaemic adults with 2 or more CVD risk factors	n3 ALA vs n6 LA, 2 years, dose unclear	Low
MARINA - Sanders 2011 [44]	Non-smoking men and women aged 45-70y	n-3 EPA+DHA at three different doses vs MUFA, 12 months, 0.45g/d or 0.9g/d or 1.8g/d EPA+DHA	Low
Martinez 2014 [124]	People treated for chronic periodontitis	n3 EPA+DHA vs unclear, 12 months, 0.18g/d EPA, 0.12g/d DHA	Moderate or high
Mate 1991 [55]	People with Crohn's Disease in remission	n3 EPA+DHA vs nil, 24 months, dose unclear	Moderate or high
MENU - Rock 2016 [125]	Overweight and obese women, of whom half were insulin resistant	n3 ALA vs nil, 12 months, dose unclear	Moderate or high
Moore 2006 [126]	Overweight or obese adults	high LCn3 & high ALA vs high LCn3 & n6 vs low LCn3 & high ALA vs low LCn3 & n6, also a control arm), 6 months, 0.1g/d or 0.65g/d LCn3, ALA doses unclear	Moderate to high
MUFFIN Miller 2016 [127]	Middle-aged men and women with metabolic syndrome	PUFA & n6 vs MUFA, 6 months, 27.6g/d PUFA	Moderate or high
Niki 2016 [128]	Patients with angina and hypertension treated with strong statins	n3 EPA vs nil, 6 months, 1.8g/d EPA ester	Moderate or high
Nishio 2014 [129]	People with untreated dyslipidaemia and thin-cap fibroatheroma	n3 EPA vs nil, both with statin, 9 months, 1.8g/d EPA	Moderate or high
Nodari 2009 [130]	People with cardiomyopathy and frequent or repetitive ventricular arrhythmia	n3 EPA+DHA vs MUFA, 6 months, 0.87g/d EPA + 1.44g/d DHA	Moderate or high
Nodari 2011 HF [131]	People with heart failure (non-ischaemic dilated cardiomyopathy)	n3 DHA+EPA vs MUFA, 12 months, 1.7g/d EPA+DHA at a ratio of 0.9 to 1.5	Moderate or high
Nogueira 2016 [132]	Patients with non-alcoholic steatohepatitis	n3 EPA+DHA vs non-fat, 6 months, 0.6g/d ALA + 0.194g/d EPA + 0.15g/d DHA	Moderate or high
OFAMI - Nilsen 2001 [133]	Patients recruited 4-8 days after confirmed MI	n3 EPA+DHA vs n6 LA, 2 years, 3.5g/d EPA+DHA	Moderate or high
OMEGA-Remodel 2016 [134-136]	People after acute MI	n3 EPA+DHA vs n6 LA, 6 months, 1.86g/d EPA + 1.5g/d DHA	Moderate or high
OmegAD 2008 [137-143]	People with mild to moderate Alzheimer's disease & stable comorbidities	n3 EPA+DHA vs. n6 LA, 6 months, 1.72g/d DHA + 600 mg EPA	Moderate or high
ORL 2013 [144]	Adults with hypertriglyceridaemia	n3 EPA+DHA high dose vs low dose vs n3 EPA, 12 months, 1.86g/d EPA + 1.5	Moderate or high

		g/d DHA or 0.93g/d EPA + 0.75g/d DHA	
Patch 2005 [145, 146]	Healthy overweight people with mild TG elevation	n3 EPA+DHA vs nil, 6 months, 1.0g/d EPA+DHA	Moderate or high
PREDIMED 2013 [147-151]	Men (55-80 years) & women (60-80 years), free of CVD but with diabetes or ≥3 CVD risk factors	PUFA vs MUFA, 60 months, dose unclear	Moderate to high
Ramirez-Ramirez 2013 [152]	People with relapsing remitting multiple sclerosis	n3 EPA+DHA vs n6 LA, 12 months, 0.8g/d EPA + 1.6g/d DHA	Moderate or high
REDUCE-IT 2018 [153, 154]	People with hypertriglyceridaemia, and with CVD or with DM and another risk factor, and on statin	LCn3 vs paraffin oil, median 4.9 years, 3.99g/d EPA	Moderate or high
Reed 2014 [45]	Adults with RA	n3 EPA+DHA vs n6 GLA, 18 months, 2.1 g EPA + 1.4 g DHA	Low
Sandhu 2016 [155]	Healthy postmenopausal women with high breast density	n-3 vs nil, 24 months, 1.86 g/d EPA + 1.5 g/d DHA	Moderate or high
Sawada 2016 [156]	People with newly-diagnosed impaired glucose metabolism and CAD	n3 EPA vs nil, 6 months, 1.8g/d EPA	Moderate or high
Skoldstam 1992 [157]	People with stable RA	n3 EPA+DHA vs n6, 6 months, 1.8g/d EPA + 1.2g/d DHA	Moderate or high
SO927 Hershman 2015 [158]	Women with early stage breast cancer receiving an aromatase inhibitor with musculoskeletal pain	n3 EPA+DHA vs n6 LA, 6 months, 3.36g/d EPA + 1.68g/d DHA	Moderate or high
Tande 2016 [159]	Healthy adult volunteers with BMI 25-35 kg/m^2	n3 EPA+DHA vs MUFA, 12months, unclear dose	Moderate or high
Tani 2017 [160]	People with stable CAD on statins	n3 EPA+DHA vs nil, 6 months, 1.8g/d EPA+DHA	Moderate or high
Tardivo 2015 [161]	Postmenopausal women with metabolic syndrome	n3 EPA+DHA vs nil, 6 months, 0.54g/d EPA + 0.36g/d DHA	Moderate or high
Tartibian 2011 [162, 163]	Sedentary postmenopausal women	n3 EPA+DHA vs nil, 6 months, 540 mg/d EPA + 360 mg/d DHA	Moderate or high
THIS DIET 2008 [164]	Recent survivors of first myocardial infarction	n3 EPA+DHA vs nil, 24 months, dose unclear	Moderate or high
Veleba 2015 [165]	Overweight/obese type 2 DM patients treated with metformin	n3 EPA+DHA vs n6 LA, 6 months, 0.75g/d EPA + 2g/d DHA	Moderate or high
Vijayakumar 2014 [166, 167]	People with stable coronary artery disease	n6 LA vs SFA, 2 years, 15% E n6	Moderate to high
Westberg 1990 [168]	Adults with a long-term systemic lupus erythematosus	n3 EPA vs MUFA, 6 months, ~3.5g/d EPA+DHA	Moderate or high
Witte 2012 [169-171]	Healthy older adults (50-80 years)	n3 EPA+DHA vs n6 LA, 6 months, 1.32g/d EPA + 0.88g/d DHA	Moderate or high

Wright 2008 [172]	People with systemic lupus erythematosus	n3 EPA+DHA vs MUFA, 6 months, 1.8g/d EPA + 1.2g/d DHA	Moderate or high

Footnotes

AF = atrial fibrillation
ALA = alpha-linolenic acid
BMI = body mass index
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CHD = coronary heart disease
CVD = cardiovascular disease
DBP = diastolic blood pressure
DHA = docosahexaenoic acid
DM = diabetes mellitus
DPA = docosapentaenoic acid
E = dietary energy
EPA = eicosapentaenoic acid or icosapentaenoic acid
HDL = high density lipoprotein
HRT = hormone replacement therapy
HT = hypertension
LA = linoleic acid
LCn3 = long-chain omega 3
MI = myocardial infarction
MUFA = mono-unsaturated fatty acids
n3 = omega 3
n6 = omega 6
PUFA = poly-unsaturated fatty acids
PTCA = percutaneous
RA = rheumatoid arthritis
SFA = saturated fatty acids
TG = serum triglycerides
TIA = transient ischaemic attack

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