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Effects of omega-3, omega-6 and total polyunsaturated fats on inflammatory bowel disease and long-term effects on markers of inflammation: A Systematic Review and Meta-analysis

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Additional Tables and Figures. Ajabnoor et al, PUFA & IBD SR

Contents

Additional Table 1. Characteristics of all included studies, including risk of bias and references

Study name & references	Participants	Intervention & comparison, duration, dose	Summary risk of bias
AFFORD 2014 [1, 2]	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
Almallah 1998 [3, 4]	Individuals with ulcerative colitis with only distal disease	n3 EPA+DHA vs n6 LA, 6 months, 3.2g/d EPA + 2.4g/d DHA	Moderate to high
AlphaOmega - ALA [5, 6]	60-80 year olds with previous MI	n3 ALA vs MUFA, 40 months, ALA 2g/d	Low
AlphaOmega - EPA+DHA [5, 6]	60-80 year olds with previous MI	n3 EPA+DHA vs MUFA, 40 months, EPA+DHA 0.4g/d	Low
Araujo 2014 [7]	People with RA	n3 vs unclear control, 6 months, dose unclear	Moderate to high
ASCEND 2012 [8, 9]	People with DM, without apparent vascular disease	n-3 EPA + DHA vs MUFA, median 7.4 years, 460mg/d EPA + 380mg/d DHA	Low
Balfego 2016 [10]	Drug-naive patients with type 2 DM	n3 EPA+DHA vs mixed fats, 6 months, dose unclear	Moderate or high
Belch 1988 [11]	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 [12]	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
Belluzzi 1997 [13]	Individuals with CD in remission 1 month after ileal resection	n3 EPA+DHA vs mixed fat), 12 months, 1.8g/d EPA + 0.9g/d DHA	Moderate to high
Berbert 2005 [14]	People with RA	n3 EPA+DHA vs n6 LA, 24 weeks, 1.8g/d EPA & 1.2g/d DHA	Moderate or high
Bo 2017 [15]	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 [16]	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 [17]	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 [18]	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 [19]	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 [20]	Generally healthy individuals with obesity	n3 DHA vs MUFA, 6 months, 500mg/d DHA then 250mg/d	Moderate or high
Derosa 2009 [21]	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 [22]	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 [23-25]	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 [26-31]	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
DREAM Asbell 2018 [32, 33]	Adults with dry eye	LCn-3 vs MUFA, 12 months, 2g EPA + 1g DHA/d	Low
Ebrahimi 2009 [34]	People with metabolic syndrome	n3 EPA+DHA vs nil, 6 months, 180mg/d EPA, 120mg/d DHA	Moderate or high
ELIA - Takaki 2011 [35]	People with CAD and dyslipidaemia on statins	n3 EPA vs nil, 11 months, 1.8g/d EPA	Moderate or high
ENRGISE 2016 [36-38]	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 [39]	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 [40]	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 [40]	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 [41, 42]	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 [43]	People with chronic heart failure	n3 EPA+DHA vs MUFA, 6 months, 0.9g/d EPA+DHA	Moderate or high
Finnegan 2003 [44, 45]	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 [46-48]	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 [49-53]	People with peripheral artery disease	n3 ALA vs mixed fat, 12 months, unclear ALA dose	Low
Greenfield 1993 [54]	People with stable UC for >1 year and on <10mg prednisolone/day	n3 EPA vs n6 GLA vs MUFA, 6 months, 1.12g/d EPA & 0.73g/d DHA	Moderate to high
Hawthorne 1992 [55]	People with established UC with ≥2 relapses in past 3 years	n3 EPA vs MUFA, 12 months, 4.5g/d EPA + 1.08g/d DHA	Moderate or high
Kanorsky 2007 [56]	People with persistent atrial fibrillation	n3 vs nil, 12 months, dose and type unclear	Moderate to high
Krebs 2006 [57]	Overweight hyperinsulinaemic women	n3 EPA+DHA vs n6 LA, 6 months, 1.3g EPA+ 2.9g DHA	Moderate or high
Kremer 1995 [58]	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 [59]	People with psoriatic arthritis	LCn3 vs MUFA, 6 months, 1.5g/d EPA, 1.5g/d DHA	Moderate to high
Kumar 2008 [60]	People with RA	n6 GLA vs MUFA, 9 months, 1.32g/d GLA	Moderate to high
Lalia 2015 [61]	Insulin resistant adults	n3 EPA+DHA vs MUFA, 6 months, 2.7g/d EPA+ 1.2g/d DHA	Moderate or high
Lau 1993 [62]	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 [63]	People with RA and active synovitis	n6 GLA vs mixed fats including LA, 24 weeks, 1.4g/d GLA	Moderate to high
Leventhal 1994 [64]	People with RA and active synovitis	n6 GLA & n3 ALA vs n6 LA, 24 weeks, 2g/d GLA	Moderate to high
Li 2015 [65]	People diagnosed with pathological non-alcoholic steatohepatitis (NASH)	n3 EPA+DHA vs nil, 6 months, dose unclear	Moderate or high
Loeschke 1996 [66]	People with UC in remission	n3 EPA+DHA vs n6 LA, 24 months, 5.1g/d EPA+DHA	Moderate or high
Lorenz-Meyer 1996 [67]	People with CD in remission (but with a recent relapse)	n3 EPA+DHA vs n6 LA, 12 months, 3.3g/d EPA + 1.8g/d DHA	Low
Mantzaris 1996 [68]	People with UC in clinical, endoscopic & histological remission	n3 EPA+DHA Vs MUFA, 12 months, 3.2g/d EPA & 2.1g/d DHA	Moderate to high
MARGARIN - Bemelmans 2002 [69, 70]	Hypercholesterolaemic adults with 2 or more CVD risk factors	n3 ALA vs n6 LA, 2 years, dose unclear	Low
MARINA - Sanders 2011 [71]	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 [72]	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 [73]	People with Crohn's Disease in remission	n3 EPA+DHA vs nil, 24 months, dose unclear	Moderate or high
MENU - Rock 2016 [74]	Overweight and obese women, of whom half were insulin resistant	n3 ALA vs nil, 12 months, dose unclear	Moderate or high
Moore 2006 [75]	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 [76]	Middle-aged men and women with metabolic syndrome	PUFA & n6 vs MUFA, 6 months, 27.6g/d PUFA	Moderate or high
Niki 2016 [77]	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 [78]	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 [79]	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 [80]	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 [81]	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 [82]	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 [83-85]	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 [86-92]	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 [93]	Adults with hypertriglyceridaemia	n3 EPA+DHA high dose vs low dose vs n3 EPA, 12 months, 1.86g/d EPA + 1.5 g/d DHA or 0.93g/d EPA + 0.75g/d DHA	Moderate or high
Patch 2005 [94, 95]	Healthy overweight people with mild TG elevation	n3 EPA+DHA vs nil, 6 months, 1.0g/d EPA+DHA	Moderate or high
PREDIMED 2013 [96-100]	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 [101]	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 [102, 103]	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 [104]	Adults with RA	n3 EPA+DHA vs n6 GLA, 18 months, 2.1 g EPA + 1.4 g DHA	Low
Sandhu 2016 [105]	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 [106]	People with newly-diagnosed impaired glucose metabolism and CAD	n3 EPA vs nil, 6 months, 1.8g/d EPA	Moderate or high
Skoldstam 1992 [107]	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 [108]	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 [109]	Healthy adult volunteers with BMI 25-35 kg/m^2	n3 EPA+DHA vs MUFA, 12months, unclear dose	Moderate or high
Tani 2017 [110]	People with stable CAD on statins	n3 EPA+DHA vs nil, 6 months, 1.8g/d EPA+DHA	Moderate or high
Tardivo 2015 [111]	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 [112, 113]	Sedentary postmenopausal women	n3 EPA+DHA vs nil, 6 months, 540 mg/d EPA + 360 mg/d DHA	Moderate or high
THIS DIET 2008 [114]	Recent survivors of first myocardial infarction	n3 EPA+DHA vs nil, 24 months, dose unclear	Moderate or high
Varghese 2000 [115]	People with active and extensive ulcerative colitis	n3 vs n6, 6 months, 5.6mg/d (sic) n3 (unclear whether ALA or LCn3)	Moderate to high
Veleba 2015 [116]	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 [117, 118]	People with stable coronary artery disease	n6 LA vs SFA, 2 years, 15% E n6	Moderate to high
Westberg 1990 [119]	Adults with a long-term systemic lupus erythematosus	n3 EPA vs MUFA, 6 months, ~3.5g/d EPA+DHA	Moderate or high
Witte 2012 [120-122]	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 [123]	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

Additional Table 2. GRADE assessment of certainty of evidence relating to effects of LCn3 on IBD outcomes

High compared to low LCn3 (primary IBD outcomes)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low LCn3 (primary IBD outcomes)	Risk with High				
IBD relapse	473 per 1,000	**402 per 1,000** (340 to 478)	**RR 0.85** (0.72 to 1.01)	1196 (10 RCTs)	⨁⨁◯◯ LOW [a,b]	Increasing LCn3 may reduce the risk of IBD relapse.
IBD worsening	392 per 1,000	**334 per 1,000** (279 to 404)	**RR 0.85** (0.71 to 1.03)	748 (2 RCTs)	⨁⨁◯◯ LOW [a,c,d]	Increasing LCn3 may reduce the risk of IBD symptoms worsening.
IBD severity	The mean IBD severity was **0**	MD **0** (0 to 0)	-	18 (1 RCT)	⨁◯◯◯ VERY LOW [e,f]	The effect of increasing LCn3 on IBD severity was unclear as the evidence was of very low quality.
IBD diagnosis	3 per 1,000	**3 per 1,000** (2 to 6)	**RR 1.10** (0.63 to 1.92)	16015 (2 RCTs)	⨁⨁◯◯ LOW [f]	Increasing LCn3 may increase the risk of IBD diagnosis.
C-Reactive Protein (CRP) assessed with: mg/l	-	SMD **0.09 lower** (0.21 lower to 0.03 higher)	-	15278 (39 RCTs)	⨁◯◯◯ VERY LOW [g,h,i]	The effect of increasing LCn3 on CRP was unclear as the evidence was of very low quality.
Erythrocyte sedimentation rate (ESR) assessed with: mm/h	-	SMD **0.23 lower** (0.44 lower to 0.01 lower)	-	368 (7 RCTs)	⨁⨁⨁◯ MODERATE [h]	Increasing LCn3 probably reduces ESR.
Interleukin 6 (IL-6) assessed with: pg/ml	-	SMD **0.35 lower** (0.62 lower to 0.07 lower)	-	2234 (22 RCTs)	⨁◯◯◯ VERY LOW [g,h,j]	The effect of increasing LCn3 was unclear as the evidence was of very low quality.
Faecal calprotectin	The mean faecal calprotectin was **0**	MD **16.1 higher** (37.62 lower to 69.82 higher)	-	34 (1 RCT)	⨁⨁◯◯ LOW [k]	Increasing LCn3 may increase faecal calprotectin.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Imprecision: 95% CI includes little or no effect, downgraded once.
b. Publication bias: funnel plot suggests that some small studies may be missing, downgraded once.
c. Risk of bias: neither trial was at low summary risk of bias or low risk from compliance problems, downgraded once.
d. Publication bias: funnel plot not possible, but fixed and random effects meta-analyses suggested similar effect sizes, not downgraded.
e. Risk of bias: neither of the two included studies were at low summary risk of bias, but one was at low risk from compliance problems. Downgraded once.
f. Imprecision: 95% CI include both benefits and harms, downgraded twice.
g. Inconsistency: I2 > 50%, downgraded once
h. Imprecision: 95% CI included benefits as well as no effect, downgraded once.
i. Publication bias: funnel plot suggested some small trials with lower CRP in the LCn3 arm were missing, if these studies were added back they would suggest a greater reduction by LCn3 of CRP. Similarly, there was a small difference between the results of fixed- and random-effects meta-analyses. Downgraded once.
j. Risk of bias: while the main analysis suggested reduced IL-6, this effect was absent in the two trials at low summary risk of bias. Downgraded once.
k. Imprecision: 95% CI included both benefits and harms, downgraded twice.

Additional Table 3. Effects of LCn3 on IBD relapse

Sensitivity analysis (SA) or Subgroup type	Subgroup	Studies	Participants	Risk Ratio (M-H, Random, 95% CI)*	p-value for subgroup differences
Main analysis		10	1196	0.85 [0.72, 1.01]	-
Effects on specific diseases	Crohn's disease	6	1003	0.78 [0.60, 1.01]	0.30
	Ulcerative colitis	4	193	0.96 [0.72, 1.27]	
SA fixed effects		10	1196	0.85 [0.75, 0.97]	-
SA Low risk of bias		2	206	0.70 [0.30, 1.66]	-
SA Low risk of bias for compliance		4	224	0.76 [0.49, 1.18]	-
SA ≥100 participants		3	873	0.93 [0.80, 1.08]	-
Subgroup by intervention type	dietary advice	0	0	Not estimable	0.14
	supplemental foods	0	0	Not estimable	
	Supplementary capsules	9	1168	0.87 [0.74, 1.03]	
	any combination	1	28	0.37 [0.12, 1.15]	
Subgroup by LCn3 dose	LCn3 ≤150mg/d	0	0	Not estimable	0.15
	LCn3 150 to ≤250mg/d	0	0	Not estimable	
	LCn3 >250 to ≤400mg/d	0	0	Not estimable	
	LCn3 >400 to ≤2400mg/d	1	20	0.54 [0.04, 7.36]	
	LCn3 >2.4g/d to ≤4.4g/d	4	840	0.73 [0.53, 1.01]	
	LCn3 >4.4g/d	4	308	1.01 [0.83, 1.22]	
	dose unclear	1	28	0.37 [0.12, 1.15]	
Subgroup by duration	6 months to <12 months	1	20	0.54 [0.04, 7.36]	0.90
	12 months to <24 months	7	1084	0.85 [0.70, 1.02]	
	24 months to <48 months	2	92	0.71 [0.26, 2.00]	
	48+ months	0	0	Not estimable	
Subgroup by replacement	n3 vs SFA	2	102	0.44 [0.27, 0.71]	0.02
	n3 vs MUFA	3	129	0.88 [0.61, 1.28]	
	n3 vs n6	2	199	1.05 [0.84, 1.32]	
	n3 vs non-fat placebo, nil or unclear	3	766	0.86 [0.71, 1.05]	
Subgroup by age	Mean age <40 years	6	1005	0.93 [0.81, 1.07]	0.23
	Mean age 40-50 years	3	160	0.64 [0.36, 1.13]	
	Mean age >50+ years	0	0	Not estimable	
	Mean age unclear	1	31	0.38 [0.09, 1.65]	
Subgroup by sex	Over 70% male	0	0	Not estimable	0.27
	30%-70% male/female balance	9	1165	0.86 [0.73, 1.02]	
	Over 70% female	0	0	Not estimable	
	Sex unclear	1	31	0.38 [0.09, 1.65]	
Subgroup by IBD status at baseline	In remission	5	234	0.64 [0.38, 1.08]	0.23
	Stable on low dose steroid medication	4	827	0.88 [0.75, 1.03]	
	Recent relapse	1	135	1.05 [0.80, 1.37]	
Subgroup by medication taken	No meds taken	1	28	0.37 [0.12, 1.15]	0.28
	>50% using 5-ASA	4	193	0.96 [0.72, 1.27]	
	>50% using a corticosteroid	3	873	0.93 [0.80, 1.08]	

	Meds unclear	0	0	Not estimable	

*Except for fixed effects analysis where noted.

Additional Table 4. Effects of LCn3 on IBD worsening

Sensitivity analysis (SA) or Subgroup type	Subgroup	Studies	Participants	Risk Ratio (M-H, Random, 95% CI)*
Main analysis		2	748	0.85 [0.71, 1.03]
Subgroup by disease	CD	2	748	0.85 [0.71, 1.03]
	UC	0	0	Not estimable
SA fixed effects		2	748	0.85 [0.70, 1.02]
SA low summary risk of bias		0	0	-
SA low risk of compliance problems		0	0	-

Additional Table 5. Effects of LCn3 on IBD diagnoses

Sensitivity analysis (SA) or Subgroup type	Studies	Participants	Risk Ratio (M-H, Random, 95% CI)*
Main analysis	2	16015	1.10 [0.63, 1.92]
SA fixed effects	2	16015	1.10 [0.63, 1.92]
SA low risk of bias	2	16015	1.10 [0.63, 1.92]
SA low risk of compliance problems	1	535	1.60 [0.07, 39.15]

Additional Table 6. Effects of LCn3 on CRP, mg/l

Sensitivity analysis (SA) or Subgroup type	Subgroup	Studies	Participants	Std. Mean Difference (IV, Random, 95% CI)*	p-value for subgroup differences
Main analysis		39	15278	-0.09 [-0.21, 0.03]	-
Test reported as	CRP	13	1305	-0.28 [-0.75, 0.19]	0.32
	hs-CRP	26	13973	-0.04 [-0.10, 0.02]	
SA fixed effects		39	15278	-0.06 [-0.12, -0.01]	-
SA low summary risk of bias		4	2845	-0.06 [-0.13, 0.02]	-
SA low risk for compliance problems		24	13672	-0.04 [-0.10, 0.03]	-
SA ≥100 participants		21	14381	-0.04 [-0.10, 0.02]	-
Intervention type	dietary advice	1	71	0.27 [-0.20, 0.73]	0.41
	supplemental foods	3	2531	-0.05 [-0.16, 0.07]	
	supplements	33	12085	-0.13 [-0.30, 0.04]	
	any combination	2	591	-0.18 [-0.56, 0.21]	
LCn3 dose (mg/d)	≤ 150	0	0	Not estimable	0.97
	150 to ≤250	1	31	Not estimable	
	>250 to ≤400	5	2607	-0.04 [-0.15, 0.08]	
	>400 to ≤2400	14	2035	-0.02 [-0.15, 0.11]	
	>2400 to ≤4400	13	10084	-0.07 [-0.18, 0.05]	
	>4400	1	146	-0.05 [-0.38, 0.27]	
	dose unclear	5	375	-0.55 [-1.60, 0.50]	
Replacement	n3 vs SFA	2	80	0.25 [-0.31, 0.81]	0.28
	n3 vs MUFA	8	1959	-0.07 [-0.17, 0.02]	
	n3 vs n6	11	1995	-0.07 [-0.23, 0.10]	
	Higher n3 vs lower n3	2	1548	0.02 [-0.08, 0.12]	
	n3 vs non-fat placebo or nil or unclear	18	9774	-0.27 [-0.60, 0.07]	
Duration	6 months to <12 months	26	2593	-0.17 [-0.37, 0.04]	0.34
	12 months to <24 months	8	1271	0.02 [-0.12, 0.16]	
	24 months to <48 months	4	3235	-0.03 [-0.17, 0.11]	
	48+ months	1	8179	Not estimable	
Sex	>70% male	13	12610	-0.27 [-0.60, 0.05]	0.43
	30-70% male/female balance	18	2130	-0.05 [-0.15, 0.05]	
	>70% female	8	538	-0.08 [-0.27, 0.11]	
Mean age	<40y	0	0	Not estimable	0.58
	40-50y	6	356	0.05 [-0.22, 0.31]	
	50-60y	17	2499	-0.16 [-0.38, 0.05]	
	60-70y	11	11578	-0.04 [-0.18, 0.10]	
	70-80y	2	660	0.04 [-0.26, 0.33]	
	>80y	0	0	Not estimable	
	unclear	3	185	-0.22 [-0.63, 0.18]	
Medications taken	No 5-ASA, NSAID or corticosteroids taken	21	5754	-0.04 [-0.10, 0.03]	0.90

	>50% using 5-ASA	1	26	0.07 [-0.70, 0.84]	
	>50% using corticosteroid	0	0	Not estimable	
	>50% using NSAIDs	3	204	-0.09 [-0.39, 0.20]	
	>50% taking combination 5-ASA, NSAID, corticosteroid	0	0	Not estimable	
	unclear/not stated	14	9294	-0.23 [-0.58, 0.12]	
Diseases at baseline	IBD	0	0	Not estimable	0.67
	Rheumatoid Arthritis	3	100	-0.09 [-0.57, 0.38]	
	Systematic Lupus Erythematosus	0	0	Not estimable	
	NASH & NAFLD	3	246	-1.13 [-3.82, 1.57]	
	Metabolic syndrome & Diabetes	8	8654	-0.20 [-0.48, 0.09]	
	At risk for CVD	16	5253	-0.04 [-0.13, 0.05]	
	Healthy	5	629	0.05 [-0.11, 0.20]	
	Other health conditions	4	396	-0.09 [-0.29, 0.11]	

Additional Table 7. Effects of LCn3 on ESR, mm/h

Sensitivity analysis (SA) or Subgroup type	**Studies**	**Participants**	**Std. Mean Difference (IV, Random, 95% CI)**
Main analysis	7	368	-0.23 [-0.44, -0.01]
SA fixed effects	7	368	-0.23 [-0.44, -0.01]
SA risk of bias	1	78	-14.00 [-25.33, -2.67]
SA compliance	2	121	-0.31 [-0.84, 0.22]

Additional Table 8. Effects of LCn3 on IL-6, pg/ml

Sensitivity analysis (SA) or Subgroup type	Subgroup	Studies	Participants	Std. Mean Difference (IV, Random, 95% CI)*	p-value for subgroup differences
Main analysis		22	2234	-0.35 [-0.62, -0.07]	-
SA fixed effects		22	2234	-0.34 [-0.44, -0.23]	-
SA Low summary risk of bias		2	71	-0.11 [-0.67, 0.44]	-
SA Low risk of compliance problems		16	1450	-0.37 [-0.76, 0.02]	-
SA ≥100 participants		6	1412	-0.67 [-1.41, 0.07]	-
Intervention type	dietary advice	0	0	Not estimable	0.002
	supplemental food	1	32	0.18 [-0.51, 0.88]	
	supplements	18	1615	-0.46 [-0.75, -0.17]	
	any combination	3	587	0.41 [0.00, 0.81]	
Dose of LCn3, mg/d	≤ 150	0	0	Not estimable	0.79
	150 to ≤250	0	0	Not estimable	
	>250 to ≤400	2	78	-0.10 [-0.95, 0.75]	
	>400 to ≤ 2400	13	1678	-0.38 [-0.76, -0.01]	
	>2400 to ≤4400	6	506	-0.24 [-0.69, 0.20]	
	>4400	0	0	Not estimable	
	unclear	1	32	0.18 [-0.51, 0.88]	0.19
Study duration, months	6 to <12	17	1268	-0.23 [-0.43, -0.04]	
	12 to < 24	3	461	-1.13 [-2.53, 0.28]	
	24 to <48	2	505	0.40 [-0.52, 1.32]	
	48+	0	0	Not estimable	
Replacement	LCn3 vs SFA	1	49	0.30 [-0.27, 0.86]	0.14
	LCn3 vs MUFA	4	289	-1.04 [-2.09, 0.01]	
	LCn3 vs n6	9	1362	-0.30 [-0.62, 0.01]	
	LCn3 vs protein	1	41	0.15 [-0.51, 0.81]	
	LCn3 vs non-fat placebo or nil or unclear	7	493	-0.21 [-0.55, 0.12]	
Mean age, years	<40	1	39	-1.40 [-2.11, -0.69]	0.02
	40-50	2	96	-0.20 [-0.76, 0.35]	
	50-60	6	383	-0.20 [-0.57, 0.17]	
	60-70	7	561	-0.61 [-1.31, 0.08]	
	70-80	4	1035	-0.16 [-0.41, 0.08]	
	>80	0	0	Not estimable	
	Unclear	2	120	0.57 [0.05, 1.08]	
Sex	>70% male	4	699	-1.76 [-2.31, -1.22]	<0.00001
	30-70% male/female balance	12	1174	-0.28 [-0.47, -0.09]	
	>70% female	5	301	-0.16 [-0.49, 0.16]	
	Unclear	1	60	0.57 [0.05, 1.08]	
IBD at baseline	IBD study	1	32	0.53 [-0.53, 1.58]	0.10
	Non-IBD study	21	2226	-0.35 [-0.63, -0.08]	

Baseline health status	IBD	1	32	0.53 [-0.53, 1.58]	0.25
	NASH & NAFLD	1	49	0.30 [-0.27, 0.86]	
	Metabolic syndrome & Diabetes	5	276	-0.22 [-0.57, 0.13]	
	at risk for CVD	7	1109	-0.62 [-1.58, 0.35]	
	Healthy	6	431	-0.30 [-0.52, -0.09]	
	Other	3	361	-0.45 [-1.27, 0.38]	
Medications used	No 5-ASA, NSAID or corticosteroid taken	11	1433	-0.65 [-1.16, -0.14]	-
	>50% using 5-ASA	0	0	Not estimable	
	>50% using corticosteroid	0	0	Not estimable	
	>50% using NSAIDs	0	0	Not estimable	
	>50% taking combined NSAID, corticosteroid or 5-ASA	0	0	Not estimable	
	Unclear	11	801	-0.12 [-0.35, 0.11]	

Additional Table 9. Effects of LCn3 on secondary inflammatory markers

Outcome	**Studies**	**Participants**	**Std. Mean Difference (IV, Random, 95% CI)**
2.5 TNF-alpha, pg/ml	18	1774	-0.45 [-0.81, -0.09]
2.6 ICAM-1, ng/ml	5	639	0.04 [-0.43, 0.50]
2.7 VCAM-1, ng/ml	4	388	-0.18 [-0.87, 0.51]

Additional Table 10. GRADE assessment of certainty of evidence relating to effects of ALA on IBD outcomes

High compared to low ALA (primary IBD outcomes)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low ALA (primary IBD outcomes)	Risk with High				
IBD remission	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
IBD relapse	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
IBD worsening	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
IBD severity	The mean IBD severity was **0**	not pooled	-	(0 RCTs)	-	No evidence found.
IBD diagnosis (new cases)	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
CRP (C-Reactive Protein) assessed with: mg/L	-	SMD **0** (0.08 lower to 0.07 higher)	-	2715 (4 RCTs)	⨁⨁⨁⨁ HIGH	Increasing LCn3 has little or no effect on CRP.
ESR (Erythrocyte Sedimentation Rate) assessed with: mm/h	not pooled	not pooled	-	(0 RCTs)	-	No evidence found.
IL-6 (interleukin 6) assessed with: pg/ml	-	SMD **0.04 lower** (0.33 lower to 0.24 higher)	-	255 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	Increasing LCn3 may have little or no effect on IL-6.
Faecal calprotectin assessed with: ??	The mean faecal calprotectin was **0**	not pooled	-	(0 RCTs)	-	No evidence found.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias: none of the included trials were at low summary risk of bias. Downgraded once.
b. Imprecision: 95% CI includes benefit and harm, downgraded once.

Additional Table 11. Effects of ALA on CRP, mg/l

Analysis	Studies	Participants	Std. Mean Difference (IV, Random, 95% CI)
Main analysis	4	2715	-0.00 [-0.08, 0.07]
Subgroup by CRP mg/l	1	86	-0.14 [-0.56, 0.28]
Subgroup by hs-CRP mg/l	3	2629	0.00 [-0.08, 0.08]
SA fixed effects	4	2715	-0.00 [-0.08, 0.07]
SA low summary risk of bias	3	2589	-0.01 [-0.10, 0.09]
SA compliance	3	2629	0.00 [-0.08, 0.08]

Additional Table 12. Effects of ALA on IL-6, pg/ml

Analysis	Studies	Participants	Std. Mean Difference (IV, Random, 95% CI)
Main analysis	3	255	-0.04 [-0.33, 0.24]
SA fixed effects	3	255	-0.04 [-0.33, 0.24]
SA low summary risk of bias	0	0	Not estimable
SA compliance	3	255	-0.04 [-0.33, 0.24]

Additional Table 13. GRADE assessment of certainty of evidence relating to effects of omega-6 on IBD outcomes

High compared to low omega 6 (primary IBD outcomes) for health problem or population

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low omega 6 (primary IBD outcomes)	Risk with High				
IBD remission	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
IBD relapse	143 per 1,000	**77 per 1,000** (6 to 1,000)	**RR 0.54** (0.04 to 7.36)	20 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	The effect of increasing omega-6 on IBD relapse is unclear as the evidence is of very low quality.
IBD worsening	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
IBD severity assessed with: stool consistency, solid=0, loose=1, watery=2	The mean IBD severity was **0.6**	MD **0.3 lower** (0.73 lower to 0.13 higher)	-	20 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	The effect of increasing omega-6 is unclear as the evidence is of very low quality.
IBD diagnosis (new cases)	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
CRP (C-Reactive Protein) assessed with: mg/L	The mean CRP (C-Reactive Protein) was **3.16** mg/L	MD **0.19 mg/L higher** (0.28 lower to 0.66 higher)	-	228 (2 RCTs)	⨁⨁◯◯ LOW [d,e]	Increasing omega-6 may have little or no effect on CRP.
ESR (Erythrocyte Sedimentation Rate) assessed with: mm/h	The mean ESR (Erythrocyte Sedimentation Rate) was **4** mm/h	MD **4 mm/h higher** (10.55 lower to 18.55 higher)	-	75 (3 RCTs)	⨁◯◯◯ VERY LOW [a,c]	The effect of increasing omega-6 is unclear as the evidence is of very low quality.
IL-6 (Interleukin 6) - not measured	-	-	-	-	-	No evidence found.
Faecal calprotectin	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 RCTs)	-	No evidence found.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias: the single included trial was not at low summary risk of bias. Downgraded once.
b. Imprecision: the 95% CI included very big harms and very big benefits (there were only 2 events). Downgraded twice.
c. Imprecision: the 95% CI included big benefits and big harms. Downgraded twice.
d. Risk of bias: neither of the included trials were at low summary risk of bias. Downgraded once.
e. Imprecision: the 95% CI included both benefits and harms. Downgraded once.

Additional Table 14. Effects of omega-6 on CRP, mg/L

Analysis	Studies	Participants	Mean Difference (IV, Random, 95% CI)
Main analysis	3	262	0.19 [-0.28, 0.66]
Subgroup by CRP	1	34	Not estimable
Subgroup by hs-CRP	2	228	0.19 [-0.28, 0.66]
SA fixed effects	3	262	0.19 [-0.28, 0.66]
SA low RoB	0	0	Not estimable
SA low risk for compliance problems	0	0	Not estimable

Additional Table 15. Effects of omega-6 on ESR, mm/h

Analysis	Studies	Participants	Mean Difference (IV, Random, 95% CI)
Main analysis	3	75	4.00 [-10.55, 18.55]
SA Fixed effects	3	75	0.27 [-0.78, 1.32]
SA Low summary RoB	0	0	Not estimable
SA Low risk for compliance problems	0	0	Not estimable

Additional Table 16. GRADE assessment of certainty of evidence relating to effects of total PUFA on IBD outcomes

High compared to low total PUFA (primary IBD outcomes)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low total PUFA (primary IBD outcomes)	Risk with High				
IBD remission	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
IBD relapse	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
IBD worsening	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
IBD severity	The mean IBD severity was **0**	not pooled	-	(0 RCTs)	-	No evidence found.
IBD diagnosis (new cases)	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found.
CRP	The mean CRP was **3.4** mg/L	MD **0.21 mg/L higher** (0.06 lower to 0.49 higher)	-	385 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	The effect of increasing total PUFA is unclear as the evidence was of very low quality.
ESR	not pooled	not pooled	-	(0 RCTs)	-	No evidence found.
IL-6 assessed with: pg/ml	The mean IL-6 was **1.8** pg/ml	MD **0.08 pg/ml lower** (0.18 lower to 0.02 higher)	-	611 (2 RCTs)	⨁⨁◯◯ LOW [a,d]	Increasing total PUFA may have little or no effect on IL-6.
faecal calprotectin	not pooled	not pooled	-	(0 RCTs)	-	No evidence found.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

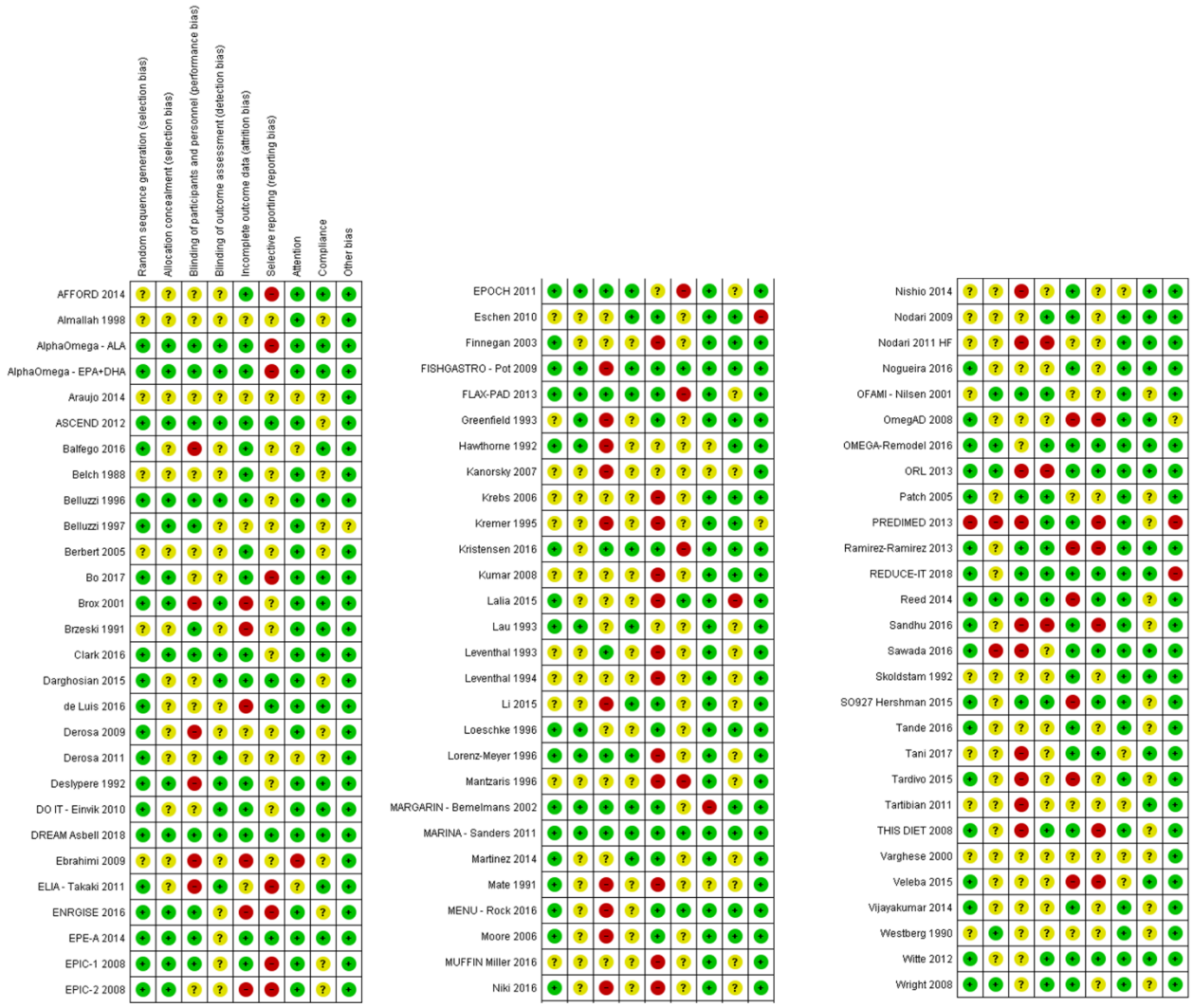
a. Risk of bias: none of the included studies were at low summary risk of bias. Downgraded once.
b. Inconsistency: I2 >50%. Downgraded once.
c. Imprecision: SMD not statistically significant.
d. Imprecision: 95% CI includes both benefit and no effect. Downgraded once.

Additional Table 17. Effects of total PUFA on CRP, mg/L

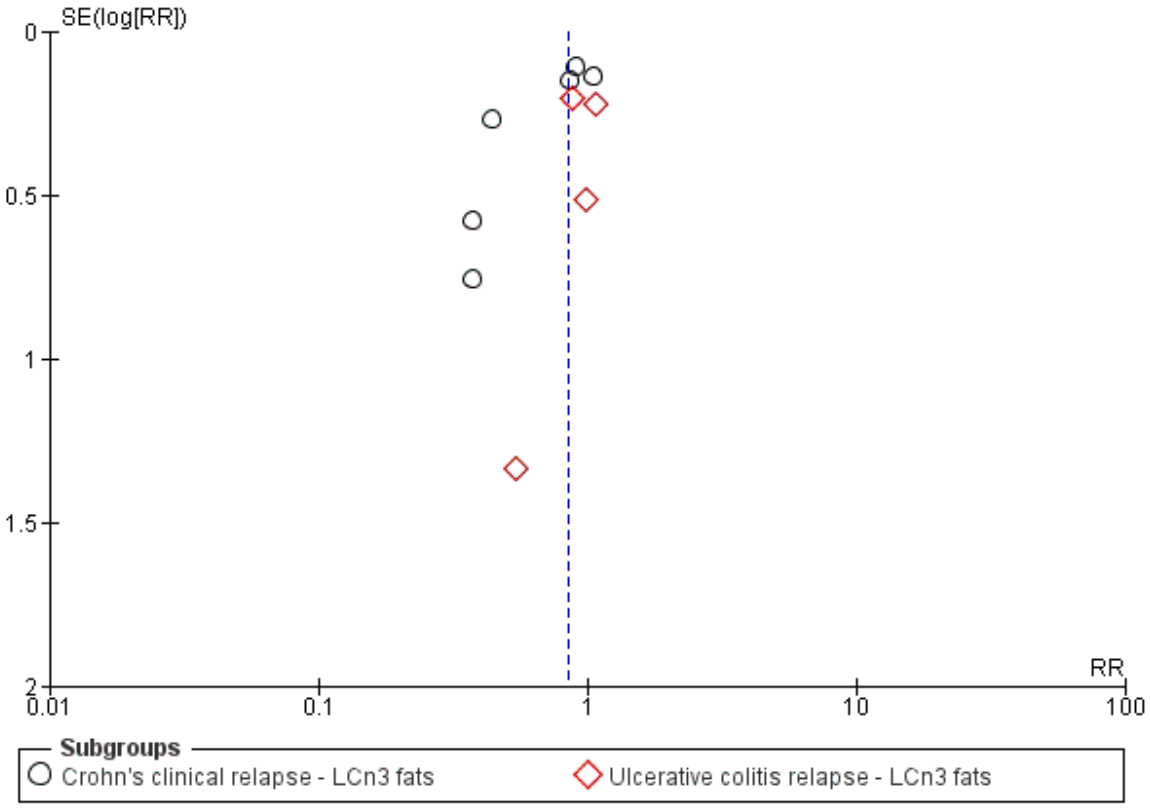
Analysis	Studies	Participants	Mean Difference (IV, Random, 95% CI)
Main analysis	4	385	0.21 [-0.06, 0.49]
Subgroup by CRP	2	221	0.23 [-0.09, 0.55]
Subgroup by hs-CRP	2	164	0.01 [-1.22, 1.24]
SA Fixed Effects	4	385	0.18 [-0.04, 0.40]
SA Low summary risk of bias	1	154	0.23 [-0.09, 0.55]
SA Low risk for compliance problems	0	0	Not estimable

Additional Table 18. Effects of total PUFA on IL-6, pg/ml

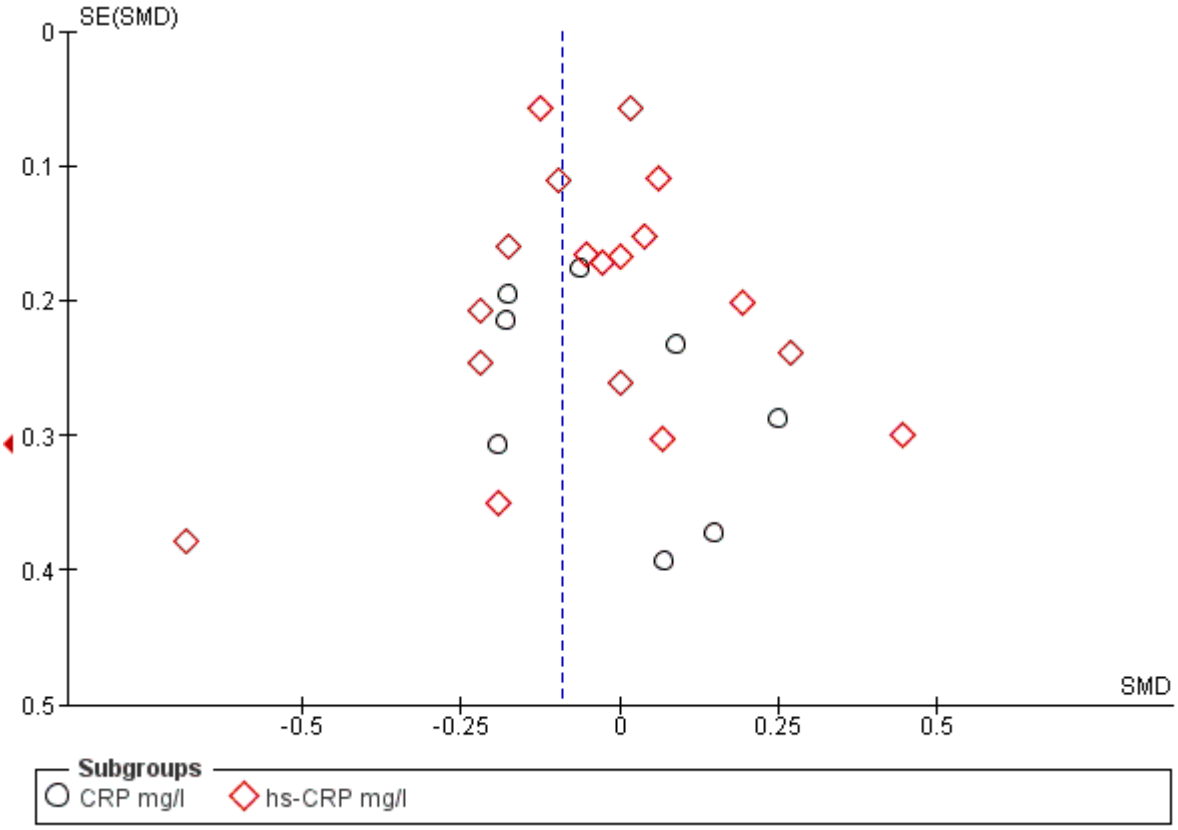
Analysis	Studies	Participants	Mean Difference (IV, Random, 95% CI)
Main analysis	2	611	-0.08 [-0.18, 0.02]
SA fixed effects	2	611	-0.09 [-0.24, 0.07]
SA Low summary risk of bias	0	0	Not estimable
SA Low risk of compliance problems	1	126	-0.13 [-0.48, 0.22]



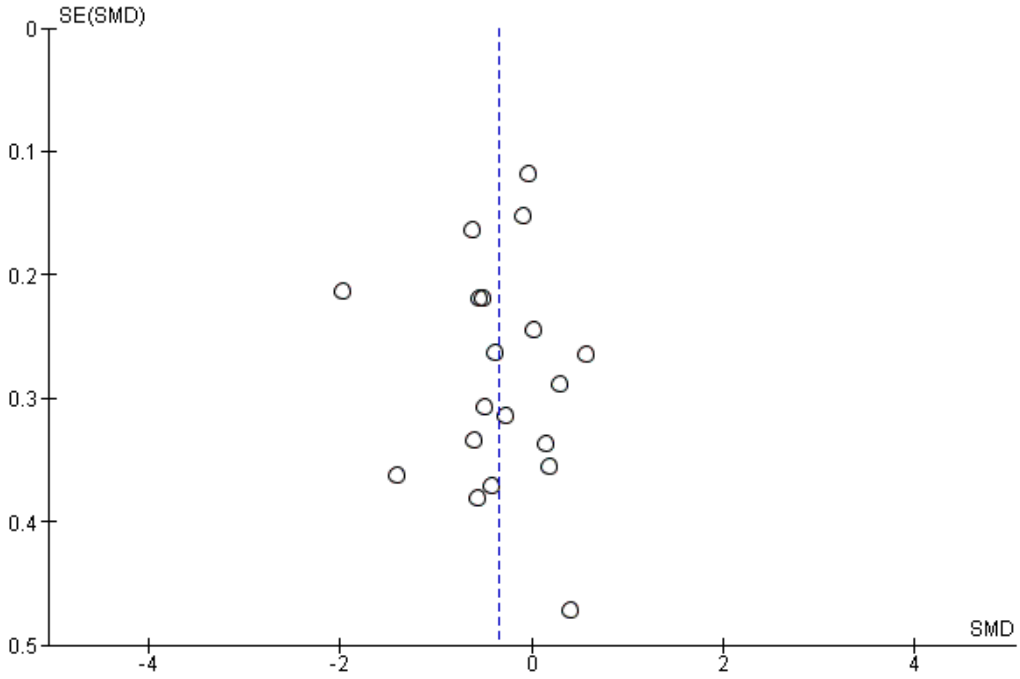
Additional Figure 1. Risk of bias assessment for each of the included studies.



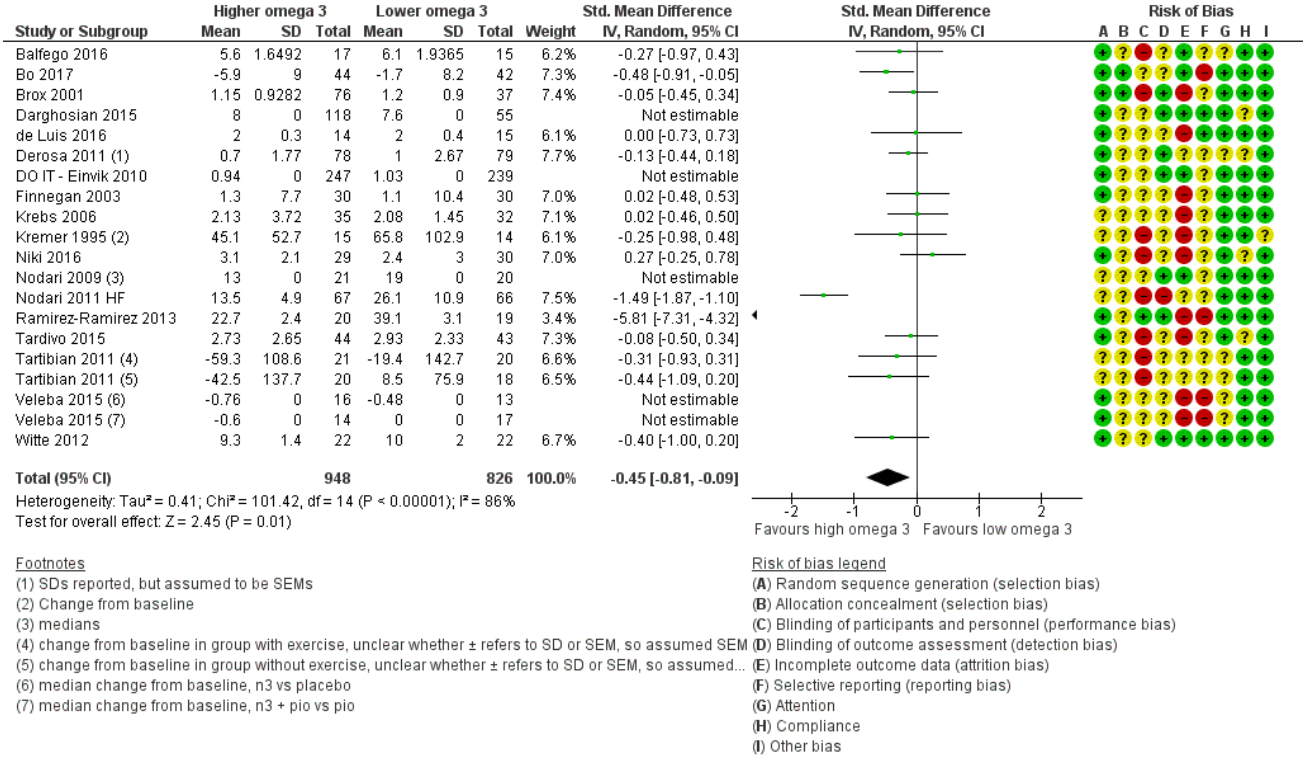
Additional Figure 2. Funnel plot of the effects of LCn3 on relapse in IBD.



Additional Figure 3. Funnel plot of the effects of LCn3 on CRP.



Additional Figure 4. Funnel plot of the effects of LCn3 on IL-6.



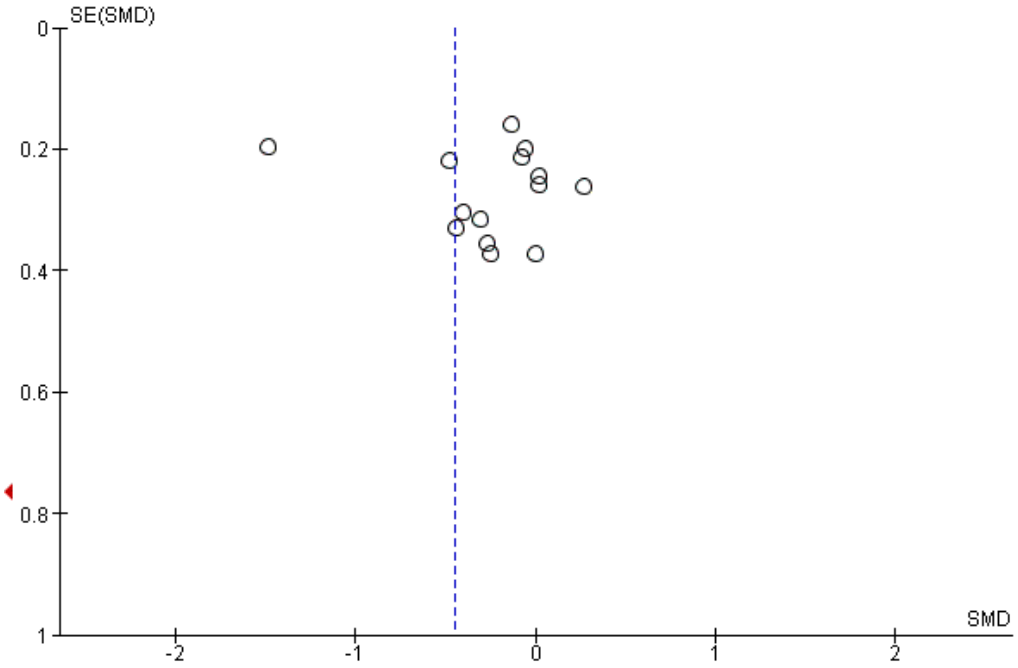
Study or Subgroup	Higher omega 3 Mean	SD	Total	Lower omega 3 Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Balfego 2016	5.6	1.6492	17	6.1	1.9365	15	6.2%	-0.27 [-0.97, 0.43]
Bo 2017	-5.9	9	44	-1.7	8.2	42	7.3%	-0.48 [-0.91, -0.05]
Brox 2001	1.15	0.9282	76	1.2	0.9	37	7.4%	-0.05 [-0.45, 0.34]
Darghosian 2015	8	0	118	7.6	0	55		Not estimable
de Luis 2016	2	0.3	14	2	0.4	15	6.1%	0.00 [-0.73, 0.73]
Derosa 2011 (1)	0.7	1.77	78	1	2.67	79	7.7%	-0.13 [-0.44, 0.18]
DO IT - Einvik 2010	0.94	0	247	1.03	0	239		Not estimable
Finnegan 2003	1.3	7.7	30	1.1	10.4	30	7.0%	0.02 [-0.48, 0.53]
Krebs 2006	2.13	3.72	35	2.08	1.45	32	7.1%	0.02 [-0.46, 0.50]
Kremer 1995 (2)	45.1	52.7	15	65.8	102.9	14	6.1%	-0.25 [-0.98, 0.48]
Niki 2016	3.1	2.1	29	2.4	3	30	7.0%	0.27 [-0.25, 0.78]
Nodari 2009 (3)	13	0	21	19	0	20		Not estimable
Nodari 2011 HF	13.5	4.9	67	26.1	10.9	66	7.5%	-1.49 [-1.87, -1.10]
Ramirez-Ramirez 2013	22.7	2.4	20	39.1	3.1	19	3.4%	-5.81 [-7.31, -4.32]
Tardivo 2015	2.73	2.65	44	2.93	2.33	43	7.3%	-0.08 [-0.50, 0.34]
Tartibian 2011 (4)	-59.3	108.6	21	-19.4	142.7	20	6.6%	-0.31 [-0.93, 0.31]
Tartibian 2011 (5)	-42.5	137.7	20	8.5	75.9	18	6.5%	-0.44 [-1.09, 0.20]
Veleba 2015 (6)	-0.76	0	16	-0.48	0	13		Not estimable
Veleba 2015 (7)	-0.6	0	14	0	0	17		Not estimable
Witte 2012	9.3	1.4	22	10	2	22	6.7%	-0.40 [-1.00, 0.20]
Total (95% CI)			**948**			**826**	**100.0%**	**-0.45 [-0.81, -0.09]**

Heterogeneity: Tau² = 0.41; Chi² = 101.42, df = 14 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.45 (P = 0.01)

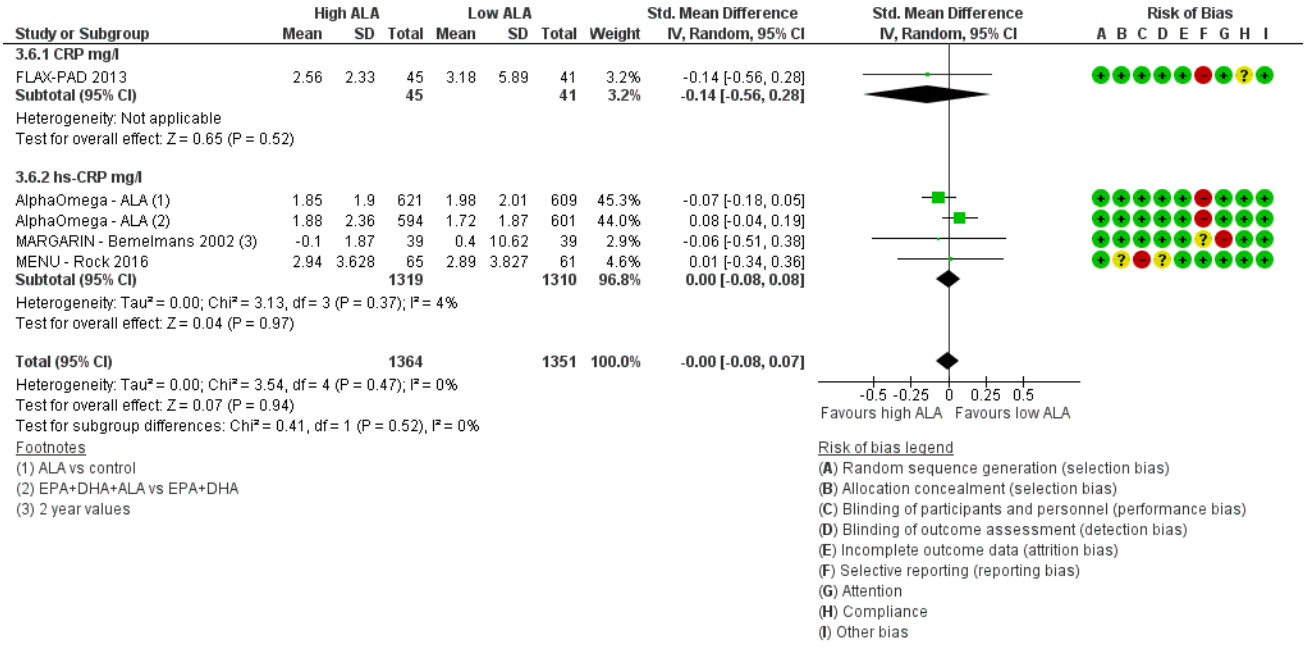
Footnotes
(1) SDs reported, but assumed to be SEMs
(2) Change from baseline
(3) medians
(4) change from baseline in group with exercise, unclear whether ± refers to SD or SEM, so assumed SEM
(5) change from baseline in group without exercise, unclear whether ± refers to SD or SEM, so assumed...
(6) median change from baseline, n3 vs placebo
(7) median change from baseline, n3 + pio vs pio

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Attention
(H) Compliance
(I) Other bias

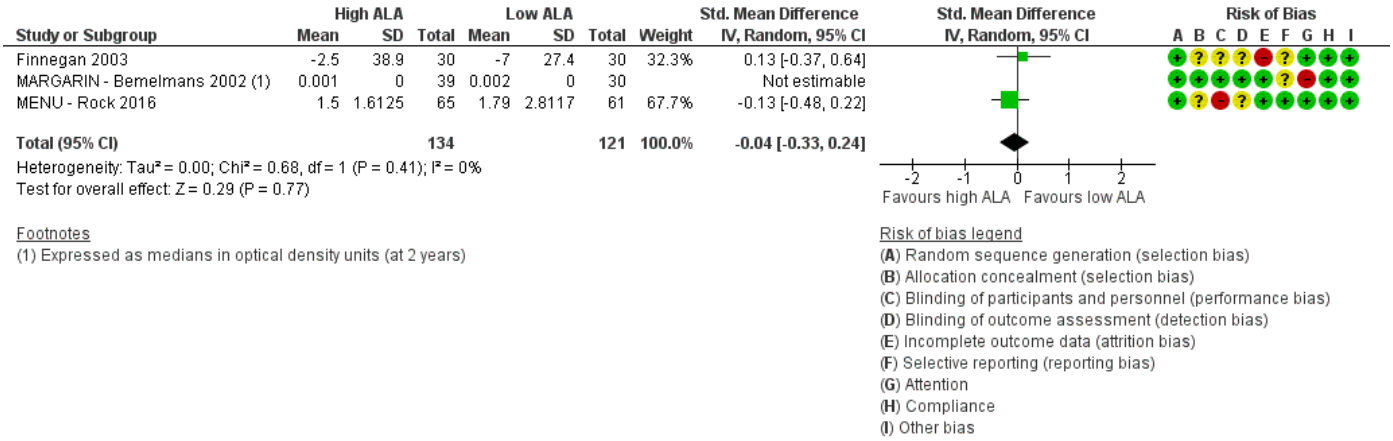
Additional Figure 5. Forest plot of meta-analysis on effects of LCn3 on TNF-alpha using SMD in random effects meta-analysis.



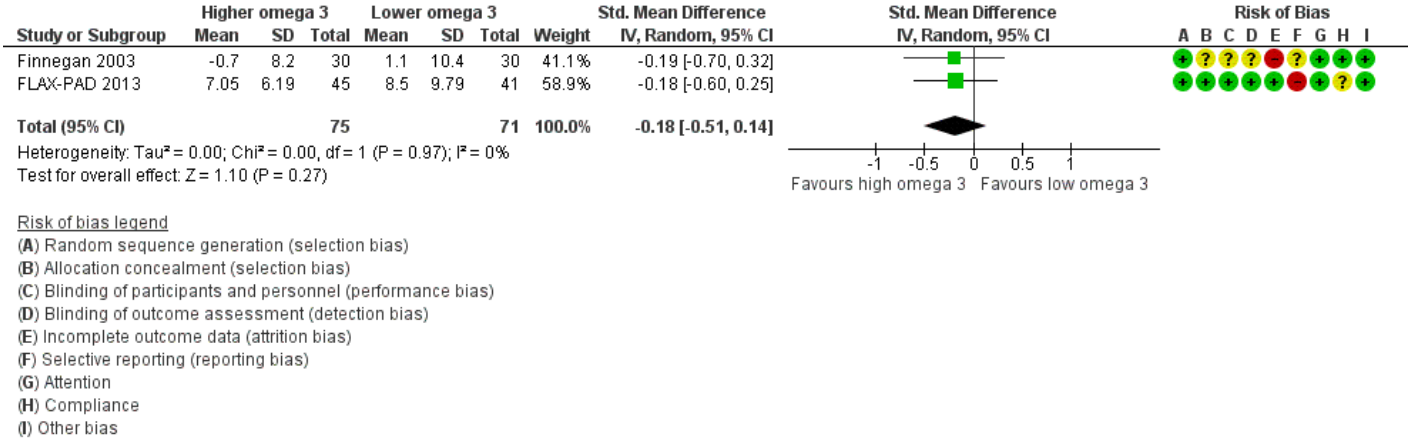
Additional Figure 6. Funnel plot of the effects of LCn3 on TNF-alpha.



Additional Figure 7. Forest plot of meta-analysis on effects of ALA on CRP, mg/l, using SMD in random effects meta-analysis.



Additional Figure 8. Forest plot of meta-analysis on effects of ALA on IL-6, pg/ml, using SMD in random effects meta-analysis.



Additional Figure 9. Forest plot of meta-analysis on effects of ALA on TNF-alpha, pg/ml, using SMD in random effects meta-analysis.

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