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Assessing the effects of cod liver oil/omega-3 polyunsaturated fatty acids on health outcomes

Dr James Brown

Afatscientist Ltd.

For enquiries please contact james@afatscientist.uk or ben@adurocommunications.co.uk

Contents

Summary Points

- Omega-3 PUFA supplements appear, in general, to be safe and well tolerated.
- Use of omega-3 PUFA/marine oil supplements seem to reproducibly increase the levels of EPA and DHA in the blood and in some cells/tissues.
- Many people could benefit from an increased intake of omega-3 fatty acids. The typical UK diet contains relatively low amounts of these.
- Omega-3 PUFA/marine oils may have a role in treatment of various mental disorders, such as depression and anxiety
- Omega-3 PUFA/marine oils appear to reduce the risk of heart disease. It may help to reduce the risk by reducing blood levels of TAG, preventing atherosclerosis and reducing blood pressure
- Omega-3 PUFA/marine oils appear to improve behaviour in children with ADHD or ASD. There is mixed evidence around the benefits of omega-3 PUFA/marine oils on development and educational attainment of children.
- Omega-3 PUFA/marine oils appear to improve joint pain in individuals with OA or RA and can lead to a reduction in use of NSAIDs.
- There is some evidence that omega-3 PUFA/marine oils may improve cognitive function in older adults with MCI or mild dementia. These findings do not appear to be repeated in more severe cases of cognitive dysfunction.

Disclaimer

Afatscientist Ltd do not accept any liability for any actions taken by individuals who read this report. The purpose of this report is to gather and assess evidence of the effects of omega-3/cod liver oil consumption in humans.

Whilst there has been extensive research across many domains of health, this report has not included areas where there are very limited studies or where the evidence suggests that there is consistent reporting of no effects and should not therefore be considered as an exhaustive or definitive report.

Inclusion/exclusion criteria

Inclusion criteria:

1. Clinical trial in human subjects
2. Published in English
3. Published as peer reviewed journal article
4. Full text available
5. Post 1990

Exclusion criteria:

1. Animal studies
2. Published in non-English language
3. Conference abstracts
4. Press releases/websites where no paper can be found, no full text available to assess quality
5. Pre-1990
6. Systematic reviews and meta-analyses (these are dealt with separately due to the possibility of them using the same studies

Grading of evidence

The studies that have been included have been graded for their quality, based upon a number of factors including the design of the study (interventional or observational, method of controlling the study etc.), whether the authors conduct and report a sample size calculation, whether they recruited enough subjects to provide reliable data and whether they were registered trials (where appropriate). In general, a Double-blinded, randomised clinical trial will start as high quality (1) , but can be reduced due to having a small sample size, no reporting of a sample size calculation or statistical power etc. Equally, an observational study will start as low (5) due to the lack of intervention but quality scoring would increase due to large sample size, registration etc. The numbering system below has been applied to all studies included:

1 – High quality
2 – High to moderate quality
3 – Moderate quality
4 – Moderate to low quality
5 – Low quality

It should also be noted that a high quality study does not necessarily represent a true image of the actual effects of omega-3, nor that a low quality study is misleading. In fact, in some areas higher quality studies which have smaller sample sizes often report effects which can disappear in larger studies, and this is somewhat concerning.

Colour coding of results

Within the table in the appendices, a colour coding scheme has been used to highlight if findings were significant, inconclusive/difficult to draw conclusions from or not significant, as demonstrated below.

	Significant
	Inconclusive
	Non-significant

Abbreviations

AD – Alzheimer's disease

ADHD - Attention deficit hyperactivity disorder

ASD - autistic spectrum disorder

CHD - coronary heart disease

CLO - cod liver oil

DHA - docosahexaenoic acid

EPA - eicosapentaenoic Acid

FO - fish oil

HDL - high-density lipoprotein

LDL - low-density lipoprotein

MCI – mild cognitive impairment

NSAID – non-steroidal anti-inflammatory drug

OA - osteoarthritis

OR - odds ratio

PUFA - polyunsaturated fatty acids

RA – rheumatoid arthritis

TAG - triacylglycerol

Mental Health/Depression

A number of studies using either CLO or FO/Omega-3 supplements have shown beneficial effects on mental health issues such as depression. Whilst the findings of the studies displayed below are not universally consistent, it is reasonable to state that evidence shows that some individuals who suffer from anxiety, depression or pre-menstrual syndrome would benefit from the use of CLO/Omega-3 supplements.

Meta-analysis by Liao et al (2019) reported that omega-3 PUFAs with EPA ≥ 60% at a dosage of ≤1 g/d would have beneficial effects on depression, however further meta-analysis by Deane et al (2019) suggested that long-chain omega-3 supplementation probably has little or no effect in preventing depression or anxiety symptoms and Zhao et al (2019) found that the limited evidence of omega-3 PUFA in the acute treatment of major depressive disorder, it did not seem to offer a clear advantage for children and adolescents. This was backed up by meta-analysis by Bloch et al which reported that current published trials suggest a small but non-significant benefit of omega-3 FAs for major depression and postulated that nearly all of the treatment efficacy observed in the published literature may be attributable to publication bias.

Conclusion: Omega-3 supplementation may be beneficial in treating some people with depression, but the evidence is not strong or consistent.

Cardiovascular Health

There is a great number of studies that have investigated the impact of omega-s PUFA/marine oils on various elements of cardiovascular health. There is strong and reproducible evidence that supplementation with omega-3 PUFA/marine oils can be an effective way of reducing levels of TAG in the blood. High TAG may contribute to hardening of arteries or thickening of the artery walls which increases the risk of stroke, heart attack and heart disease.

This is further supported by large cohort studies that have identified associations between intake of omega-3 PUFA/marine oils and risk of developing heart disease which suggest that omega-3 PUFA/marine oils are an effective method of reducing the risk of a heart disease.

Additionally, systematic review and meta-analysis suggested that FO supplementation caused a clinically significant reduction in TAG and a slight increase in HDL (Eslick et al, 2009) whilst another (Bernstein et al, 2012) reported that algal oil DHA reduced TAG by 0.2 mmol/L. A Cochrane review by Abdelhamid et al (2020) reported that moderate- and low-certainty evidence suggests that increasing omega-3 PUFA slightly reduces risk of coronary heart disease mortality and events, and reduces serum triglycerides (evidence mainly from supplement trials). Djouse et al (2012) reported in meta-analysis a lower risk of heart failure with intake of marine omega-3 fatty acids, Chowdury et al (2014) reported in their meta-analysis a risk reduction of 13% for those in the top tertile of dietary EPA + DHA intake compared with those in the lower tertile of intake, whilst Alexander et al (2017) reported in their meta-analysis that EPA+DHA may be associated with reducing CHD risk, with a greater benefit observed among higher-risk populations.

Also, meta-analysis found significant reductions in blood pressure for persons with high blood pressure (140/85 or greater).

Meta-analysis of randomised controlled trials (Pase et al, 2011) reported that omega-3 supplementation improved pulse wave velocity and arterial compliance.

Conclusion: Omega-3 supplementation may be beneficial in reducing heart disease risk for some people. The evidence is relatively consistent, and is likely mediated by reductions in TAG, blood pressure and improvements in vascular function.

Child Development/Behaviour

Low blood levels of omega-3 PUFAs are associated with poor cognitive performance and behaviour in children Montgomery et al, 2013). The evidence that is currently available is mixed, however there appears to be a relatively consistent effect of omega-3 PUFA/marine oils on behaviour in children with ADHD or ASD, and there is some evidence that some sub-areas of cognitive function/performance (such as reading or planning) may be improved in children who receive omega-3 PUFA/marine oils.

Additionally, meta-analyses have reported that omega-3 supplementation is modestly effective in the treatment of ADHD in children (Bloch and Qawasmi, 2013), Bloch et al (2011) showed in a meta-analysis that EPA was modestly effective in the treatment of ADHD, Cooper et al (2015) reported marginal evidence that n-3 PUFA supplementation effects cognition in those who are n-3 PUFA deficient but not in the general population, Jasani et al (2017) reported in their meta-analysis that formula milk with added PUFAs showed benefit for visual acuity at 12 months, but no significant benefits on neurodevelopment or infant development, Jiao et al (2014) reported in their meta-analysis that n-3 PUFA supplements may significantly improve cognitive development in infants but do not improve cognitive performance in children, adults, or the elderly, Emery et al (2020) produced a meta-analysis that reported identified beneficial effects of EPA-rich but not DHA-rich formulations in the domains of long-term memory, working memory and problem solving and a tendency towards beneficial effects in clinical rather than non-clinical populations. Conversely, James et al (2011) found in their meta-analysis no effect of omega-3 supplementation on autistic spectrum disorder symptoms and two Cochrane reviews, by Simmer et al (2011) and Jasani et al (2017) concluded that the majority of the trials have not shown beneficial effects of LCPUFA supplementation on the neurodevelopmental outcomes of term infants.

Conclusion: Omega-3 supplementation may be beneficial in improving behaviour in children with ADHD or ASD. The evidence for benefits on children's development is more conflicted, and therefore it is less clear whether or not there is a benefit of omega-3PUFA/marine oils for development in children in the general population.

Cognitive Function in Dementia or Mild Cognitive Impairment

The evidence surrounding the benefits of omega-3 consumption on the cognitive function of adults is somewhat mixed, but it does appear in general that there may be beneficial effects in some groups, such as those with MCI (Table 3.2). As supplementation appears to be well tolerated in this group it would appear to be a reasonable treatment rationale. There is significantly less reporting of impact in groups with more severe cognitive function, such as those with more severe dementia or Alzheimer's disease.

Conclusion: Omega-3 supplementation may be beneficial in improving cognitive function in individuals with early stage or mild cognitive impairment, where the evidence is reasonably consistent. There is little evidence that omega-s supplementation is beneficial in more advanced cognitive dysfunction.

Joint Pain

Old age is associated with increased risk of developing issues with bony joints, including osteoarthritis. The evidence reported here (Tables 4.1 and 4.2) shows a relatively consistent story that omega-3 supplementation can improve symptoms of joint pain associated with rheumatoid or osteoarthritis.

Additionally, meta-analyses have reported that omega-3 supplementation is effective in reducing joint pain (Goldberg and Katz, 2007) and can reduce use of NSAIDS (Ho Lee et al, 2012).

Conclusion: Omega-3 supplementation may be beneficial in improving joint pain in OA or RA patients. The evidence in this area appears to be strong and consistent. Benefits may take the form of reduced pain or reduced requirement to use NSAIDs

Appendix I: CLO/Omega-3 and mental health issues

Table 1.1 Studies reporting on the effects of CLO on depression

Raeder et al, 2007	Prospective cohort study (The Hordaland Health Study '97–'99); 21,825 subjects	Symptoms of depression and anxiety	CLO users significantly less likely to have depressive symptoms (OR 0.71). Symptoms of high levels of depression decreased with increasing CLO consumption duration (> 1 year)	4

Table 1.2 Studies reporting effects of omega-3/FO supplementation on depression/mental health

Study	Supplement Used	Trial design	Outcomes	Results	Quality
Greyner et al, 2007	FO	Randomised, Double blind controlled trial; 83 patients with major depression	HDRS and depression inventory	No significant change to depression scores	3
Marangell et al, 2003	DHA	RCT; 36 depressed patients	Montgomery-Åsberg Depression Rating Scale	No significant advantage over placebo	4
Su et al, 2008	FO	Double-blind, randomised placebo-controlled trial;	Edinburgh Depression Rating Scale;	FO reduced scores on EPDS and BDI	3

		36 pregnant women with depression	Beck Depression Inventory		
Llorente et al, 2003	DHA	Double-blind, randomised controlled trial; 138 pregnant women	Edinburgh Depression Rating Scale; Beck Depression Inventory	No difference in depression	3
Jahangard et al, 2018	Omega-3 supplement	Randomised, Double-blind and placebo-controlled study; 50 patients with major depression (treated with sertraline)	Beck Depression Inventory; Montgomery-Asberg Depression Rating Scale	Depression decreased over time with omega-3 greater than placebo	1
Kiecolt-Glaser et al, 2011	EPA/DHA mix	Double-blind RCT	Centre for Epidemiological Studies Depression Scale (CES-D); Beck Anxiety Inventory; Pittsburgh Sleep Quality Index; inflammatory markers	PUFA caused 20% reduction in anxiety symptoms; no change with depressive symptoms; reduced inflammation (IL6 and TNFa)	1
Nemets et al, 2002	EPA	Parallel-group, Double-blind addition of E-EPA or placebo to	Hamilton Depression Rating Scale	EPA reduced HDRS (clinically meaningful reduction in 60%)	4

		ongoing antidepressant therapy; 20 patients with depression			
Peet and Horrobin, 2002	Ethyl-EPA	Randomised, Double-blind controlled trial; 52 persistent depression vs 18 control	Hamilton Depression Rating Scale; Montgomery-Asberg Depression Rating Scale (MADRS); Beck Depression Inventory	52% of intention to treat of EPA group saw reduced depression score (29% in control group) whereas 69% of those who completed the course saw a reduction in depression score (this was 1g, no effect with 2g or 4g)	4
Boornbos et al, 2009*	DHA	Randomised controlled trial; DHA vs placebo vs DHA plus AA; 119 pregnant women	Edinburgh Depression Rating Scale	Supplementation did not alter depression, nor incidence or severity of post-natal depression	4
Fontani et al, 2005	FO	Blind, randomised, placebo controlled trial; 33 FO vs 16 placebo (healthy volunteers)	Profile of Mood States (POMS); Zimmermann & Fimm Attention Test procedure;	Mood profile was improved after FO with increased vigour and reduced anger, anxiety and depression states	3

Kuan-Pin et al, 2003	EPA/DHA	A preliminary Double-blind, placebo-controlled trial; 28 patients with major depressive disorder	Hamilton Rating Scale for Depression	Omega-3 group had significantly reduced score in HRSD (P<0.001)	4
Freeman et al, 2008	EPA/DHA	Randomised, placebo controlled trial; 58 women with perinatal major depressive disorder	Edinburgh Postnatal Depression Scale	No benefit of omega-3 fatty acids over placebo	4
Frangou et al, 2006	Ethyl EPA	Double-blind, randomised clinical trial; 26 individuals with bipolar depression	Hamilton Rating Scale for Depression	ethyl-EPA improved (compared with placebo)the HRSD p=0.04) and the CGI (p= 0.04) scores.	4
Lucas et al, 2009	Ethyl-EPA	Double-blind, placebo-controlled, randomized clinical trial; 102 women with psychological distress or	Psychological General Well-Being Schedule; Hopkins Symptom Checklist Depression Scale; Hamilton	In women with PD without MDE at baseline, 8-wk changes in PD and depressive scales improved significantly more with E-EPA than with placebo.	1

		depressive symptoms	Depression Rating Scale		
Rees et al, 2008	FO	Double-blind randomized placebo-controlled trial; 26women with major depression	Edinburgh Postnatal Depression Scale	No effect of FO on scores of depression	4
Kiecolt-Glaser et al, 2012*	FO (unclear)	Three-arm, Double-blind placebo-controlled four month randomized clinical trial; 138 healthy subjects	Inflammation and depression (Centre for Epidemiological Studies Depression Scale)	IL6 reduced by 10 and 12% in low and high dose arm; 0.2 and 2.3% decreases in TNFa; no change in depressive symptoms	1
Mozurkewich et al, 2013	FO	Double-Blind, Randomized Controlled Trial; 118 women at risk for depression	Edinburgh Postnatal Depression Scale; Beck Depression Inventory	Serum EPA and DHA increased in serum; no changes to depression scores	1
Behboudi-Gandevani et al, 2018		A multi-centre, balanced (1:1), placebo-controlled, parallel-group randomized clinical trial; 90 Iranian	Premenstrual symptoms screening tool (PSST); SF-12 QoL questionnaire	Improved menopausal symptoms (PSST) and quality of life	3

		women with PMS			
Sohrabi et al, 2013	DHA/EPA	An exploratory pilot trial - randomised, Double-blind clinical trial; 124 Iranian women with PMS	A visual analogue score (VAS) was used to evaluate the severity of each of the symptoms	After 45 days from starting omega-3, the mean severity of depression (P = 0.03), anxiety (P = 0.02), lack of concentration (P = 0.03) and bloating (P = 0.02) in the case group, were all significantly lower than in the control group. The duration of depression (P = 0.04) and bloating (P = 0.031) in the case group were less than in the control group	3
Watanabe et al, 2018	EPA/DHA	Randomised controlled trial; 80 nurses	Hospital Anxiety and Depression Scale (HADS)	No significant difference between treatment and control arms	1
Cohen at al, 2014	FO	Multi-centre, 3 by 2 factorial design, randomized, controlled trial; 355 women	VMS frequency and bother in peri- and postmenopausal women	No improvement in omega-3 beyond placebo	1

Appendix II: CLO/Omega-3 and cardiovascular health

Table 2.1 Studies reporting on effects of CLO on lipid profiles

Study	Trial design	Outcomes	Results	Quality
Brox et al, 2001	Double blinded, placebo controlled RCT (compared to seal oil); 120 healthy subjects	Body weight, TC, HDL, TAG, Lp(a), FFA composition, CRP, TNF-a.	No significant effect on lipids; MUFA and PUFA increased in CLO and SO	3
Vognild et al, 1998	Double blinded, randomised controlled trial (CLO vs OO vs refined WO vs unrefined WO); 266 healthy subjects	Platelet responses and serum lipids	CLO increases EPA by 188% ($p<0.01$), DHA by 56% ($p<0.01$). No change in TC, LDL, HDL or TAG	3
Lentjes et al, 2015	Cohort study (7-day diary); EPIC cohort 6656 subjects	Vitamin A and D levels;	Plasma DHA and EPA levels increased	5
Helland et al, 1998	RCT; 22 lactating mothers	Lipids in milk and plasma	Highest doses of CLO caused increase in plasma DHA; plasma EPA increased in lowest and highest dose	5

Skuladottir et al, 1990	Randomised, crossover; n? post-MI patients	Plasma lipids	Phospholipid DHA and EPA increased; Plasma TG decreased; other lipids not effected.	3
Helland et al, 2001	Double blind, RCT; 590 pregnant women	Gestational length/birth weight; lipids	DHA and EPA increased in umbilical plasma; breast milk in CLO had increased n-3 PUFAs	1
Hansen et al, 1993	Controlled, crossover; 34 healthy subjects	Lipids; platelet aggregation	TAG reduced by 0.2 mmol/l ($p<0.05$) in men; LDL increased in males by 0.28 mmol/l	5

Table 2.2 Studies reporting on cardiovascular effects of CLO

Study	Trial design	Outcomes	Results	Quality
Lentjes et al, 2014	Prospective cross-sectional study (observational) - European Prospective Investigation into Cancer (EPIC) ; 25,639 subjects	Self-reported health	CLO negatively associated with cardiovascular risk; men having MI 48% less likely to use CLO; women with diabetes 50% less likely to use supplements including CLO; Women with rheumatoid arthritis 60% increased use of CLO;	3
Lentjes et al, 2017	Prospective cross-sectional study (observational) - European	CHD deaths	Baseline supplement use was not associated with CHD mortality; Negative association between	4

	Prospective Investigation into Cancer (EPIC) ; 22,035 subjects		supplement use and CHD risk (OR 0.74)	
Haraldsdottir et al, 2015	Prevalence association study; 3326 women aged 66–96 years	Diagnosed CHD	Women who took CLO 3 x per week in adolescence or later life had reduced odds of having CHD (OR 0.6)	4

Table 2.3 Studies reporting effects of omega-3/FO supplementation on lipids/cardiovascular risk

Study	Supplement Used	Trial design	Outcomes	Results	Quality
Axelrod et al, 1994*	FO	A randomized, prospective, Double-blind, controlled study; 20 T2DM patients	CVD risk factors	Reduced total cholesterol by 0.5 mmol/l. No effect on other lipids; HbA1c reduced by 0.56% and TAG by 0.49mM; SBP reduced by 8mmHg; No change in LDL or HDL.	4
Anuzzi et al, 1991*	FO	Double-blind randomized cross-over study; 8 male T2DM patients	Glucose and lipid markers	TAG reduced; VLDL reduced by 0.5 mmol/L; LDL increased by 0.6 mmol/L; no glucose or insulin changes	4
Boberg et al, 1992*	MaxEPA	Randomized Double-blind cross-over study; 14 T2DM patients	Lipids and inflammatory markers	TAG reduced by 27%; VLDL reduced by 36%PAI-1 increased in MaxEPA group	4

Oelrish et al, 2013	Different strengths of omega-3 in FO	Secondary analysis from a Double-blind, parallel design, placebo controlled trial; 42 adults	Blood lipids	TAG reduced by 26%, LDL increased by 13%; shift in LDL subtypes (both more and less atherogenic)	4
Clark et al, 1993	FO	A Double-blind, randomized crossover trial; 26 SLE patients	Platelet membrane fatty acids, indices of renal function, a disease activity index, serum lipid levels, blood pressure, serum viscosity and red cell flexibility	TAG lowered from 1.89 to 1.02 (p=0.004); VLDL also reduced	4
Davidson et al, 2007	Omega-3 ethyl esters	Multicentre, randomized, Double-blind, placebo-controlled, parallel-group study; 254 patients on stable statin therapy with elevated TAG	Percent change in non-HDL-C from baseline to the end of treatment.	Treatment plus simvastatin decreased non-HDL-C by more than placebo plus simvastatin (9 vs 2.2% respectively). TAG reduced by 29.5%; VLDL reduced by 27%	4
Connor et al, 1993*	FO	Controlled trial; 16 T2DM patients	Lipid profile	TAG and VLDL reduced, no change in HDL or glucose	5
Maki et al, 2011	Omega-3-acid Ethyl Esters	A Double-blind, randomized, controlled crossover design; 19	Lipid profile	Reduction in random and fasting TAG (0.8 and 0.5 mmol/L respectively). No other significant changes	4

		hyperlipidaemic patients			
Krebs et al, 2006*	FO	Double blind RCT; 93 overweight females	Weight loss; lipids; insulin sensitivity	FO group showed increase LC n-3 in plasma and adipose tissue; glucose AUC reduced by FO; insulin AUC reduced by FO; TAG reduced by FO (1.4 2- 0.96 mmol/L); HDL increased by FO (1.25-1.35 mmol/L)	4
Dangardt et al, 2010*	EyeQ capsules	Double-blind, cross-overdesign with a 6-week washout period; 25 obese adolescents	Vascular function and inflammatory markers	Serum PUFA increased; No change in lipids; vascular function improved;	3
Maki et al, 2008*	FO (POM-3)	randomized, crossover trial (with simvastatin); 39 subjects with hypertriglyceridaemia	Blood lipids	Non-HDL-C reduced by 40%; VLDL reduced by 42%; TAG by 44%; total cholesterol by 31%; systolic and diastolic blood pressure	4
Shirmer et al, 2012	Omega-3-acid Ethyl Esters	Randomized crossover study; 30 non diabetic (?)	blood lipids	Reduction in TAG (18%) and TAG AUC (13%)	4
Shidfar et al, 2008	Super EPA 2000 tablets	Double blind, placebo-controlled trial; 56 patients with T2DM	Blood lipids	31% decrease in TAG; no change in lipoproteins	4
Goh et al, 1997	FO (vs LO)	Double-blind crossover comparison; 28 subjects with T2DM	Blood lipids	FO reduced TAG more than LO or OO	5

Vargas et al, 2011	FO	Randomised controlled trial; 51 women with PCOS	Glucose and lipids in circulation and OGTT	FO reduced TAG (p=0.0154) but so did flax oil)	5
Skulas-Ray et al, 2011	omega-3 fatty acid ethyl ester	Placebo-controlled, Double-blind, randomized, 3-period crossover trial; 28 patients with moderate triglyceridaemia	Blood lipids	30% reduction in TAG; no change in others	4
Hendra et al, 1990*	FO (m MaxEPA)	Double blond randomised controlled trial; 80 patients with T2DM	Blood glucose and lipids	FO reduced TAG (30%, p<0.001) but not cholesterol; blood glucose increased at 3 weeks	3
Olendzki et al, 2011	FO (vs borage oil or both)	Randomized Double-blind comparison; 156 patients with RA	Blood lipids	TAG was reduced maximally at 18 months by 0.25 mmol/L; no other lipids altered	3
McManus et al, 1996*	FO (vs LO)	Randomised Double-blind crossover; 11 patients with T2DM	Blood glucose and lipids	FO reduced TAG by almost 50% (p<0.05); no change to glucose; slight decrease in insulin sensitivity	5
Zulyniak et al, 2013	FO	Cohort study; 10 healthy males	Blood lipids	Serum TAG decreased (P = 0.0006) while the proportion of HDL-c (relative to total cholesterol) increased significantly (P = 0.0495) with FO	5
Woodman et al, 2002*	EPA or DHA	Double-blind, placebo-controlled	Blood lipids; blood pressure	FPG increased by both EPA and DHA,; no effects on HbA1c or	4

		trial; 54 patients with T2DM		insulin; Only HDL increased by 16 and 12% respectively	
Poppitt et al, 2009	FO	A Randomized, Controlled Trial; 102 patients with stroke	Cardiovascular biomarkers; mood in patients	No significant effect of FO on cardiovascular markers	2
Thusgaard et al, 2009*	FO	A Randomized, Double-Blind, Placebo-Controlled Study; 51 HIV patients	Plasma lipids and inflammatory markers	EPA/DHA increased in plasma; TAG reduced by 0.14 mmol/L; No difference for other lipids	3
Ciubotaro et al, 2003*	FO	Double-blinded, placebo-controlled supplementation trial; 30 post-menopausal women	Markers of inflammation and blood lipids	FO reduced hsCRP and IL6 (more in low FO group); TAG significantly lower in high FO group	3
Morgan & Rosenstock, 1995	FO (vs CO)	Randomised controlled trial; 40 hyperlipidaemic men with T2DM	Blood lipids	FO reduced VLDL, TAG. LDL briefly increased then returned to baseline	3
Hill et al, 2007*	FO	Randomised controlled trial; 75 over weight subjects	Body composition and cardiovascular risk factors	FO lowered TAG; increased HDL and improved vascular function; FO reduced body fat	2
Dawczynski et al, 2010*	FO	Double-blind, placebo-controlled cross-over study; 51 hypertriglyceridaemic subjects	Cardiovascular risk factors	No change in blood pressure; TAG was reduced during treatment; HDL decreased	4
Cazzola et al, 2007*	EPA	Double-blind, randomised controlled trial; 100	Cardiovascular risk factors	No effect on blood pressure; EPA reduced TAG; increased soluble	3

		young males and 69 older adults		E-selectin and recued ICAM-1	
Schuchardt et al, 2011	FO	Randomized, Double-blind, placebo-controlled, parallel design; 150 dyslipidaemic, statin treated patients	Lipid profile	TAG reduced in FO group; no other changes	1
Rizza et al, 2009*	FO	Double-blind, randomised placebo-controlled trial; 50 healthy subjects	Endothelial function	FO improved TAG and TNFa	4
Nilsson et al, 2012*	FO	Randomised controlled cross-over study; 54 older adults	Cognitive performance and cardiovascular risk factors	FO improved WM test; lowered TAG and systolic BP	1
Hu et al, 2002	Food diary	Observational cohort analysis (Nurses study); 85,000 nurses	Incident nonfatal myocardial infarction and CHD deaths	Among women, higher consumption of fish and omega-3 fatty acids is associated with a lower risk of CHD, particularly CHD deaths	3
Zhang et al, 2018	Food diary	Observational cohort study; 450,000 subjects	Mortality measures	LCn-3 PUFAs intake was associated with 15% and 18% lower CVD mortality in men and women across extreme quintiles	4

Table 2.3 Studies reporting effects of omega-3/FO supplementation on blood pressure

Study	Supplement Used	Trial design	Outcomes	Results	Quality
Axelrod et al, 1994*	FO	A randomized, prospective, Double-blind, controlled study; 20 T2DM patients	CVD risk factors	SBP reduced by 8mmHg.	4
Krebs et al, 2006*	FO	Double blind RCT; 93 overweight females	Weight loss; lipids; insulin sensitivity	No significant effect on BP	4
Simao et al, 2012	FO (plus kinako)	Parallel randomised controlled trial; 60 patients with metabolic syndrome	Markers of NO metabolism; BP; anthropometric measures	FO and kinako concomitantly significantly decreased systolic BP (SBP; P < 0·05); FO alone significantly decreased diastolic BP (p<0.05)	4
Ramel et al, 2010	Oily fish (with measured DHA content)	Randomised controlled trial; 324 overweight subjects	Body weight, diastolic BP (DBP), systolic BP (SBP), and docosahexaenoic acid (DHA) in erythrocyte membrane were measured at baseline and endpoint.	Participants showed weight loss (-5.2+/-3.2kg, P<0.001) and decreases in SBP (-4.4+/-8.6 mmHg, P<0.001) and DBP (-4.1+/-7.4 mmHg, P<0.001) after the intervention	1
Dawczynski et al, 2010*	FO	Double-blind, placebo-controlled cross-over study; 51	Cardiovascular risk factors	No change in blood pressure;	4

		hypertriglyceridaemic subjects			
Cazzola et al, 2007	EPA	Double-blind, randomised controlled trial; 100 young males and 69 older adults	Cardiovascular risk factors	No effect on blood pressure	3
Nilsson et al, 2012*	FO	Randomised controlled cross-over study; 54 older adults	Cognitive performance and cardiovascular risk factors	FO improved WM test; lowered TAG and systolic BP	1
Pase et al, 2015*		Randomised, Controlled Clinical Trial; 160	Cognitive performance, brachial blood pressure, and aortic (central) blood pressure were measured	FO significantly reduced aortic pulse pressure and aortic augmentation pressure, two measures of aortic blood pressure and aortic stiffness	1

Table 2.4 Studies reporting effects of omega-3/FO supplementation on vascular function

Study	Supplement Used	Trial design	Outcomes	Results	Quality
Dangardt et al, 2010*	EyeQ capsules	Double-blind, cross-overdesign with a 6-week washout period; 25 obese adolescents	Vascular function and inflammatory markers	vascular function improved;	4
Sanders et al, 2011	FO	Randomised parallel design	Endothelial function and arterial stiffness	No change in endothelial function or arterial stiffness	1
Rizza et al, 2009*	FO	Double-blind, randomised placebo-controlled trial; 50 healthy subjects	Endothelial function	FO improved FMD, and reduced TAG and TNFa	4
Pase et al, 2015*		Randomised, Controlled Clinical Trial; 160	Cognitive performance, brachial blood pressure, and aortic (central) blood pressure were measured	FO significantly reduced aortic pulse pressure and aortic augmentation pressure, two measures of aortic blood pressure and aortic stiffness	1

Appendix III: CLO/Omega-3 and child development/behaviour

Table 3.1 Studies reporting effects of omega-3/FO supplementation on cognitive function and behaviour in children

Study	Supplement Used	Trial design	Outcomes	Results	Quality
Yurko-Mauro et al, 2010	DHA	Randomised, Double-blind, placebo-controlled, clinical study; 485 healthy subjects	Cognitive function; MM SE; CANTAB PAL (PAL); CANTAB Pattern Recognition Memory (PRM); Verbal Recognition Memory (VRM)	DHA caused significantly fewer PAL six pattern errors; DHA was also associated with improved immediate and delayed VRM scores	2
Portillo-Reyes et al, 2014	DHA/EPA	Randomized, Double-blind, placebo and treatment clinical trial; 59 children	Neuropsychological performance	50% of children in the treatment group had greater improvement in 11 of the 18 neuropsychological variables studied. Processing speed, visual-motor coordination, perceptual integration, attention and executive function showed improvement in more than 70% of the omega-3 supplemented children.	3
Kirby et al, 2010	FO	Randomised Double-blind, placebo-	IQ, reading and spelling, working memory, attention,	EPA and DHA increased in cheek samples; PUFA had	3

		controlled trial; 348 children	impulsivity, handwriting, matching familiar figures task (MFFT)	higher mean pen pressure for handwriting; supplementation with ω-3 capsules resulted in an improvement in the number of first correct responses made to trials within the MFFT	
Chang et al, 2019	EPA	12-week, Double-blind, placebo-controlled trial; 86 children with ADHD	4 items of the Continuous Performance Test (CPT)	EPA increased attention and vigilance greater than placebo but less than impulsivity. EPA/DHA increased in blood.	1
Amminger et al, 2007	EPA/DHA	Randomized, Double-blind, placebo-controlled 6-week pilot trial; 13 children with ADHD	Aberrant Behaviour Checklist (ABC)	Omega-3 was better than placebo in treating hyperactivity and stereotypy, each with a large effect size	4
Raine et al, 2015	DHA/EPA/ALA	Randomized, Double-blind, placebo-controlled, stratified, parallel-group trial; 200 children with ADHD	Primary outcome measures were externalizing behaviour problems including aggressive behaviour. Secondary outcomes included internalizing behaviour problems	Omega-3 saw long term improvements in treatment group, parents whose children took omega-3 showed significant post-treatment reductions in their own antisocial and aggressive behaviour	1

			and parental aggressive and psychopathic behaviour.		
Johnson et al, 2009	EPA/DHA/GLA	Randomised, 3-month, omega 3/6 placebo-controlled, one-way crossover trial; 75 children with ADHD	Investigator-rated ADHD Rating Scale–IV and Clinical Global Impression (CGI) scale	A subgroup of children and adolescents with ADHD (26%), characterised by inattention and associated neurodevelopmental disorders, treated with omega 3/6 FA for 6 months responded with meaningful reduction of ADHD symptoms.	4
Belanger et al, 2009	PUFA supplement	A randomized, Double-blind, placebo-controlled study; 37 children with ADHD	The Strengths and Weaknesses in ADHD and Normal Behaviours (SWAN) and Conners' questionnaires were used	EPA/DHA increased in serum; A subgroup of eight patients (four in each group) displayed a statistically significant clinical improvement following the administration of the n-3 PUFA supplement, particularly for the inattention and global Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, total Conners' subscales	4
Cornu et al, 2017	DHA/EPA	A Double-blind placebo-controlled	The primary outcome was the change in the	This study did not show any beneficial effect of omega-3 supplement in	1

		randomised trial	Attention-Deficit Hyperactivity Disorder Rating Scale version 4 (ADHD-RS-IV). Other outcomes included safety, lexical level (Alouette test), attention (Test of Attentional Performance for Children—KiTAP), anxiety (48-item Conners' Parent Rating Scale-Revised—CPRS-R), and depression (Children's Depression Inventory—CDI)	children with mild ADHD symptoms	
Montgomery et al, 2018	DHA (algal oil)	Parallel group, fixed-dose, randomized (minimization, 30% random element), Double-blind, placebo-controlled trial (RCT)	Age-standardized measures of reading, working memory, and behaviour, parent-rated and as secondary outcome teacher-rated.	Reading, working memory, and behaviour change scores showed no consistent differences between intervention and placebo group	1
Bos et al, 2015	EPA/DHA	Double-blind randomized placebo-controlled	ADHD symptoms, fMRI of cognitive control, urine homovanillic acid,	Dietary supplementation with omega-3 fatty acids reduces symptoms of	3

		trial.; 40 boys with ADHD	and cheek cell phospholipid sampling	ADHD, both for individuals with ADHD and typically developing children	
Sheppard et al, 2017	Omega-3-6-9 Junior™	Double-blind, randomised controlled trial; 31 pre-term (<30 weeks) children	Toddler Behaviour Assessment Questionnaire – Short Form (TBAQ-SF), the Child Behaviour Checklist (CBCL), the MacArthur-Bates Communicative Development Inventory (CDI; to assess language), the Vineland Adaptive Behaviour Scales (VABS; to assess socialization), and the Infant/Toddler Sensory Profile (ITSP; to assess sensory processing)	Gesture use, but not word production, increased for children in the treatment group more than children in the placebo group	3
Paralleda et al, 2017	EPA/DHA	A randomized, crossover, placebo-controlled study; 68 children with autistic behaviours	Secondary outcome measures were Social Responsiveness Scale and Clinical Global Impression-Severity	No treatment effect (treatment-placebo order) was observed	4

Keim et al, 2018	Omega-3-6-9 Junior	Randomised, fully blinded, placebo-controlled trial; 31 pre-term children	Parent-reported ASD symptoms	Those assigned to treatment exhibited a greater reduction in ASD symptoms per the Brief Infant Toddler Social Emotional Assessment ASD scale than did those assigned to placebo	3
Ramakrishnan et al, 2016	Algal DHA	Randomised controlled trial; 797 children	McCarthy Scales of Children's Abilities (MSCA); Behavioural Assessment System for Children, Second Edition (BASC-2); Conners' Kiddie Continuous Performance Test (K-CPT)	On the K-CPT, offspring in the DHA group showed improved mean ± SD T-scores compared with those of the placebo group for omissions. No other significant findings	2
Sheppard and Cheatham, 2013	Diet history	Cross sectional study; 70 children	Cambridge Neuropsychological Test Assessment Battery	Higher intake of n-3 fatty acids predicted a better performance on the planning task than when children had lower n-3 intakes	3
Gould et al, 2014	DHA	Nested study – within a Double-blind RCT; 185 children	attention and working memory (WMIC)	No significant effects of DHA on primary or secondary outcomes.	1
Hurtado et al, 2015	FO	Double-blind, controlled, and	Binocular visual evoked potentials (VEPs);	DHA higher in blood; no difference in VEP test, a shorter latency,	1

		randomized trial,; 110 mothers		however, in the lower visual angle (7.50) in the boys of the supplemented group.	
Makrides et al, 2010	DHA	Double-blind, multicentre, randomized controlled trial; 2339 women, 726 children	Edinburgh Postnatal Depression Scale; Bayley Scales of Infant and Toddler Development	No significant effects	1
Keim et al, 2018	DHA	A randomized, fully masked, placebo-controlled trial; 377 children	Bayley Scales of Infant and Toddler Development; Bayley-III language and motor composite scores; Infant Behaviour Questionnaire–Revised and Early Childhood Behaviour Questionnaire	No improvement in cognitive development and early measures of executive function vs placebo	1
Ostadrahimi et al, 2017	FO	Triple-blind randomized controlled trial; 150 pregnant women	ages and stages questionnaire (ASQ); weight, length and head circumference	A statistically significant difference was observed only in the communication domain at the 4th month, no other significant results	2
Pivik et al, 2009	Diet record analysis	Cohort study; self-selected formula vs bottle fed vs	Psychological development	In infants fed the DHA-deficient diet, higher HR and lower values for heart rate variability measures were	5

		supplemented bottle fed		observed, indicating decreased parasympathetic tone in this group;	
Colombo et al, 2019	DHA	Randomized Double-blind clinical trial; 200 infants	Cognitive and behavioural assessments	No consistent long-term benefits were observed into childhood	1
Richardson et al, 2012		A Randomized, Controlled Trial (The DOLAB Study); 362 primary school children	Age-standardized measures of reading, working memory, and parent- and teacher-rated behaviour.	DHA improved reading in the lowest 20% of children only	1

Table 3.2 Studies reporting effects of CLO supplementation on cognitive function and behaviour in children

Study	Trial design	Outcomes	Results	Quality
Helland et al, 2003	Double-blind, randomised clinical trial; 341 mothers	Kaufman Assessment Battery for Children (K-ABC) at 4 years of age	Children who were born to mothers who had taken cod liver oil (n = 48) during pregnancy and lactation scored higher on the Mental Processing Composite of the K-ABC at 4 years of age as compared with children whose mothers had taken corn oil (n = 36; 106.4 [7.4] vs 102.3 [11.3])	4

Table 3.2 Studies reporting effects of FO/Omega-3 supplementation on cognitive function and behaviour in adults

Yurko-Mauro et al, 2010	DHA	Randomised, Double-blind, placebo-controlled, clinical study; 485 healthy subjects	Cognitive function; MM SE; CANTAB PAL (PAL); CANTAB Pattern Recognition Memory (PRM); Verbal Recognition Memory (VRM)	DHA caused significantly fewer PAL six pattern errors; DHA was also associated with improved immediate and delayed VRM scores	2
Chew et al, 2015	DHA/EPA	Observational study (AREDS2)	Battery of cognitive tests	No significant effect on cognitive function	3
Narendren et al, 2012	FO	Cross-sectional study; 13 subjects	Adjusted hit rate (AHR); N back task.	DHA improved AHR; baseline DHA predictive of n back performance	5
Antypa et al, 2009	FO	Double-blind randomized controlled trial; 54 healthy university students	Battery of cognitive tests, included measures of cognitive reactivity, attention, response inhibition, facial emotion recognition, memory and risky decision-making	FO made fewer risk averse decisions; no effects on other cognitive markers	3
Andrieu et al, 2017	FO	3-year, multicentre, randomised, placebo-controlled	Four cognitive tests (free and total recall of the Free and Cued Selective Reminding Test,15	Polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline over	1

		superiority trial with four parallel groups; 1680 participants with memory complaints	ten MMSE orientation items, the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale—Revised,16 and the Category Naming Test17 [ie, 2 min category fluency in animals])	3 years in elderly people with memory complaints	
Bauer et al, 2014	EPA and DHA	A Double-blind, counterbalanced, crossover design, with a 30-day washout period; 11 young adults	Functional magnetic resonance imaging scans were obtained during performance of Stroop and Spatial Working Memory tasks prior to supplementation and after each 30-day supplementation period	EPA-rich supplementation, participants' brains worked 'less hard' and achieved a better cognitive performance than prior to supplementation. DHA-rich supplementation is less effective than EPA-rich supplementation in enhancing neurocognitive functioning after a 30-day supplementation period in the same group of individual	3
Gao et al, 2011	Recall/diary based	Prospective cohort study; 2607 Chinese subjects	Mini-Mental State Examination (MMSE)	Daily n-3 PUFA supplements intake was significantly (p=0.024) associated with lower	4

				risk of cognitive decline (OR=0.37, 95% C.I. 0.16–0.87). The association remained significant (p=0.015) after excluding participants with baseline cognitive impairment (MMSE<24), diabetes, stroke, and cardiac diseases (OR=0.23, 95% C.I. 0.07–0.75)	
Witte et al, 2013	FO	Double-blind randomized interventional study; 121 subjects	Neuropsychological testing comprised verbal fluency, trail making test (TMT) part A and B, Stroop Color-Word test, auditory verbal learning task (AVLT), and forward and backward digit spans	FO exerts positive effects on brain functions in healthy older adults; a significant increase in executive functions after FO compared with placebo (P = 0.023	4
Terano et al, 1999	DHA	Randomised cohort trial; 20 older adults with mild to moderate CVD dementia	Mini-Mental State examination (MMSE) and Hasegawa's Dementia rating scale (HDS-R)	In the elderly with moderately severe dementia from thrombotic cerebrovascular disorder, DHA supple-mentation improved the dementia scores, and this improve- ment was accompanied with the	5

				increase in the content of DHA	
Devore et al, 2009	Dietary recall	Prospective cohort study; 5395 people	Relative risk of dementia and Alzheimer disease (AD) across categories of typical fish intake	In this Dutch cohort, who had a moderate consumption of fish and omega-3 PUFAs, these dietary factors do not appear to be associated with long-term dementia risk.	3
Kroger et al, 2009	Dietary recall	Prospective cohort study; 663 people	Relative risk of dementia and Alzheimer disease (AD) across categories of typical fish intake	No associations between n-3 PUFAs and dementia or AD were found	4
Lee et al, 2012	FO	12-month randomised, Double-blind, placebo-controlled trial; 36 low income patients with MCI	The changes of memory, psychomotor speed, executive function and attention, and visual-constructive skills were assessed using cognitive tests	The fish oil group showed significant improvement in short-term and working memory ($F = 9.890$; $\eta p 2 = 0.254$; $p < 0.0001$), immediate verbal memory ($F = 3.715$; $\eta p 2 = 0.114$; $p < 0.05$) and delayed recall capability ($F = 3.986$; $\eta p 2 = 0.121$; $p < 0.05$). The 12-month change in memory ($p < 0.01$) was significantly better in the fish oil group	5
Chiang Chu et al, 2008	FO	A 24-week, randomized, Double-blind	Alzheimer's Disease Assessment Scale	The treatment group showed better improvement on the	2

		study; 46 people with MCI or AD	(ADAS-cog); Clinician's Interview-Based Impression of Change scale which included caregiver-supplied information (CIBIC-plus)	Clinician's Interview-Based Impression of Change Scale (CIBIC-plus) than those in the placebo group over the 24 week follow-up (p = 0.008). the omega-3 fatty acids group showed significant improvement in ADAS-cog compared to the placebo group in participants with mild cognitive impairment (p = 0.03)	
Kotani et al, 2006	DHA	Randomised group design; 40 patients with AD or MCI	Repeatable battery for the assessment of neuropsychological status (RBANS)	MCI-A group showed a significant improvement of the immediate memory and attention score - DHA supplementation can improve the cognitive dysfunction due to organic brain damages or aging	4

Appendix IV CLO/Omega-3 and joint pain

Table 4.1 Studies reporting on CLO and Joint Pain/rheumatic issues

Study	Trial design	Outcomes	Results	Quality
Brunborg et al, 2008	Cohort; comparison of seal oil and CLO in 38 IBD patients	joint pain intensity; rheumatic complaints	CLO causes significant improvement (p=0.02) and global rheumatic complaints (p=0.007)	5
Galarraga et al, 2008	Dual centre, Double blind placebo controlled RCT; 97 patients with RA	Daily NSAID requirement; disease activity, CRP, pain, grip strength	Primary outcome (NSAIDs) reduced by >30% in 59% of patients in CLO arm. No significant effects for other outcomes	3
Stammers et al, 1992	Double blind, placebo controlled RCT; 86 OA patients	Pain; daily activities	No significant effect of CLO on pain or daily activities	3
Gruenwald et al, 2009	Multi centre, Double blind comparison study of CLO vs CLO plus glucosamine; 182 patients with severe OA.	Pain score; WOMAC pain scores; stiffness and function	CLO plus glucosamine reduced pain by 44% (p=0.044), OA symptoms by 48-56%.	4
Gruenwald et al, 2002	Pilot study; 43 RA patients	Unclear (no link to full text)	Decrease in morning stiffness (52%, p<0.001), painful joints (40%, p<0.001) and	5

			pain intensity (67.5%, p value???)		

Table 4.2 Studies reporting on FO/Omega-3 and Joint Pain/rheumatic issues

Geusens et al, 1994	FO	Randomised controlled trial	Physicians inspection, self-reported pain, NSAID use	Significant improvement in the patient's global evaluation and in the physician's assessment of pain was observed only in those taking 2.6 g/day of omega-3. The proportions of patients who improved and of those who were able to reduce their concomitant anti-rheumatic medications were significantly greater with 2.6 g/day	2
Kremer et al, 1995	FO	Double-blind, placebo-controlled, prospective study; 60 RA patients	Physician's evaluation, self-reported pain.	In the group taking fish oil, there were significant decreases from baseline in the mean (+/- SEM) number of tender joints (5.3 +/- 0.835; P < 0.0001), duration of morning stiffness (-67.7 +/- 23.3 minutes; P = 0.008), physician's	2

				and patient's evaluation of global arthritis activity (-0.33 +/- 0.13; P = 0.017 and -0.38 +/- 0.17; P = 0.036, respectively), and physician's evaluation of pain (-0.38 +/- 0.12; P = 0.004)	
Maroon and Bost, 2006	FO	Prospective cohort study; 250 patients with non-surgical neck or back pain	Pain questionnaire	Fifty-nine percent discontinued to take their prescription NSAID medications for pain. Sixty percent stated that their overall pain was improved, and 60% stated that their joint pain had improved. Eighty percent stated they were satisfied with their improvement, and 88% stated they would continue to take the fish oil.	3
Alfaddagh et al, 2018	FO	A Secondary Analysis of a Randomized Clinical Trial; 291 subjects	Change in pain, stiffness, and physical function was assessed by the Western Ontario and McMaster Universities Arthritis Index. Minutes of exercise per week were recorded, and	In the intention-to-treat analysis, compared with controls, those on Lovaza had better physical function (mean difference, -11.0%, 95% confidence interval	2

			musculoskeletal events were reported.	[CI] -18.5% to -3.5%, P = .004), better total Western Ontario and McMaster Universities Arthritis Index scores (mean difference, -9.8%, 95% CI -16.6% to -3.0%, P = .005), more exercise per week (135 minutes vs 197 minutes, respectively, P = .028), and less joint replacement (11 vs 1, respectively, P = .002. The per-protocol analysis also showed less stiffness compared with controls (mean difference, -11.5%, 95% CI -22.9% to -0.1%, P = .048	
Hill et al, 2016	FO	A randomised, Double-blind, multicentre trial; 202 patients	Low dose vs high dose FO; he primary endpoints were Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score at 3, 6, 12 and 24 months, and change in cartilage volume at 24 months	Although there was improvement in both groups, the low-dose fish oil group had greater improvement in WOMAC pain and function scores at 2 years compared with the high-dose group	1
Bahadori et al, 2010	FO	Double-blind, randomized, placebo-controlled study; 23 patients	A decrease in swollen and tender joint counts was the primary efficacy measure	Swollen joint count was significantly lower in the omega-3 FA group compared	2

		with moderate to severe RA		with the placebo group after 1 week of infusion (P = .002) as well as after 2 weeks of infusion (P = .046)	
Remans et al, 2004	FO	Double-blind placebo-controlled, parallel group study; 66 patients with RA	The primary end point was the change in tender joint count at 2 and 4 months	No significant change from baseline in tender joint count or any of the other clinical parameters was detected in either group	4
Berbert et al, 2005	FO	Parallel randomised controlled trial; 43 patients with RA	Disease activity was measured by clinical and laboratory indicators at the beginning of the study and after 12 and 24 wk. Patients' satisfaction in activities of daily living was also measured.	There was a statistically significant improvement in FO group in relation to control with respect to joint pain intensity, right and left handgrip strength after 12 and 24 wk, duration of morning stiffness, onset of fatigue, Ritchie's articular index for pain joints after 24 wk, ability to bend down to pick up clothing from the floor, and getting in and out of a car after 24 wk.	