British Journal of Nutrition (2012), **107**, S23–S52
doi:10.1017/S0007114512001456

Dietary sources of omega 3 fatty acids: public health risks and benefits

J. A. Tur*, M. M. Bibiloni, A. Sureda and A. Pons

Research Group on Community Nutrition and Oxidative Stress, Universitat de les Illes Balears, Guillem Colom Bldg Campus, E-07122 Palma de Mallorca, Spain

Abstract

Omega 3 fatty acids can be obtained from several sources, and should be added to the daily diet to enjoy a good health and to prevent many diseases. Worldwide, general population use omega-3 fatty acid supplements and enriched foods to get and maintain adequate amounts of these fatty acids. The aim of this paper was to review main scientific evidence regarding the public health risks and benefits of the dietary sources of omega-3 fatty acids. A systematic literature search was performed, and one hundred and forty-five articles were included in the results for their methodological quality. The literature described benefits and risks of algal, fish oil, plant, enriched dairy products, animal-derived food, krill oil, and seal oil omega-3 fatty acids.

Key words: Omega 3: Public health: Health risks: Health benefits: Systematic review

Omega 3 fatty acids can be obtained from several sources, and should be added to the daily diet to enjoy a good health and to prevent many diseases. The European Food Safety Agency (EFSA) proposed a recommended daily intake of 250 mg/d eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for adults, because this intake is negatively related to cardiovascular diseases (CVD) risk in a dose-dependent way up to 250 mg/d (1–2 servings/week of oily fish) in healthy subjects[1]. The American Heart Association (AHA) recommended for the general population a consumption of fish, at least twice a week[2], estimating a consumption of one portion (125 g) of oily fish (2 g/100 g EPA and DHA) and one portion of lean fish (0·2 g/100 g), which results in an mean intake of 3 g/week or 430 mg/d of DHA and EPA. AHA also established intakes of 1 g of EPA and DHA from fish or fish oils for subjects with clinical history of CVD and a 2–4 g supplement for subjects with high blood triacylglycerides (TAG)[3]. The World Health Organization (WHO) recommended a regular fish consumption (1–2 servings/week; providing 200–500 mg/serving of EPA and DHA) for the general population, as being protective against coronary heart disease and ischemic stroke[4]. WHO also indicates that vegetarians and not fish-eaters are recommended to ensure adequate intake of plant sources of alpha-linolenic acid (ALA), as some of it (0·5–20 % depending on various factors) is metabolized to EPA[5,6]. Worldwide, general population use omega-3 fatty acids supplements and enriched foods to get and maintain adequate amounts of these fatty acids, i.e.: milk and dairy products are every day consumed foods and constitute a good and popular source of omega-3 fatty acids, to produce 'healthier' milks and dairy products[7]. The aim of this paper was to review main scientific evidence regarding the public health risks and benefits of the dietary sources of omega-3 fatty acids

Methods

A systematic literature search was performed up to April 2011. The literature search was conducted in Medlars Online International Literature (MEDLINE), via PubMed©; Scopus; OvidSP (Food Science and Technology Abstracts); EMBASE©, and Latin American and Caribbean Heath Sciences Literature (LILACS), using the following terms: 'Fatty acids, omega-3'[Major] OR 'alpha-linolenic acid'[Mesh] OR 'docosahexaenoic acids'[Mesh] OR 'eicosapentaenoic acid'[Mesh] AND ('adverse effects'[Mesh] OR 'contraindications'[Mesh] OR 'standards'[Mesh] OR 'supply and distribution'[Mesh] OR 'therapeutic use'[Mesh] OR 'toxicity'[Mesh] AND ('humans' [MeSH Terms] AND ('Clinical Trial'[ptyp] OR 'Randomized Controlled Trial'[ptyp])).

Using the above mentioned data bases, 2476 articles were selected. Duplicates, review articles and non-relevant articles were excluded (*n* 2310). After reading the literature list of the remaining articles, and suggestions from other experts about relevant papers, 35 were included in the results. Fifty-four of the remaining 201 articles were rejected for the reasons shown in Fig. 1. Finally, just one hundred and forty-seven articles were included in the results. The articles were reviewed by at least two reviewers and were taken into account for the selection criteria listed on the JADAD scale

* **Corresponding author:** Dr J. A. Tur, fax +34 971 173184, email pep.tur@uib.es

British Journal of Nutrition

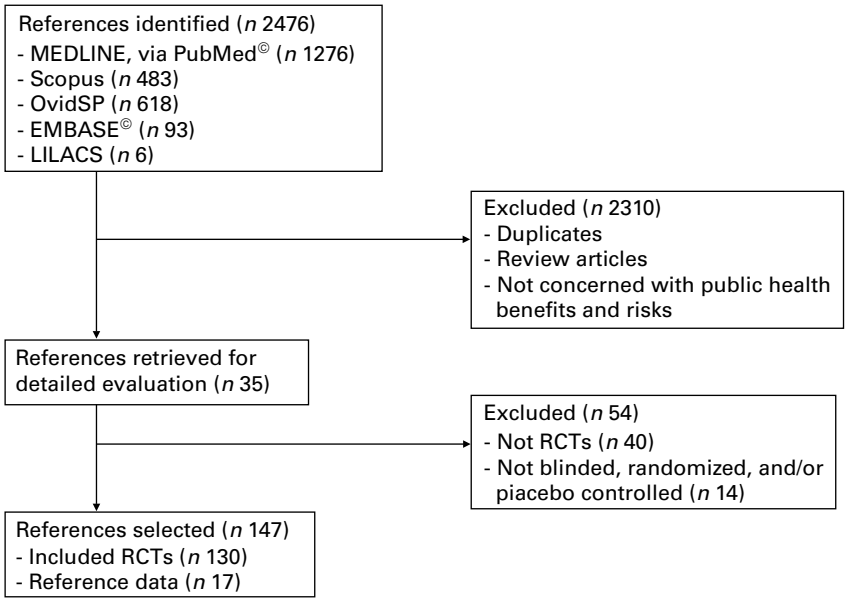

Fig. 1. Literature search flow chart.

or Oxford Quality Scoring System, a procedure to independently assess the methodological quality of a clinical trial. Reviewers extracted data from the published reports. Table 1 summarises the design of and the results provided by the 147 articles finally selected.

Results

Algal omega-3 fatty acids

Clinical trials with algal DHA-rich oil supplementation resulted in potentially beneficial changes in some markers of cardiometabolic risk: decrease in VLDL and increase in LDL and HDL particle sizes, and reduction in VLDL, and total TAG concentrations, blood pressure and heart rate, and oxidative stress, indicating comparable efficacies to fish oil. Algal-DHA was safe and well tolerated[8]. Unlike fish oil, algal-DHA seldom caused gastrointestinal complaints such as fishy taste and eructation, attributes of importance for patient compliance in high-dose therapy.

The consumption of *Ulkenia* sp. microalgae oil (0·94 g DHA/d) for 8 weeks decreased plasma TAG, and increased plasma total cholesterol, LDL- and HDL-cholesterol in normolipidaemic vegetarians. DHA-rich oil from *Ulkenia* sp. is well tolerated and a suitable vegetarian source of *n*-3 LC-PUFAs[9].

Schizochytrium sp. microalgae provided substantial quantities of the docosapentaenoic acid (22 : 5*n*-6; DPA). Subjects received 4 g/d of this microalgae oil for 4 wk (providing 1·5 g/d DHA and 0·6 g/d DPA) and showed increased plasma concentrations of arachidonic acid (ARA), adrenic acid, DPA and DHA, increased DPA and DHA in erythrocyte phospholipids, increased total, LDL- and HDL-cholesterol, and increased Factor VII coagulant activity. This oil was well tolerated, without adverse effects[10].

Fish oil omega-3 fatty acids

The consumption of equal amounts of EPA and DHA from oily fish on a weekly basis or from fish-oil capsules on a daily basis was equally effective at enriching blood lipids with *n*-3 long-chain polyunsaturated fatty acids (*n*-3 LC-PUFAs)[11]. Fish oil *n*-3 LC-PUFAs are readily incorporated into the healthy heart and skeletal muscle membranes, and may reduce both whole-body and myocardial O_2 demand during exercise, without a decrement in performance. Fish oil also increased *n*-3 LC-PUFA contents of erythrocytes[12], lowered heart rate during incremental workloads to exhaustion, and lowered steady-state submaximal exercise heart rate and whole-body O_2 consumption, but time to voluntary fatigue was not altered[13].

Adding DHA (fish-oils) to staple foods reduced CVD morbidity and mortality[14], and has been recommended after myocardial infarction. Increased fish or fish-oil consumption has been associated with reduced risk of cardiac mortality, especially sudden death, by means of membrane stabilization in the cardiac myocite, inhibition of platelet aggregation, favourable modifications of the lipid profile, and decrease in systolic and diastolic blood pressure, probably due to the shift of balance between vasoconstrictive and vasodilator eicosanoids toward vasodilatation and reduction of the inflammatory response of the endothelium. Fish oil showed a propranolol-like blood pressure-lowering effect. Plasma norepinephrine and thromboxane B_2 formation were likewise reduced, whereas plasma renin activity increased[15]. Dietary intervention with fish oil *n*-3 LC-PUFAs reduced platelet-monocyte aggregation, and suggested that reduced platelet activation provides a potential mechanism through which fish oils confer their cardiovascular preventative benefits[16], and reduces atherothrombotic risk in patients with hyperlipoproteinemia[17].

British Journal of Nutrition

Table 1. Description of the studies included in this review

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes: Health benefits	Outcomes: Health risks	Reference
Algae						
	36 overweight or obese adults	4·5 mo randomized controlled double-blind trial	2 g/d algal DHA or placebo	To decrease in VLDL and increase in LDL and HDL particle sizes, and reduction in VLDL, and total TAG concentrations, blood pressure and heart rate, and oxidative stress	Fishy taste and eructation	Neff *et al.*[8]
	Normolipidaemic vegetarians (87 females, 27 males)	8-wk double-blind, placebo-controlled, parallel design intervention study	*Ulkenia* sp. microalgae oil (0·94 g DHA/d)	To decrease plasma TAG, and increase plasma total cholesterol, LDL- and HDL-cholesterol in normolipidaemic vegetarians	None	Geppert *et al.*[9]
	39 men and 40 women	4-wk double-blind randomised placebo-controlled parallel-design trial	4 g/d *Schizochytrium* sp. oil (1·5 g/d DHA, 0·6 g/d DPA)	To increase plasma concentrations of arachidonic acid (ARA), adrenic acid, DPA and DHA, and DPA and DHA in erythrocyte phospholipids, and total, LDL- and HDL-cholesterol, and increased Factor VII coagulant activity	None	Sanders *et al.*[10]
Fish oil						
	Healthy premenopausal female (21–49 y)	16-wk randomized controlled trial	485 mg/d EPA and DHA from 2 servings of oily fish/wk (*n* 11) or from 1–2 capsules/d (*n* 12)	EPA + DHA in RBCs increased significantly more rapidly in the fish group than in the capsule group during the first 4 wk, but rates did not differ significantly between groups thereafter	None	Harris *et al.*[11]
	69 subjects (36 male, 31 female, mean age 53 y) with fasting serum TAG ≥1·1 mmol/l and 44 BMI > 25 kg/m^2	12-wk randomized, double-blind, placebo-controlled parallel intervention	2, 4, 6 g/d of DHA-rich fish oil (26 % DHA, 6 % EPA)	For every 1 g/d increase in DHA intake, there was a 23 % reduction in TAG, 4·4 % increase in HDL-cholesterol and 7·1 % increase in LDL-chol.	None	Milte *et al* [12]
	16 well-trained men (cyclists)	8-wk double-blind, parallel design	8 × 1 g capsules/d olive oil (control) or fish oil	To lower heart rate (including peak heart rate) during incremental workloads to exhaustion, steady-state submaximal exercise heart rate, whole-body O_2 consumption, and heart pressure product	None	Peoples *et al.*[13]
	213 middle-aged men and women with untreated elevated total cholesterol or blood pressure	5-wk double-blind, factorial placebo-controlled randomized trial	bread, cereal bars and cracker biscuits fortified with 2 g fish oils (DHA)	To reduce CVD morbidity and mortality	None	Harrison *et al.*[14]
	47 male patients with mild hypertension	40-wk randomized, double-blind, placebo-controlled intervention	fish oil capsules (9 g/d equivalent to 1·8 g/d of EPA and 1·1 g/d of DHA)	To decrease plasma norepinephrine and thromboxane B_2 formation, and increase plasma renin activity	None	Singer *et al.*[15]
	14 male adults	4-wk double-blind intervention, parallel design	500 g/d oil rich fish	Inverse correlation between platelet-monocyte aggregation and plasma omega-3 fatty acid concentrations	None	Din *et al.*[16]
	26 male hypercholesterolemic patients	6-wk placebo-controlled, double-blind intervention	216 mg/d EPA, 140 mg/d DHA, 390 mg/d gamma-LA, 3480 mg/d LA	To decrease MDA formation, total, and LDL cholesterol, triglycerides, and platelet activation	None	Pirich *et al.*[17]
	84 patients with low self-reported fish intake accepted for cardiac surgery (cardiopulmonary bypass)	63-d randomized, double-blind intervention, parallel design	fish oil (6 g EPA + DHA/d) for either 7, 14, or 21 d before surgery	*n*-3 fatty acids are rapidly incorporated into human myocardial phospholipids at the expense of ARA	None	Metcalf *et al.*[18]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	14 patients heart failure	18-wk randomized, placebo-controlled, double-blind intervention	8 g/d *n*-3 LC-PUFAs	To decrease TNF-α production in heart failure and improve body weight	None	Mehra *et al.*[19]
	107 patients percutaneous transluminal coronary angioplasty	6-mo randomized, placebo-controlled, double-blind intervention	10 capsules of fish oil (3 g/d, containing 1·8 g EPA, 1·2 g DHA, *n* 58) besides aspirin and calcium blockers, beginning 4·3 d (control group just aspirin and calcium blockers, *n* 49) before coronary angioplasty	Restenosis after coronary angioplasty is not reduced by supplemental fish oils	None	Kaul *et al.*[20]
	229 postmenopausal women with coronary artery disease	1-y prospective cohort study	Fish and *n*-3 PUFA intake by food frequency questionnaire	Consumption of ≥2 servings of fish or ≥1 serving of tuna or dark fish per week was associated with smaller increases in the percentage of stenosis	None	Erkkilä *et al.*[21]
	60 patients with coronary heart disease	6-wk double-blinded intervention study	100 g/wk of different Atlantic salmon	Significant reductions of serum triglycerides and of sVCAM-1 and IL-6		Seierstad *et al.*[22]
	4680 men and women (40–59 y) from 17 population-based samples in China, Japan, United Kingdom, and United States	Cross-sectional epidemiologic study	Association between *n*-3 LC-PUFAs intake and blood pressure (four 24-h recalls)	Inverse relation of *n*-3 LC-PUFAs intake and blood pressure	None	Ueshima *et al.*[23]
	44 720 participants	6-y follow up of Women's Health Initiative clinical trials	Association between fish oil intake and atrial fibrillation (food frequency questionnaire)	No evidence of an association between fish or omega-3 fatty acid intake and incident atrial fibrillation	None	Berry *et al.*[24]
	1148 subjects	Meta-analysis of randomized double-blind, placebo-controlled, parallel-group trials	2 g/d (4 capsules) fish oil (961 mg *n*-3 LC-PUFAs: 464 mg EPA, 335 mg DHA, and 162 mg other *n*-3 LC-PUFAs), 12 mo; 1·8 g/d fish oil (42 % EPA, 30 % DHA) or placebo (olive oil: 73 % oleic acid, 12 % palmitic acid, 0 % EPA/DHA), 2 y	Findings do not support a protective effect of *n*-3 LC-PUFAs from fish oil on cardiac arrhythmia	None	Brouwer *et al.*[25]
	20 health subjects (10 women)	Randomized, placebo-controlled, double-blind, crossover study	Participants reported to the laboratory on 2 separate days and received 1 of 2 treatment conditions: High-fat meal (1 g EPA and DHA from fish oil supplement) or high-fat meal with placebo (lactose capsules). Each visit was separated by at least 72 h but no more than 14 days.	Brachial artery flow-mediated dilation remained unchanged, and resting forearm blood flow and total hyperaemia were elevated after the supplementation	None	Fahs *et al.*[26]
	102 patients with confirmed stroke	12-wk randomized controlled trial	3 g/d encapsulated fish oil (1·2 g total omega-3: 0·7 g DHA; 0·3 g EPA)	No effects on CVD biomarkers or mood in patients with ischemic stroke	None	Poppitt *et al.*[27]
	11 subjects with epilepsy	Randomized, double-blind two-period crossover clinical trial.	4-wk baseline; 12-wk treatment: 8 capsules/d; 9600 mg of fish oil/d (2880 mg/d of *n*-3 LC-PUFAs: 1728 mg/d EPA + 1152 mg/d DHA) or soybean oil (placebo); 4-wk washout period; 12-wk treatment crossover.	To decrease seizure severity and triglycerides, and increase HDL.	None	DeGiorgio *et al.*[28]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	17 healthy middle-aged (35–64 y) subjects	Randomized, placebo-controlled, double-blind, crossover study	4-wk intervention (fish oil capsules with every meal, 1260 mg EPA, 540 mg DHA) or placebo and 4-wk wash out	No changes in the fatty acid composition of plasma and erythrocyte phospholipids	None	Watanabe *et al.*[29]
	16 normolipidemic subjects (9 women)	8-wk randomized controlled trial	6 g/d (6 capsules) fish oil (3 g *n*-3 LC-PUFAs)	Increase of total glutathione, homocystein, and NO plasma concentrations.	None	Piolot *et al.*[30]
	12 T2DM normotriglyceridemic subjects without insulin treatment	9-wk two-armed, parallel, placebo-controlled, randomized	5·9 g/d *n*-3 LC-PUFAs (1·8 g 20 : 5*n*-3, 3·0 g 22 : 6*n*-3)	Decrease of VLDL and increase of HDL size particles, increase of small LDL concentration, and no effect on oxidized LDL	None	Mostad *et al.*[31]
	200 mildly hypercholesterolaemic Indian adults aged 35–55 y	4-wk 2 × 2 factorial, double-blind controlled trial	Once-a-day yoghurt drink (2 g/d plant sterols) and capsules (2 g/d fish oil *n*-3 LC-PUFAs)	Reduction in LDL-chol. and triglycerides, and increase in HDL-chol. concentrations	None	Khandelwal *et al.*[32]
	338 adult men	30-y follow-up survey of the Dutch and Finnish cohorts of the Seven Countries Study	Intake of total, saturated, and monounsaturated fatty acids and dietary cholesterol 20 y before diagnosis	High intake of fat, especially that of saturated fatty acids, contributes to the risk of glucose intolerance and T2DM	None	Feskens *et al.*[33]
	25 639 men and women (40–79 y)	10-y follow-up survey of the EPIC-Norfolk Study	Assessment of fish and seafood intake by means of FFQ	Higher total fish intake (≥ 1 vs < 1 portions/wk) was associated with a lower risk of diabetes	None	Patel *et al.*[34]
	175 men and women (64–87 y)	4-y follow-up survey	Assessment of fish and seafood intake by means of cross-check dietary history method	In elderly population, the habitual consumption of a small amount of fish may protect against the development of impaired glucose tolerance and T2DM	None	Feskens *et al.*[35]
	3 cohort studies. NHS (1976; 121 700 female nurses 30–55 y at baseline); NHS2 (1989; 116 609 female nurses 26–46 y at baseline); and HPFS (1986; 51 529 male health care professionals 39–78 y at baseline)	Large cohort follow-up surveys	Assessed of diet using FFQ, administered at 4-y intervals during the follow-up period	No evidence that higher consumption of LC-PUFA and fish reduces the risk of T2DM	None	Kaushik *et al.*[36]
	8 T2DM male subjects	8 wk randomized controlled trial	8 g/d *n*-3 LC-PUFAs, as marine-lipid concentrate capsules	Triglyceride and cholesterol plasma levels decreased, no alteration of HDL-chol. levels, but increased fasting and meal.-stimulated glucose concentrations.	Marine-lipid concentrate capsules supplying large amounts of *n*-3 LC-PUFAs should be used cautiously in the T2DM patient	Friday *et al.*[37]
	162 healthy individuals	3 mo randomized placebo-controlled trial	3·6 g/d *n*-3 LC-PUFAs	Moderate supplementation of fish oil does not affect insulin sensitivity, insulin secretion, beta-cell function or glucose tolerance	None	Rivellese *et al.*[38]
	12 T2DM men	Randomized, double-blind, crossover study	6 g/d of either fish oil or sunflower oil, separated by a 2-mo washout interval	Moderate dose of fish oil did not lead to deleterious effects on glycemic control or whole-body insulin sensitivity in T2DM men, with preserved TAG lowering capacities	None	Luo *et al.*[39]
	10 T2DM subjects (42–65 y)	Randomized, double-blind, crossover study	No supplementation (baseline); 10 g/d fish oil concentrate (30 % omega 3FAs); 10 g/d safflower oil; over separate 3-wk periods	Dietary fish oil supplementation adversely affected glycemic control in T2DM subjects without producing significant beneficial effects on plasma lipids	None	Borkman *et al.*[40]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	36 328 women (mean age 54·6 y)	12·4-y follow-up survey of the Women's Health Study (1992–2008)	Assessment of fish and seafood intake by means of FFQ and self-reported of T2DM	n.d.	Increased risk of T2DM with the intake of *n*-3 LC-PUFAs, especially with higher intakes (≥0·20 g/d of *n*-3 or ≥2 servings/d of fish)	Djoussé *et al.*[41]
	2397 participants	Cross-sectional and 1-y longitudinal, multicenter randomized trial (Look AHEAD survey)	Assessment of fish and seafood intake by means of FFQ	Marine *n*-3 LC-PUFAs intake is inversely associated triglycerides and weakly with HDL-chol.	None	Belalcazar *et al.*[42]
	162 healthy individuals	3-mo randomized placebo-controlled trial	3·6 g/d fish oil *n*-3 LC-PUFAs	Moderate supplementation of fish oil does not affect insulin sensitivity, insulin secretion, beta-cell function or glucose tolerance	None	Giacco *et al.*[43]
	12 normotriglyceride T2DM subjects	9-wk two-armed, parallel, placebo-controlled, randomized trial	5·9 g/d fish oil (1·8 g 20 : 5*n*-3, 3·0 g 22 : 6*n*-3)	To increase HDL size and small LDL concentration, no effect on oxidized LDL, and decreased insulin sensitivity	None	Mostad *et al.*[44]
	25 young iron-deficient women (18–30 y)	9-wk randomised cross-over dietary intervention study	Diet contained 2 portions of salmon, 2 cans of water-packed tuna (56 g each), 1 can of sardines in olive oil, 1 portion of lean fish, 1 portion of red meat, 2 portions of poultry and 2 eggs per week	Insulin levels significantly decreased and insulin and HDL-chol. sensitivity significantly increased	None	Navas-Carretero *et al.*[45]
	42 healthy subjects	4 wk randomized placebo-controlled trial	Fish oil rich EPA (4·7 g/d), or DHA (4·9 g/d)	Supplementation with DHA, but not with EPA, suppresses T lymphocyte activation. EPA alone does not, therefore, influence CD69 expression	None	Kew *et al.*[46]
	324 subjects (20–40 y) with BMI 27·5–32·5 kg/m^2	8-wk randomized controlled trial	salmon (3 × 150 g/wk, 2·1 g/d *n*-3 LC-PUFAs); cod (3 × 150 g/wk, 0·3 g/d *n*-3 LC-PUFA); fish oil capsules (1·3 g/d *n*-3 LC-PUFAs); control (sunflower oil capsules, no seafood)	Subjects that ate fish experienced weight loss, and decreases triglyceride levels, in inflammation parameters, and systolic and diastolic blood pressure. Salmon consumption was the most effective. Body weight, leptin and insulin levels decreased, and ghrelin increased. Weight loss explained the effects of fatty seafood on leptin and ghrelin, but not insulin	None	Ramel *et al.*[47,48,75] Gunnarsdottir *et al.*[79]
	92 male subjects (35–70 y)	8-wk randomized, parallel-arm, food-based intervention study	Lunches with pork/chicken/beef (*n* 30); freshwater fish (*n* 30); or oily fish (*n* 32)	Reduced serum levels of triglycerides and interleukin-6 and increased levels of HDL-chol.	None	Zhang *et al.*[49]
	10 elite athletes with and 10 without exercise-induced bronchoconstriction	3-wk randomized double-blind crossover study	Fish oil capsules (3·2 g/d EPA; 2·2 g/d DHA) or placebo capsules (olive oil)	No effect on preexercise pulmonary function, but improved post-exercise pulmonary function, and decreased leukotriene, 9α, and 11β -prostaglandin, TNFα, interleukin-1β	None	Mickleborough *et al.*[50]
	36 patients with end-stage renal disease	6-mo double-blind, permuted-randomized, and placebo-controlled trial	2 soft-gel pills/d (1 g each) of fish oil supplements (960 mg/d EPA; 600 mg/d DHA)	Decrease of C-RP levels	None	Bowden *et al.*[51]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	33 subjects with myocardial infarction or unstable ischemic attack	8-wk randomized, parallel-arm, food-based clinical trial	Lunches with fatty fish (*n* 11), lean fish (*n* 12) or control (lean beef, pork and chicken) (*n* 10), 4 meals/wk	Decrease of lipids which are potential mediators of lipid-induced insulin resistance and inflammation	None	Lankinen *et al.*[52]
	727 women (43–69 y)	Cross-sectional survey of a cohort of the Nurses' Health Study I	Assessment of fish and seafood intake (and *n*-3 LC-PUFAs) by means of FFQ	*n*-3 LC-PUFAs intake were inversely related to sICAM-1 and sVCAM-1, CRP, and E-selectin.	None	López-García *et al.*[53]
	60 patients with severe acute pancreatitis	2-wk randomized controlled trial	Intravenous supplementation with fish oil *n*-3 LC-PUFAs emulsion (0·2 g/kg/d)	Parenteral supplementation with omega-3 fish oil emulsion lower the magnitude and persistence time of the systemic inflammatory response syndrome	None	Xiong *et al.*[54]
	64 patients with stable mild rheumatoid arthritis	12-mo randomized double-blind placebo controlled trial	10 capsules/d (171 mg/capsule EPA, and 114/mg capsule DHA)	Significant reduction in non-steroidal anti-inflammatory drug requirement from month 3rd	None	Lau *et al.*[55]
	250 patients with nonsurgical neck or back pain	4-mo randomized controlled trial	Fish oil EPA + DHA (1200 mg/d)	*n*-3 LC-PUFAs supplementation showed equivalent effect of ibuprofen in reducing arthritic pain	None	Maroon *et al.*[56]
	97 patients with rheumatoid arthritis	9-mo randomized, prospective, investigator-initiated dual centre, double-blind placebo-controlled trial	10 g/d (10 capsules) of cod liver oil (150 mg EPA,70 mg DHA)	Cod liver oil supplements containing *n*-3 LC-PUFAs decreased non-steroidal anti-inflammatory drug requirement	None	Galarraga *et al.*[57]
	19 patients with rheumatoid arthritis	2 y randomized controlled trial	Intervention: 1) Fish oil EPA 2·7 g/d and DHA 1·8 g/d 2) Fish oil EPA 270 mg/d and DHA 180 mg/d	EPA increases ciclooxygenase inhibitory activity of paracetamol in rheumatoid arthritis patients	None	Caughey *et al.*[58]
	12 asthmatic patients	1-y randomized double-blind placebo controlled trial	1 g/d EPA + DHA (Liparmonyl®)	A positive effect on forced expiratory volume in 1 s was observed after the 9 month of treatment	None	Dry *et al.*[59]
	216 adult participants (54 ± 12 y; 47 % female)	6-mo multi-center, parallel, randomized, controlled intervention study	Two 150-g portions/wk (salmon or cod)	Serum CRP concentrations were lower after salmon and cod consumption, but exploratory analysis of local markers of inflammation in the colon or faeces did not reveal this effect	None	Pot *et al.*[60]
	15 healthy men (26 ± 3 y) BMI 23·8 ± 1·9 kg/m^2	3–4 wk randomized placebo controlled trial	7·2 g/d fish oil, (providing 1·1 g/d 20 : 5 (*n*-3) and 0·7 g/d 22 : 6 (*n*-3) fatty acids)	Fish oil exert beneficial effects in sepsis though non-inflammatory	None	Michaeli *et al.*[61]
	302 participants (167 men; 135 women; 66–80 y)	26 wk randomized double-blind controlled trial	Intervention: 1) 1·8 g EPA + DHA/d 2) 0·4 g EPA + DHA/d 3) 4·0 g high-oleic acid sunflower oil.	EPA + DHA intake changed the expression of 1040 genes, and decreased expression of genes involved in inflammatory- and atherogenic-related pathways	None	Bouwens *et al.*[62]
	36 girls (18–22 y)	3-mo randomized placebo controlled trial	15 mL/d fish oil (550 mg EPA; 205 mg DHA)	Marked reduction in low back pain and abdominal pain, and fewer rescue doses of ibuprofen	None	Moghadamnia *et al.*[63]
	270 Pregnant women (18–41 y)	Randomized placebo controlled trial	Intervention from 22 wk to delivery: 1) modified fish oil; 2) 5-methyl-tetrahydro-folate 3) both; 4) placebo	Fish oil supplementation during the second half of pregnancy appears not to decrease antioxidant status	None	Franke *et al.*[64]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	98 pregnant women and their infants assessed at 2·5 y	Randomized double-blind placebo controlled trial	Intervention from 20 wk to delivery: Fish oil (2·2 g/d DHA, 1·1 g/d EPA) or olive oil;	Children in the fish oil-supplemented group attained a higher score for eye and hand coordination, positively with *n*-3 and negatively with *n*-6. Neutrophil production of inflammatory LTB4 was inversely related to *n*-3 LC-PUFAs intake. LTB5 levels were positively correlated with *n*-3, particularly EPA, and negatively with *n*-6	None	Dunstan *et al.*[65] Prescott *et al.*[67]
	388 adults (men and women)	German study centres within the European Community Respiratory Health Study II	Assessment of fish and seafood, and *n*-3 LC-PUFAs intake by food frequency questionnaire	Adult females with a high fish and DHA intake showed a lower rate of allergic sensitisation	None	Schnappinger *et al.*[66]
	121 Lactating mothers of 143 preterm infants born of <33 wk gestation	Randomized double-blind placebo controlled trial	Intervention from enrolment to delivery: 1) 6 capsules/d tuna oil (900 mg DHA, 195 mg EPA, 54 mg AA) 2) 6 capsules/d soy oil (1·6g LA, 177 mg ALA);	DHA was higher in milk of supplemented mothers	None	Smithers *et al.*[68]
	145 pregnant women, affected by allergy themselves or having a husband or previous child with allergies	Randomized placebo controlled trial	Intervention from 25 wk gestation to average 3–4 mo breast-feeding: 1·6 g/EPA and 1·1 g/d DHA or placebo	The period prevalence of food allergy was lower in the omega-3 group, as well as incidence of IgE-associated eczema	None	Furuhjelm *et al.*[69]
	83 healthy infants	2×2 intervention randomized controlled trial	Intervention from 9 to 12 mo: $3{\cdot}4 \pm 1{\cdot}1$ mL/d and cow's milk or infant formula	Irrespective of gender, there was a positive association between the 9–12-mo changes in RR interval and erythrocyte *n*-3 LC-PUFAs	None	Lauritzen *et al.*[70]
	24–28 young adults (18–30 y) and 24–28 elderly (>65 y)	Randomized controlled trial	1) 680 mg/d DHA and 323 mg/d EPA;3 wk 2) 1480 mg/d EPA and 250 mg/d DHA; 6wk	The EPA-predominant supplement raised DHA only in the young, and the DHA-predominant supplement raised EPA more in the young	None	Fortier *et al.*[71]
	302 cognitively healthy elderly participants (>65 y)	26-wk randomized double-blind, placebo-controlled trial	1800 mg/d EPA-DHA, 400 mg/d EPA-DHA, or placebo capsules	There was not overall effect of 26 weeks of EPA and DHA supplementation on cognitive performance, nor the quality of life of healthy older individuals, neither mental well-being	None	Van de Rest *et al.*[72,73,76]
	1864 subjects (809 men and 1055 women	8-y follow-up survey of the SU.VI.MAX Study (1994–2002)	Assessment of fish and seafood, and *n*-3 LC-PUFAs intake by means of six 24-h recalls	Fatty fish or *n*-3 LC-PUFAs consumption higher than 0·10 % of energy intake had lesser risk of depressive episode and of recurrent depressive episodes, but not of single depressive episode. It was stronger in men and in non-smokers. Smokers eating fatty fish had an increased risk of recurrent depression	None	Astorg *et al.*[74]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	105 participants >65 y with neovascular age-related macular degeneration	Cross-sectional population-based EUREYE study	Assessment of fish and seafood, and *n*-3 LC-PUFAs intake by food frequency questionnaire	Eating oily fish at least once per week is associated with a reduction of the neovascular age-related macular degeneration	None	Augood *et al.*[77]
	63 overweight treated hypertensive subjects	16-wk randomized controlled trial	Daily fish meal (3·65 g/d *n*-3 LC-PUFAs)in a weight-loss regimen or control group	Incorporating a daily fish meal into a weight-loss regimen was more effective than either measure alone at improving glucose-insulin metabolism and dyslipidemia	None	Mori *et al.*[78]
	233 health subjects (31 ± 5 y; BMI 28·3 ± 1·5 kg/m^2)	8-wk randomized controlled trial	1) <260 mg/d *n*-3 LC-PUFAs (*n* 112) 2) >1300 mg/d *n*-3 LC-PUFAs (*n* 121)	*n*-3 LC-PUFAs group modulates postprandial satiety in overweight and obese volunteers during weight loss	None	Parra *et al.*[80]
	26 overweight or moderately obese (BMI 28–33 kg/m^2) men and women	Randomized controlled trial	2 wk control diet (0 % fish oil, 0·5 % ALA) plus 2 wk *n*-3 LC-PUFAs diet (1·4 % energy in the form of EPA, DPA, and DHA from fish oil, and 2·2 % ALA from plant oil)	Dietary *n*-3-PUFA do not play an important role in the regulation of food intake, energy expenditure, or body weight in humans	None	Kratz *et al.*[81]
	13 patients (11 female, 2 male, 21–81 y) with polymorphic light eruption	3-mo randomized controlled trial	5 capsules twice daily (1 g fish oil, 18 % EPA, 12 % DHA),	Reduction of UV-induced inflammation by dietary fish oil	None	Rhodes *et al.*[82]
	51 HIV-infected patients treated with antiretroviral therapy	12-wk randomized double-blind, placebo-controlled trial	2 capsules of Omacor twice daily or 2 capsules (*n* 26) of placebo (*n* 25)	Fish oil *n*-3 LC-PUFAs slightly decreased plasma triglycerides and induced anti-inflammatory effects by increasing formation of anti-inflammatory LTB5	None	Thusgaard *et al.*[83]
	310 671 women (25–70 y)	6·4 y follow-up of the European Prospective Investigation Into Cancer and Nutrition (1992–1998)	Assessment of breast cancer and fish and seafood, and *n*-3 LC-PUFAs intake by food frequency questionnaire	No associations with breast cancer risk were observed	None	Engeset *et al.*[84]
	40 patients with stage III non-small cell lung cancer	4-wk randomized double-blind, placebo-controlled trial	2 cans/d of protein energy-dense oral nutritional supplement (2·0 g EPA + 0·9 g DHA/d) or an isocaloric control supplement	Fish oil *n*-3 LC-PUFAs supplement has immune-modulating effects and improve nutritional status in patients with non-small cell lung cancer	None	Van der Meij *et al.*[85]
	12 patients with advanced lung cancer	6-wk randomized double-blind, placebo-controlled trial	2 g/d capsules (fish oil, fish oil + placebo, or fish oil plus celecoxib)	patients receiving fish oil + placebo or fish oil + celecoxib showed more appetite, less fatigue, and lower C-reactive protein, improved body weight and muscle strength	None	Cerchietti *et al.*[86]
	20 patients with pancreatic cancer	3-wk randomized double-blind, placebo-controlled trial	Two cans (each can: 310 kcal, 16·1 g protein,1·09 g EPA) of a fish oil-enriched supplement per day in addition to their normal food intake	Performance status, weight-gain, and appetite were significantly improved at 3 wk	None	Barber *et al.*[87]
	47 866 US men aged 40–75 y with no cancer history in 1986	14 y follow-up of Health Professionals Follow-Up Study (1986–2000)	Assessment of fish and seafood, and *n*-3 LC-PUFAs intake in 1986, 1990, and 1994 by using a 131-item semiquantitative food-frequency questionnaire	Increased dietary intakes of ALA may increase the risk of advanced prostate cancer. EPA and DHA intakes may reduce the risk of total and advanced prostate cancer	None	Leitzmann *et al.*[88]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes: Health benefits	Outcomes: Health risks	Reference
	16 commonly consumed fish species	MeHg and *n*-3 LC-PUFAs content of fish species	Dose–response relationships for MeHg and omega-3 FA effects on coronary heart disease and neurodevelopment	*n*-3 LC-PUFAs benefits outweighed cardiovascular and neurodevelopmental MeHg risks for some species (e.g., farmed salmon, herring, trout). Other species were associated with a small net benefit (e.g., flounder, canned light tuna)	MeHg risks outweighed cardiovascular and neurodevelopmental *n*-3 LC-PUFAs benefits for some species (e.g., swordfish, shark). Other species were associated with a small net risk (e.g., canned white tuna, halibut)	Ginsberg *et al.*[96]
Plant						
	88 healthy non-smoking men and premenopausal women (33 y)	12-wk double-blind, parallel randomized controlled trial	Sunflower oil (placebo), flaxseed oil (1 g/d ALA), hempseed oil (0·3 g/d ALA), or fish oil (0·6 g/d EPA + DHA)	Plasma ALA levels increased after 6 wk; no differences in total cholesterol, LDL-C, HDL-chol., TAG, LDL oxidation, platelet aggregation, or inflammation markers (CRP, TNF-α)	None	Kaul *et al.*[123]
	79 healthy non-smoking men and premenopausal women (19–45 y)	6-wk double-blind, parallel randomized controlled trial	ALA (3·4 g/d), EPA (2·2 g/d), or DHA (2·3 g/d) via enriched margarines	LDL and -ALA levels increased; fasting serum TAG decreased; no differences in total cholesterol, LDL-chol., or HDL-chol.	None	Egert *et al.*[124]
	62 men (>40 y)	12-wk parallel randomized controlled trial	Different doses of flax oil, fish oil, and sunflower oil in capsules; ALA doses were 1·2 g/d, 2·4 g/d, and 3·6 g/d	2·4 and 3·6 g/d of ALA significantly increased erythrocyte ALA and EPA levels; no differences in inflammation markers (CRP, TNF-α, sVCAM-1), total cholesterol, TAG, or HDL-chol.	None	Barceló-Coblijn *et al.*[125]
	59 healthy male prisoners	12-wk single-blind study	Diet with 3·2 g/d extra ALA	No effect on waist circumference, weight, BMI, systolic blood pressure; diastolic blood pressure decreased and HDL-chol. increased in non-smokers	None	Sioen *et al.*[126]
	62 men and post-menopausal women (44–75 y) with hypercholesterolemia	10-wk blind, parallel randomized controlled trial	Low-fat diet with extra flaxseed or with wheat bran (control); ALA dose (3·4 g/d)	Serum ALA levels increased; LDL-C decreased after 5 wk but not after 10 wk; lipoprotein(A) decreased and insulin sensitivity (HOMA-IR index) improved; no effect on inflammation (IL-6, hs-CRP) or oxidative stress (ox-LDL, urinary isoprostane); HDL-chol. decreased	None	Bloedon *et al.*[127]
	199 menopausal women (49–65 y)	52-wk blind parallel trial	40 g/d flaxseed or wheat germ; ALA 8·8 g/d	Serum ALA levels increased; modest effects on apolipoproteins A-I and B; no effects on LDL electrophoretic characteristics or markers of hemostasis and inflammation	None	Dodin *et al.*[128]
	1891 cases with first nonfatal MI and 1 891 population-based controls; matching for age, sex, and area of residence	Case-control study	Assessment of ALA intake from FFQ	Inverse association between MI and ALA intake	None	Campos *et al.*[129]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	3575 white men and women (45–64 y)	14·3 y follow-up of Atherosclerosis Risk in Communities Study (prospective cohort study)	Association of plasma ALA with incident heart failure	ALA status was not associated with incident heart failure	None	Yamagishi *et al.*[130]
	2009 men (50 y)	30·7 y follow-up of Uppsala Longitudinal Study of Adult Men (prospective cohort study)	Association of ALA in serum cholesterol esters with CVD mortality	Multivariable-adjusted hazard ratio was 1·10 (1·00–1·21) per 1-SD increase in serum ALA	None	Warensjö *et al.*[131]
	40 cases of ischemic stroke, 40 cases of hemorrhagic stroke and 40 healthy controls; matching for age and sex	Case-control study	Association of ALA in erythrocytes with risk of ischemic and hemorrhagic stroke	Erythrocyte ALA concentrations in hemorrhagic stroke patients and ischemic stroke patients were not significantly different from controls; inverse association of ALA with ischemic stroke	None	Park *et al.*[132]
	2174 men (42–60 y)	17·7 y of follow-up of Kuopio Ischemic Heart Disease Risk Factor Study (prospective cohort study)	Association of serum ALA with incident atrial fibrillation	Multivariable-adjusted hazard ratio for serum ALA (compared to Q1) was Q2: 1·26 (95 % CI, 0·84–1·89), Q3: 0·74 (0·46–1·20), and Q4: 1·14 (0·7–1·79)	None	Virtanen *et al.*[133]
	265 out-of hospital sudden cardiac arrest patients and 415 community members; matching for age, sex, and calendar year	Case-control study	Association of ALA in erythrocytes with risk of sudden cardiac death	Multivariable-adjusted OR over quartiles of ALA in erythrocytes (compared to Q1): Q2 was 1·7 (95 % CI, 1·0–3·0), Q3 was 1·9 (1·1–3·3), Q4 was 2·5 (1·3–4·8); association independent of erythrocyte levels of EPA and DHA, linoleic acid, and trans fatty acids	None	Lemaitre *et al.*[134]
	150 moderately hyperlipidemic subjects	6-mo randomized placebo-controlled, parallel study	0·8 or 1·7 g EPA + DHA/d, 4·5 or 9·5 g ALA/d, or an *n*-6 PUFA control (FA incorporated into 25 g of fat spread and 3 capsules/d)	Fasting or postprandial lipid, glucose, plasma α-tocopherol, antioxidant or insulin concentrations or in blood pressure was not significantly different between treatments. Fasting triglycerides after EPA + DHA intervention was lower than after ALA intervention. Susceptibility of LDL to oxidation was higher after the EPA + DHA intervention.	None	Finnegan *et al.*[135]
	57 elderly (≥65 y) patients (19 male, 38 female)	Case-control study	Association of ALA in erythrocytes with risk for mild dementia (Mini-Mental Status Examination)	Multivariate-adjusted regression analysis showed that a higher level of ALA significantly decreased the risk of mild dementia after adjusting for age, sex, and height	None	Malgeunsinae *et al.*[136]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	23 subjects (49·3 ± 1·6 y; 20 male, 3 female), BMI 25–35 kg/m^2	Randomized, 3-period crossover design	Average American Diet (34 % total fat, 13 % SFA, 13 % MUFA, 9 % PUFA (7·7 % LA, 0·8 % ALA); LA Diet (37 % total fat, 9 % SFA, 12 % MUFA, 16 % PUFA (12·6 % LA, 3·6 % ALA); α-LA Diet (38 % total fat, 8 % SFA, 12 % MUFA, 17 % PUFA (10·5 % LA, 6·5 % ALA). Walnuts and flaxseed oil: ALA predominant sources. Diet periods lasted 6 wk, separated by 3-wk compliance break during which subjects consumed their usual diet.	N-telopeptide levels were significantly lower following the ALA diet. There was no change in levels of bone-specific alkaline phosphatase across the three diets. Concentrations of NTx were positively correlated with the proinflammatory cytokine TNF-α for all three diets	None	Griel *et al.*[137]
	34 T2DM (52·4 ± 1·5 y) patients (17 male, 17 female)	12-wk randomized controlled trial	Participants consumed a selection of bakery products containing no flax (*n* 9), milled flaxseed (*n* 13; 32 g/d), or flaxseed oil (*n* 12; 13 g/d)	Flaxseed and flaxseed oil groups increased plasma phospholipid *n*-3 LC-PUFAs, but not DHA, and the flaxseed oil group had more EPA and DPA in plasma phospholipids than the flaxseed group. All groups had similar caloric intakes. Control group experienced a 4 % weight gain, and both flax groups had constant body weights	None	Taylor *et al.*[138]
	59 middle-aged dyslipidaemic men	12-wk randomized two-group, parallel-arm controlled trial	Dietary supplementation with flaxseed oil, rich in ALA (8 g/d)	Supplementation with ALA resulted in significantly lower systolic and diastolic blood pressure levels	None	Paschos *et al.*[139]
	62 men and post-menopausal women with pre-study low density LDL-chol. (130–200 mg/dl)	10-wk randomized controlled trial	40 g/d ground flaxseed-containing baked products or matching wheat bran products while following a low fat, low cholesterol diet	Flaxseed was well-tolerated, and increased serum levels of ALA, reduced LDL-chol. at 5 wk, but not at 10 wk, reduced HOMA-IR index, but not affect markers of inflammation (IL-6, hs-CRP) or oxidative stress (ox LDL, urinary isoprostanes). In men, flaxseed reduced HDL-chol. concentrations at 5 and 10 wk.	None	Bloedon *et al.*[127]
	35 non-diabetic, dyslipidemic men (38–71 y)	12-wk randomized controlled trial	15 ml/d of flaxseed oil rich in ALA (8·1 g; *n* 18), or 15 ml/d safflower oil (11·2 g LA; *n* 17; control group)	Plasma levels of adiponectin did not change after the increase in ALA flaxseed oil supplementation did not change body mass index, serum lipid concentrations, LDL density, and TNF-α, and adiponectin plasma levels	None	Paschos *et al.*[140]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	56 participants (49 female, 7 male; 20–70 y) without coronary heart disease	26-wk randomized double-blind, placebo-controlled trial	3 g/d of ALA from flaxseed oil in capsules (*n* 31) or olive oil containing placebo capsules (*n* 25)	Changes in plasma HDL-chol., LDL-chol., and triglyceride concentrations did not differ between the groups. Concentration of plasma total cholesterol, and less atherogenic LDL1 and LDL2 subfractions were higher in the flaxseed oil group	None	Harper *et al.*[141]
	10 young (25 ± 3 y) health adults (5 female, 5 male)	4-wk randomized controlled trial	50 g flaxseed/d or control (no flaxseed)	ALA was increased significantly in adipose tissue, and *n*-3 LC-PUFAs were increased in plasma lipids. Plasma LDL-chol. was also reduced by up to 8 %, and total urinary lignan excretion was increased more than fivefold. Antioxidant vitamins and lipid hydroperoxides in plasma were not significantly affected by flaxseed consumption. Bowel movements per week increased by 30 % while flaxseed was consumed	None	Cunnane *et al.*[142]
	150 healthy men and women (25–72 y)	6-mo randomized, double-blind, placebo-controlled parallel study	Placebo (no additional *n*-3 LC-PUFAs), 4·5 or 9·5 g ALA/d, and 0·77 or 1·7 g EPA + DHA/d. The *n*-3 LC-PUFAs were provided in 25 g fat spread plus 3 oil capsules.	An intake of ≤ 9·5 g ALA/d or ≤ 1·7 g EPA + DHA/d does not alter the functional activity of neutrophils, monocytes, or lymphocytes, but it changes the fatty acid composition of mononuclear cells	None	Kew *et al.*[143]
	244 healthy term infants (12–16 d; minimum birth weight of 2500 g)	Randomized, double-blind, placebo-controlled parallel study	Infants received study formulas from 14 to 120 days of age: Control (soy-based formula without supplementation); DHA + ARA (soy-based formula supplemented with minimum birth weight of 2500 g, 17 mg DHA/100 kcal from algal oil and 34 mg ARA/100 kcal from fungal oil)	Percentages of DHA and ARA in total RBC and plasma phospholipids were significantly higher in infants in the DHA + ARA group at 120 d of age. Growth rates did not differ significantly between feeding groups. Both formulas supported normal growth and were well tolerated	None	Hoffman *et al.*[144]
	48 young subjects (13 male, 35 female)	Randomized, double-blind, placebo-controlled parallel study	2-wk wash-in diet rich in MUFA (21 % energy) followed by 3-wk experimental *n*-3 LC-PUFAs enriched diets with about 1 % of energy of ALA, EPA or DHA. *n*-3 LC-PUFAs were provided with special rapeseed oils and margarines	Dietary intake of ALA, EPA or DHA led to a significant enrichment of the respective fatty acid in the LDL particles, with dietary EPA preferentially incorporated. ALA enrichment did not enhance LDL oxidizability	None	Egert *et al.*[145]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes: Health benefits	Outcomes: Health risks	Reference
Enriched dairy products						
	8 normolipidaemic volunteers, habitual partial skim milk drinkers and non-eaters of fish during the study	6-wk randomized controlled trial	500 ml/d partial skim milk,1 mo; then switched to 500 ml/d novel commercially available milk preparation, supplying 400 mg/d *n*-3 LC-PUFAs (300 mg EPA + DHA; 15 mg vitamin E)	The intake of a milk preparation providing low amounts of EPA + DHA to healthy individuals led to marked increases of *n*-3 LC-PUFAs and vitamin E in plasma and in associated increase in HDL-chol. and decrease in triglycerides	None	Visioli *et al.*[146]
	30 subjects (45–65 y)	8-wk randomized controlled trial	500 ml/d of semi-skimmed milk, 4 wk; and then 500 ml/d of enriched *n*-3 LC-PUFAs milk (60 mg/100 mL EPA and DHA)	*n*-3 LC-PUFAs enriched milk produced a significant decrease in plasma concentration of triglycerides, total and LDL cholesterol accompanied by a reduction in plasma levels of homocysteine, vascular cell adhesion molecule 1, and an increase in folic acid concentration. Plasma and LDL oxidability and vitamin E concentration remained unchanged	None	Baró *et al.*[147] Carrero *et al.*[148]
	51 patients (25 female, 26 male) mildly hypertriacylglycerolemic	Randomized, double-blind, placebo-controlled cross-over trial	Both groups received 15-wk intervention (3g/d *n*-3 LC-PUFAs) and control dairy products consecutively with a 10-wk washout phase between the two treatments	The consumption of *n*-3 LC-PUFAs-enriched dairy products resulted in a significant improvement of cardiovascular risk factors	None	Dawczynski *et al.*[149]
	25 health subjects (12 male, 13 female, 19–68 y)	Single-blind, randomized, controlled crossover study	Subjects received a control (33·3 g of fat, with 30 g provided by the test oil: palm olein and soybean oil, ratio 4:1) and a *n*-3 LC-PUFAs-rich meal (23·2 g of control oil and 6·8 g fish oil, providing 2·0 g EPA and 2·7 g DHA, equivalent to two portions of oily fish) on two occasions in a random order. Postprandial measurements were made at 30, 60, 90, 120, 180 and 240 min	Consumption of *n*-3 LC-PUFAs-rich meal had an attenuating effect on augmentation index and stiffness index	None	Chong *et al.*[150]
	88 children (3–9 y)	7-mo randomized, controlled trial	Consumption of 500 mL/d of a PUFA enriched dairy drink (60 % olive oil, 20 % peanut, and 20 % sunflower), containing a quarter of the saturated fat present in standard whole milk	Enriched dairy drink reduce serum levels of total cholesterol and LDL-chol., without reducing caloric intake	None	Estévez-González *et al.*[151]
	31 men (30–60 y) mildy hyperlipidemic and normotensive	Randomized controlled trial	4·5 g/d EPA plus DHA capsules (*n* 25); control (*n* 6); 3-wk baseline period plus 5-wk intervention	Changes in total cholesterol, LDL-chol., apolipoprotein B, and blood pressure with *n*-3 LC-PUFAs were not significantly different from changes for the control diet.	None	Cobiac *et al.*[152]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	297 subjects (25–65 y) with moderate CVD risk	1-y longitudinal, randomized, controlled, double-blind intervention study	Intervention: 1) 500 mL/d of enriched milk (EPA, DHA, oleic acid, folic acid, and vitamins A, B_6, D, and E), 2) 500 mL/d of skimmed milk, and 3) 500 mL/d of semi-skimmed milk (control group)	Consumption of enriched milk increases serum folate and HDL-chol., decreases plasma triglycerides, total cholesterol, and LDL-chol. Serum glucose, homocysteine, and C-reactive protein remained unchanged.	None	Fonollá *et al.*[153]
	60 male patients (60–67 y) with peripheral vascular disease and intermittent claudication	1-y longitudinal, randomized, controlled, double-blind intervention study	Intervention: The supplement group consumed 500 mL/d of a fortified dairy product containing EPA, DHA, oleic acid, folic acid, and vitamins A, B_6, D, and E. The control group consumed 500 mL/d of semiskimmed milk with added vitamins A and D.	Plasma concentrations of EPA, DHA, oleic acid, folic acid, and vitamins B_6 and E increased after treatment with supplements. Plasma total cholesterol and ApoB concentrations decreased in the supplemented group, and total homocysteine decreased in those patients with high initial concentrations. Walking distance before the onset of claudication increased in the supplemented group, and ankle-brachial pressure index values increased.	None	Carrero *et al.*[154]
	40 male MI patients (50–60 y)	1-y longitudinal, randomized, controlled, double-blind intervention study	Intervention: The supplement group consumed 500 mL/d of a fortified dairy product containing EPA, DHA, oleic acid, folic acid, and vitamins A, B_6, D, and E. The control group consumed 500 mL/d of semiskimmed milk with added vitamins A and D.	Plasma concentrations of EPA, DHA, oleic acid, folic acid, vitamin B_6, and vitamin E increased after supplementation. Plasma total and LDL-chol., apolipoprotein B, and hs- CRP concentrations decreased in the supplemented group, and plasma total homocysteine decreased in both groups. There were no changes in heart rate, blood pressure, or cardiac electrocardiographic parameters in either group	None	Carrero *et al.*[155]
	72 patients with metabolic syndrome	3-mo controlled and open-label clinical trial, of parallel design	Iintervention:500 ml/d of semi-skimmed milk (control group, *n* 36), and 500 ml/d of enriched (5·7 g oleic acid, 0·2 g EPA + DHA, 150 μg folic acid and 7·5 mg vitamin E, *n* 36) semi-skimmed milk	EPA and DHA enriched skimmed milk reduced total cholesterol, LDL-chol., triglycerides, and apolipoprotein B serum levels, and glucose and homocysteine plasma levels	None	Benito *et al.*[156]
	74 healthy normolipidemic men and women (19–43 y)	6-wk randomized controlled trial	Intervention: 4·4 g/d ALA (ALA group), 2·2 g/d EPA (EPA group), and 2·3 g/d DHA (DHA group). Fatty acid ethyl esters were incorporated into margarines, which replaced the participant's normal spread	The ALA, EPA, or DHA intake led to a significant enrichment of the LDL with the respective *n*-3 LC-PUFAs. ALA, EPA, or DHA intake did not affect fasting serum concentrations of total and LDL-cholesterol, but fasting serum triglyceride concentrations significantly decreased. DHA intake significantly increased serum HDL cholesterol, whereas no changes were found with ALA or EPA intake	None	Egert *et al.*[124]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes: Health benefits	Outcomes: Health risks	Reference
Animal-derived foods						
	Two groups of animals were used in each of two separate trials	Randomized controlled trial	(1) Hereford steers supplemented (or not) with ground flaxseed (907 g/d) for 71 d, and (2) Angus steers supplemented (or not) with ground flaxseed (454 g/d for 3 d followed by 907 g/d for 110 d)	For the Hereford group, flaxseed-supplemented rations increased 18 : 3*n*-3 (4·0-fold), 20 : 5*n*-3 (1·4-fold), and 22 : 5*n*-3 (1·3-fold) mass as compared with the control, and increased total *n*-3 mass about 1·7-fold. For the Angus group, flaxseed ingestion increased masses and composition of *n*-3 FA similarly to that for the Herefords and doubled the total *n*-3 FA mass.	No adverse effects on FA composition by grilling steaks to an internal temperature of 64°C. N-3 LC-PUFAS did not affect gene expression	Kronberg *et al.*[158]
	36 growing-finishing pigs, with an average initial weight of 24·8 ± 2·6 kg (mean ± SD)	Randomized controlled trial	Control diet, or one of three diets containing 50 g/kg fish silage and different levels of fish fat (2·5, 5·5 or 9·5 g/kg). The diets were either fed until the time of slaughter, or 60 kg live weight followed by the control diet	No significant differences in growth performance or carcass quality were found among diets. The total levels of *n*-3 LC-PUFAs were highest for the 9·5 and the 5·5 g/kg fish fat diets when they were fed until slaughter.	The diets containing 2·5 and 9·5 g/kg fish fat until slaughter caused off-flavour of bacon after both 1 and 6 mo of frozen storage, and of loin muscle after 6 mo frozen storage	Kjos *et al.*[159]
	600 crossbred pigs	Randomized controlled trial	4 treatments: 0 % tuna oil in diet (T0; control), 1 % unrefined tuna oil in diet fed from 35 to 90 kg of unrefined tuna oil in diet offered during the early (35–60 kg BW; T3-E) or late stage of fattening (75 to 90 kg of BW; T3-L)	Feeding tuna oil during a short period at the end of fattening (T3-L) or permanently during fattening (T1) proved to be similarly efficient in increasing *n*-3 fatty acid content of lean and adipose tissue (to about 1·6-fold of T0). By contrast, only two-thirds of this increase was found when the same amount of tuna oil had been fed exclusively during early fattening (T3-E).	Flavour and acceptability were most favourable in pigs receiving tuna oil in the early fattening period (T3-E), whereas it was less favourable ($P < 0·05$) in those fed tuna oil throughout fattening (T1)	Jaturasitha *et al.*[160]
	20 healthy adult volunteers	Randomized controlled trial	Sensory quality assessment of *n*-3 LC-PUFAs-rich functional Bruehwurst sausages made with a range of *n*-3 PUFA sources	TBARS values of the sausages were low, even after storage. Microbiological and physico-chemical properties of the sausages were generally unaffected by addition of omega-3 fatty acid sources.	Some of the omega-3 fatty acid sources tested caused off-flavours, not always described as “fishy”	Muench *et al.*[161]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	Eighty-eight 40-week-old ISA Brown laying hens	Randomized controlled trial	The trial lasted for 28 d and started after a pre-experimental period of 21 d, where animals received the same experimental treatments: 9 diets: 3 levels *n*-3 FA supplementation (2·9, 3·7 and 4·5 g/kg) from 3 different sources (marine algae oil, and two marine fish oils rich in EPA or in DHA), plus 2 diets (fixed CLA (2·5 g/kg) and HOSO (30 g/kg). Feed and water were supplied *ad libitum*. The hens received 15 h light/d throughout the experiment. Room temperature was also controlled at about 24°C.	An increase in *n*-3 PUFA supplementation had little effect on proportions of CLA, MUFA, SFA or total PUFA in yolk fat, but increased *n*-3 LC-PUFAs and decreased *n*-6 LC-PUFA. An increment of dietary *n*-3 LC-PUFAs impaired linearly egg acceptability by consumers.	None	Cachaldora *et al.*[162]
	25 healthy adult volunteers	Randomized double-blind crossover trial	Subjects fed 3wk with 5 normal eggs/wk, and next 3 wk fed with enriched eggs/wk. A second group received eggs in the inverse sequence. Enriched eggs from hens feed tuna oil 5 % (9 times more *n*-3 LC-PUFAs)	Decrease in serum triglycerides. No change on LDL-chol., and HDL-chol.	None	Bovet *et al.*[163]
	126 28-week-old Warren laying hens with similar body weight (2 kg) and egg parameters were randomly divided into 7 groups of 18 birds each (6 replicates/group)	6-wk randomized controlled trial	Hens received one of these diets (all were isoenergetic): Control (complete diet); control containing 10 g/kg linseed oil; control containing 49·5 g/kg fish oil; control supplemented with 16·7 g/kg DHA-rich *Schizochytrium* sp.microalgae; control supplemented further supplemented with 5·5 mg/kg potassium iodide; control supplemented further supplemented with 2·03 mg/kg sodium selenite; control supplemented further supplemented with 5·5 mg/kg potassium iodide and 2·03 mg/kg sodium selenite.	Improvement in egg weight and in the DHA content of yolks by feeding hens a microalgae-rich diet, which avoids the unpleasant flavours associated with fish oil supplementation	None	Rizzi *et al.*[164]
Krill oil						
	76 overweight obese men and women	4-wk randomized double-blind parallel arm trial	Capsules containing 2 g/d of krill oil, menhaden oil, or control (olive oil)	Krill oil supplementation increased plasma EPA and DHA, decreased plasma urea, and was well tolerated	None	Maki *et al.*[167]
	120 patients with hyperlipidemia	Multi-center, 3-mo, prospective, randomized study followed by a 3-mo, controlled follow-up of patients treated with 1 g and 1·5 g krill oil daily	Four groups: 1) Krill oil at BMI-dependent daily dosage 2–3 g/d. 2) Krill oil 1–1·5 g/d. 3) Fish oil (180 mg EPA + 120 mg DHA/g fish oil; 3 g/d). 4) Placebo	Krill oil decreased total cholesterol, LDL, and triglycerides, and increasing HDL levels	None	Bunea *et al.*[168]

Table 1. *Continued*

Dietary source	Participants	Design	*n*-3 LC-PUFAs intervention and doses	Outcomes		Reference
				Health benefits	Health risks	
	70 adult women with premenstrual syndrome	3-mo randomized double-blind controlled trial	Intervention with 1 g/soft gels (2 times/d with meals) of either Neptune krill oil or fish oil (18 % EPA + 12 % DHA)	Neptune krill oil decreased dysmenorrhea and emotional symptoms of premenstrual syndrome and was more effective for the complete management of premenstrual symptoms compared to fish oil	None	Sampalis *et al.*[169]
Seal oil						
	19 healthy, normocholesterolemic subjects	42-d randomized controlled trial	20 g of encapsulated seal oil (EPA; DHA; DPA) or 20 g of vegetable oil (control) per day	Seal oil supplementation decreased the *n*-6/*n*-3 ratio and increased EPA, DHA, and DPA and the ratio of EPA/ARA and DHA/ARA in the serum phospholipid and NEFA, while exhibiting a modest beneficial effect on fibrinogen and protein C levels	None	Conquer *et al.*[170]
	144 patients with nonalcoholic fatty liver disease and hyperlipidemia	Randomized controlled trial	Two groups: 1) recommended diet and 2 g *n*-3 PUFA from seal oils. 2) recommended diet and 2 g placebo. Intervention 3 times /d	*n*-3 LC-PUFAs from seal oils is safe and efficacious for patients with nonalcoholic fatty liver disease associated with hyperlipidemia and can improve their total symptom scores, ALT, serum lipid levels and normalization of ultrasonographic evidence	None	Zhu *et al.*[171]

Abbreviations: ALA: α-linolenic acid; ARA: arachidonic acid; CLA: conjugated linoleic acid; BMI: body mass index; CD69: cluster of differentiation 69; CRP: C-reactive protein; CVD: cardiovascular diseases; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; EPA: eicosapentaenoic acid; FFQ: food frequency questionnaire; HOMA-IR index: homeostasis model assessment-insulin resistence; hs-CRP: high-sensitivity C-reactive protein; HOSO: high-oleic sunflower oil; IL-6: interleukine-6; LA: linoleic acid; LTB4: leukotriene B4: LTB5: leukotriene B5; MDA: malondialdehyhe; MeHg: methylmercury; MI: myocardial infaction; MUFA: monounsaturated fatty acids; *n*-3 LC-PUFAs: omega-3 long chain polyunsaturated fatty acids; NO: nitric oxide; RBCs: red blood cells; SFA: saturated fatty acids; sICAM-1: soluble cell adhesion molecules-1; sVCAM-1: vascular cell adhesion molecules-1; TAG: triacylglycerides; TBARS: thiobarbituric acid reactive substances; T2DM: type II diabetes mellitus; TNFα: tumor necrosis factor-alpha; nd: no data.

Daily intake of fish oil *n*-3 LC-PUFAs for 37 months decreased 16% all causes of mortality and 24% the incidence of death due to myocardial infarction. This benefit putatively arises from the incorporation of EPA and DHA into cardiomyocyte phospholipids at the expense of ARA during high-dose fish-oil supplementation[18]. Fish oil consumption decreased tumour necrosis factor-alpha (TNFα) production in healthy subjects and improves body weight in severe heart failure[19]. However, restenosis after coronary angioplasty was not reduced by supplemental fish oil[20].

Consumption of fish has been associated with a significantly reduced progression of coronary atherosclerosis in women with coronary artery disease[21]. Atlantic salmon fillets very high in *n*-3 LC-PUFAs of marine origin seemed to impose favourable biochemical changes (reductions of serum triglycerides, vascular cell adhesion molecule-1 and interleuki *n*-6) in patients with coronary heart disease[22]. Findings from short- and long-term randomized trials pointed out that fish *n*-3 LC-PUFAs intake are inversely related to blood pressure, either on hypertensive or nonhypertensive persons, with small estimated effect size[23].

After 6-year follow up, the age-adjusted models showed no evidence of an association between fish consumption or omega-3 fatty acid intake and incident of atrial fibrillation (AF) in a large sample of older, postmenopausal women (44 720 participants from the Women's Health Initiative clinical trials) who were not enrolled in a dietary modification intervention arm and without AF at baseline[24]. Fish oil *n*-3 LC-PUFAs have not a protective effect on cardiac arrhythmia. Current data neither proved nor disproved a beneficial or a detrimental effect for subgroups of patients with specific underlying pathologies[25].

DHA and EPA rich fish-oil supplements taken with a high-fat meal preserved impairments in endothelial function[26]. There was no effect on cardiovascular biomarkers or mood in patients with ischemic stroke submitted to 12 wk of treatment with moderate-dose fish oil supplements (3 g/d fish oil containing 1·2 g total omega-3: 0·7 g DHA; 0·3 g EPA). It is possible that insufficient dose, short duration of treatment, and/or oxidation of the fish oils may have influenced these outcomes[27].

Beneficial effects of fish oil *n*-3 LC-PUFAs on cardiac risk factors and heart rate variability have been also found in people with epilepsy[28]. However, the administration of five fish oil capsules with every meal (1260 mg/d EPA and 540 mg/d DHA) in healthy middle-aged Japanese men with a high level of fish consumption for 4 weeks did not demonstrate a decrease in plasma TAG, cholesterol, LDL-cholesterol, and whole-blood viscosity. Further, no changes in the fatty acid composition of plasma and erythrocyte phospholipids were noted[29]. A progressive and significant increase in total hyperhomocysteinemia was observed after 8 weeks of dietary supplementation with 6 g/d of fish oil. This increase was not associated with changes in plasma folate or vitamin B_{12} concentrations[30].

In comparison with corn oil, fish oil tended to increase HDL and decreased LDL concentration, and to decrease insulin sensitivity, but it has no effect on oxidized LDL[31]. Once-a-day intakes of plant sterol-enriched yoghurt drink (2 g plant sterols/d) and fish oil capsules (2 g/d fish oil *n*-3 LC-PUFAs) reduced 15% TAG and increased 5·4% HDL-cholesterol in mildly hypercholesterolaemic 35–55 y-o adults[32].

A 30-year follow-up survey of the Dutch and Finnish cohorts of the Seven Countries Study showed that an increase in the fish consumption was inversely related to glycaemia[33]. To take ≥1 versus <1 portion/week of fish was associated with a lower risk of T2DM[34]. Moreover, the risk of T2DM in an elderly population was lowered by increased fish and *n*-3 LC-PUFAs consumption[35]. However, a large epidemiological study of healthy adults showed that the relative risk of T2DM was slightly higher in women who consumed ≥5 servings fish/wk than those who consumed fish ≤1/mo, after adjustment by other dietary and lifestyle risk factors. The authors explained the results by the fact that toxins such as dioxins and methylmercury may interrupt insulin signalling pathways. The authors also hypothesized that *n*-3 LC-PUFAs may contribute to higher glucose concentrations through other mechanisms, i.e.: *n*-3 LC-PUFAs can decrease glucose utilization and increase glucagon-stimulated C-peptide, or increase hepatic gluconeogenesis[36]. Several clinical studies also reported that *n*-3 LC-PUFAs may worsen glucose tolerance and insulin resistance in T2DM patients who consumed large amounts of fish oil[37–40]. It has been pointed out that these negative effects were due to the high doses of *n*-3 LC-PUFAs used, such as ≥10 g/d fish oil.

A prospective study of 36 328 women (mean age 54·6 y) who participated in the Women's Health Study (1992–2008) suggested an increased risk of T2DM with the intake of marine *n*-3 LC-PUFAs, especially with high intakes (≥0·2 g omega-3/d or ≥2 servings of fish/d)[41]. However, unfavourable associations between marine *n*-3 LC-PUFAs intake and glucose control was not found[42]. In healthy individuals a moderate supplementation of fish oil did not affect insulin sensitivity, insulin secretion, beta-cell function or glucose tolerance[43]. Further, in a crossover study of subjects with T2DM, enrichment with fish oil *n*-3 LC-PUFAs failed to affect insulin sensitivity and secretion[44], but another randomized crossover dietary intervention study with two 8-week periods reported that an increase in oily fish consumption increased insulin sensitivity in young iro *n*-deficient women[45].

Current evidence indicates that fish oil EPA and DHA can prevent the development of inflammatory diseases by affecting different steps of the immune response. DHA, but not EPA, suppresses T lymphocyte activation[46]. The capacity of *n*-3 LC-PUFAs to modulate the synthesis of eicosanoids, activity of nuclear receptor and transcription factors, and production of resolvins, may also mitigate inflammatory processes already present. In a 8-wk intervention trial, 324 subjects (aged 20–40 years, and BMI 27·5–32·5 kg/m^2) that took salmon (3 × 150 g/wk, 2·1 g/d LC-PUFA) or cod (3 × 150 g/wk, 0·3 g/d *n*-3 LC-PUFAs) or fish oil capsules (1·3 g/d *n*-3 LC-PUFAs) showed significant decreases in inflammation parameters (high-sensitivity C-reactive protein, interleuki *n*-6, glutathione reductase, and prostaglandin $F_2\alpha$), a mechanism by which PUFAs reduce CVD, but also they experienced weight loss (−5·2 ± 3·2 kg)[47], and decreased diastolic and systolic blood pressure[48]. Similar results were obtained in

subjects (35–70 years) after an 8-wk food-based intervention trial taking salmon, an oily fish[49]. Dietary fish oil *n*-3 LC-PUFAs supplementation had a markedly protective effect in suppressing exercise-induced bronchoconstriction in elite athletes, which may be attributed to their antiinflammatory properties. Fish oil *n*-3 LC-PUFAs supplementation decreased leukotriene (LT)E4, 9α, 11β-prostaglandin F2, LTB4, TNFα, and interleukin-1β[50].

n-3 LC-PUFAs are potentially useful anti-inflammatory agents. To intake fish oil 960 mg/d of EPA and 600 mg/d of DHA can decrease C-reactive protein levels[51]. An 8-wk consumption of fatty fish decreased lipids which are potential mediators of lipid-induced insulin resistance and inflammation[52]. Dietary *n*-3 fatty acids have been associated with lower levels of inflammation and endothelial activation, which may partially explain the effect of *n*-3 LC-PUFAs in preventing cardiovascular disease[53].

Parenteral supplementation with fish oil *n*-3 LC-PUFAs emulsion decreased the magnitude and persistence time of the systemic inflammatory response syndrome (SIRS), markedly retrieve the unbalance of the pro-/anti-inflammatory cytokines, improve severe condition of illness and may provide a new way to regulate the SIRS[54].

Fish oil *n*-3 LC-PUFAs reduced the requirement for nonsteroidal antiinflammatory drugs (NSAID) in patients with rheumatoid arthritis[55], and are a safer alternative to NSAID for treatment of nonsurgical neck or back pain[56]. Cod liver oil supplements containing *n*-3 LC-PUFAs may be used as NSAID-sparing agents in rheumatoid arthritis patients[57]. The combination of fish oil and paracetamol suppressed PGE_2 synthesis by an amount equivalent to that from maximum therapeutic doses of NSAID, and enhanced suppression of nociceptive PGE_2 synthesis and thereby provided additive symptomatic benefits[58]. Asthma, another highly prevalent chronic inflammatory disease, may also positively respond to fish oil supplements[59].

In spite of a high intake of fish oil, *n*-3 LC-PUFAs may be associated with decreased inflammation. A 12-wk randomized, double-blind placebo-controlled intervention trial in healthy subjects aged 50–70 years did not show that 3·5 g/d fish oil (1·5 g/d *n*-3 LC-PUFAs) significantly affected the serum inflammatory response (it did not significantly affect serum concentrations of cytokines, chemokines or cell adhesion molecules), nor did patterns of inflammatory markers[60].

Fish oil *n*-3 LC-PUFAs blunted the endocrine stress response and the increase in body temperature, but had no impact on cytokine production after endotoxin challenge, which has been shown to mimic several aspects of sepsis. These findings conflict with the postulated anti-inflammatory effects of fish oil on ARA metabolism and cytokine release. These results suggest that fish oil may exert beneficial effects in sepsis though non-inflammatory[61]. However, the use of immunonutrition including fish oil in critical ill patients or patients with severe sepsis may exert an excess mortality. All of which require further research.

A high fish oil EPA and DHA intake (1·8 g EPA and DHA/d, 26 weeks) changed the expression of 1040 genes, and resulted in a decreased expression of genes involved in inflammatory- and atherogenic-related pathways, such as nuclear transcription factor kappaB signaling, eicosanoid synthesis, scavenger receptor activity, adipogenesis, and hypoxia signaling[62].

Thirty six girls aged 18–22 years were supplemented 3 months with 15 mL fish oil daily (550 mg/d EPA; 205 mg/d) by means a cross-over clinical trial. They reduced symptoms of dysmenorrhoea, low back pain and abdominal pain, and needed significantly fewer rescue doses of ibuprofen while using fish oil[63].

Pregnant women aged 18–41 years supplemented from week 22 with modified fish oil showed high thiobarbituric acid-reactive substances (TBARS), an oxidative stress index in lipids, at week 30, and minor changes of uric acid increased and beta-carotene as well as trolox-equivalent antioxidative capacity (TEAC) from week 20 to delivery. Fish oil *n*-3 LC-PUFAs supplementation improved infant neurological development, it causes additional increase of oxidative stress at week 30, but it also did not decrease antioxidant status during the second half of pregnancy[64]. Maternal fish oil supplementation during pregnancy (2·2 g/d DHA and 1·1 g/d EPA from 20 weeks' gestation until delivery) was safe for the foetus and infant, and might have potentially beneficial effects on the child's eye and hand coordination[65].

Fish intake also plays a protective role in the development of allergic diseases in women because of its high *n*-3 LC-PUFAs contents. It is not understood why this association was only seen in females, but gender-related differences in metabolism of PUFA could be a possible explanation[66]. Supplementation of pregnant women with allergic disease with fish oil (3·7 g/d of *n*-3 LC-PUFAs) for the final 20 weeks of pregnancy decreased neutrophil LTB4 production, pro-inflammatory IL-6 responses and regulatory IL-10 responses by lipopolysaccharide-stimulated neonatal mononuclear cells, and a trend for less inflammatory products (LTB5) in neonates. It provides evidence that fish *n*-3 LC-PUFAs can influence early immune development[67]. Milk of lactating mothers supplemented with tuna oil had high DHA and ALA contents, which are important nutrients in the infant preterm diet[68]. The maximum DHA levels in human breast milk exceed 1 % of total fatty acids in high-fish-consuming populations. Consumption of DHA-rich human milk as sole source of nutrition provided approximately 315 mg/d in infants 1–6 months of age, and appeared to be a safe level of intake, without adverse events in infants. Daily maternal supplementation with either fish oil 1·6 g EPA and 1·1 g DHA or placebo in pregnant women affected by allergy themselves or having a husband or previous child with allergies from the 25th gestational week to average 3–4 months of breastfeeding, decreased the period prevalence of food allergy, as well as the incidence of IgE-associated eczema during the first year of life in infants with a family history of allergic disease[69]. The *n*-3 LC-PUFAs-status in late infancy affected heart rhythm in infants similar to that observed in adults, and influenced on brain development and CNS function, irrespectively of gender[70].

Elderly people are susceptible to cardiovascular and neurological illnesses, which seem to be related in part to lower intake of *n*-3 fatty acids[71]. Furthermore, supplementation with high or low doses of fish oil *n*-3 LC-PUFAs for 26

weeks influenced neither the cognitive performance[72], nor the quality of life of healthy older individuals, measured by means of the WHO's quality of life questionnaire[73].

Subjects consuming fatty fish or with an intake of *n*-3 LC-PUFAs higher than 0·10 % of energy intake had a significantly low risk of depressive episode and of recurrent depressive episodes, but not of single depressive episode. These associations were stronger in men and in non-smokers, but smokers eating fatty fish had an increased risk of recurrent depression. Then, usual intake of fatty fish or *n*-3 LC-PUFAs may decrease the risk of recurrent depression in non-smokers[74].

Few effects of *n*-3 LC-PUFAs on cognition and mood states, few risk-averse decisions, and improved scores on the control/perfectionism scale of the cognitive reactivity measure have been also found, but no effects on other cognitive tasks[75]. A randomized, double-blind, placebo-controlled trial did not observed effect of EPA and DHA supplementation for 26 wk on mental well-being in older (≥65 years) population[76]. Eating oily fish at least once per week were associated with a reduction of neovascular age-related macular degeneration[77].

Incorporating a daily fish meal rich in *n*-3 LC-PUFAs into a weight-loss regimen was more effective than either measure alone at improving glucose-insulin metabolism and dyslipidemia, and also reduced cardiovascular risk[78]. Controlled trials using whole fish as a test meal were encouraged to be able to elucidate the role of different constituents of fish for human health[79]. Validated visual analogue scale assessment revealed low hunger sensations in volunteers (31 ± 5 years; BMI 28·3 ± 1·5 kg/m^2) after an intervention (>1300 mg/d of *n*-3 LC-PUFAs) on the last 2 wk of an 8-wk energy-restricted balanced diet (weight loss = −5·9 ± 3·1 %). Therefore, *n*-3 LC-PUFAs seems to modulate postprandial satiety in overweight and obese volunteers during weight loss, and may be considered nutritional factors with a potential to modulate food intake[80]. However, a controlled randomized dietary trial showed that dietary *n*-3 LC-PUFAs do not play an important role in the regulation of food intake, energy expenditure, or body weight in humans[81].

The sunburn response is markedly reduced by dietary fish oil rich in *n*-3 LC-PUFAs. Reduction of UV-induced inflammation by fish oil may be due, at least partially, to lowered PGE_2 levels, suggesting a clinical application for fish oil *n*-3 LC-PUFAs[82].

Treatment of antiretroviral treated HIV-infected patients with fish oil *n*-3 LC-PUFAs slightly decreased plasma TAG and induced anti-inflammatory effects by increasing formation of anti-inflammatory LTB5. No other changes were observed[83].

Some in vitro and animal studies have suggested an inhibitory effect of marine *n*-3 fatty acids on breast cancer growth, but no significant associations between intake of total fish and breast cancer risk were observed in 310 671 women aged 25–70 years at recruitment into the European Prospective Investigation Into Cancer and Nutrition[84]. Oral nutritional supplement containing fish oil 2·0 g/d EPA and 0·9 g/d DHA had immune-modulating effects and could improve nutritional status in patients with non-small cell lung cancer (NSCLC) undergoing multimodality treatment[85]. A combination of fish oil *n*-3 LC-PUFAs and cyclooxygenase-2 inhibitor decreased some of the signs and symptoms associated with a Systemic Immune-Metabolic Syndrome (i.e.: paraneoplastic hemopathies, hypercalcemia, coagulopathies, fatigue, weakness, cachexia, chronic nausea, anorexia, and early satiety among others) could be ameliorated[86]. Fish oil EPA-enriched supplement (1·09 g/d) may reverse cachexia in advanced pancreatic adenocarcinoma, and showed weight-gain at both 3 (1 kg) and 7 weeks (2 kg)[87]. Increased intakes of dietary ALA may increase the risk of advanced prostate cancer, whereas EPA and DHA intakes may reduce the risk of total and advanced prostate cancer[88].

Until now, we have listed a number of studies that have clearly remarked the benefits of fish oil *n*-3 LC-PUFAs. However, some concerns about potential health risks derived from the environmental pollutants and contaminants found in fish have been also raised. One of the most dangerous contaminants is methylmercury (MeHg). Mercury is emitted into the atmosphere from several sources. From the atmosphere, mercury cycles from rainwater into lakes and oceans, where it is converted by the action of microorganisms into organic MeHg, which is well absorbed and actively transported into tissues by a widely distributed carrier protein[89,90]. The concentration of MeHg in any given fish species depends on the degree of local environmental contamination and on the predatory nature and lifespan of the species. The concentration of MeHg in fish is increased by fish eating other fish for food. Fish that are not predatory, shorter-lived or smaller species, such as sardines, salmon, flounder, canned light tuna and shrimp, therefore have very low levels of MeHg. By contrast, longer-living and predatory fish such as shark, tuna, swordfish and orange roughly have higher levels of MeHg. Interestingly, the much-maligned farmed fish have the lowest levels of MeHg. Although MeHg *per se* is very neurotoxic, in fish MeHg is bound to cysteine, and this compound has a tenth of the toxicity of pure MeHg[91,92]. MeHg can bind to the sulfhydryl groups of enzymes, ion channels, and receptors, inhibiting important antioxidant systems and increasing the production of reactive oxygen species and free radicals[90,93]. Health effects of very high doses of MeHg exposure are well-documented and include paresthesias, ataxia, and sensory abnormalities in adults, and delayed cognitive and neuromuscular development in children following in utero exposure[90,94]. MeHg crosses the placenta, and exposure to the fetus is a function of maternal exposure[95]. Following very high gestational exposure, severe neurodevelopmental abnormalities can occur in children. However, the health effects of chronic low level mercury exposure are scarcely well-established.

Estimated *n*-3 LC-PUFAs benefits outweighed cardiovascular and neurodevelopmental MeHg risks for some species (farmed salmon, herring, trout); however, the opposite was true for others (swordfish, shark). Other species were associated with a small net benefit (flounder, canned light tuna) or a small net risk (canned white tuna, halibut)[96].

More typical MeHg exposures from fish consumption are far lower. Among US women of childbearing age, the median

levels of hair mercury were 0·19 ppm overall, and 0·34 ppm among women who consumed more than three servings of fish per month[97]. These low exposure levels do not produce clinically detectable neurologic symptoms or signs in children. In studies in the Faroe Islands[98,99], New Zealand[100,101], and Poland[102], higher gestational mercury exposure was associated with lower scores on some neurologic tests, but not on most of them. In the Seychelles, however, higher gestational MeHg exposure was associated with higher scores on some neurologic tests[103,104]. Maternal fish intake during gestation was associated with better visual recognition memory scores, while maternal hair mercury was associated with lower visual recognition memory scores[105], suggesting that overall fish consumption (which provides DHA, likely beneficial for neurodevelopment) and MeHg exposure may have opposing effects. Gestational mercury exposure was not associated with neurodevelopmental scores, but it was associated with better neurodevelopmental scores in other human populations[106].

It should be useful in establishing advisories for a wide variety of commercially available and locally caught fish, assuming that the requisite MeHg and *n*-3 LC-PUFAs data are available[95,107–112]. This caution should be extended to other foods fortified with fish oil *n*-3 LC-PUFAs, such as eggs and milk. However, exceeding the tolerable daily intake was just noticed for heavy seafood consumers. Wild and farmed fish are generally both similar in *n*-3 LC-PUFAs contents but may vary in terms of potential toxins, but they affected proteins and not fatty acids.

Accordingly, the Environmental Protection Agency published a focused advisory for women of childbearing age, nursing mothers, and young children[113]. The allowable upper limit of daily intake, for methylmercury of 0·1 μg/kg per d (approx. 50 μg/week for a 70 kg woman)[95]. Four fish species (shark, swordfish, king mackerel, and tilefish) exceed this limit in a single serving. So, women of childbearing age, nursing mothers, and young children should avoid these specific species, but they could consume a variety of other fish up to 2 servings/week (including up to 1 serving/week of albacore tuna) to receive the important health benefits[112]. The US Institute of Medicine recommended that pregnant women restrict their intake of fish with a higher MeHg content (shark, tuna, or swordfish) to 1 meal per 2 weeks; however, these women can eat 2–3 meals of other fish per week (sardines, salmon, or shrimp)[91]. The importance of this conservative reference dose for health effects in adults remains still unclear[113].

The results of studies of mercury exposure and cardiovascular disease incidence in adults provide inconclusive evidence for cardiovascular toxicity of mercury exposure. Of note, in the only two studies that observed positive associations between mercury exposure and cardiovascular risk, the net effect of fish consumption was still beneficial[114–116].

Sensorimotor symptoms in adults, most commonly paresthesias, can be seen following very high methylmercury exposure from accidents[90,94,117] or prolonged high intakes of mercury-containing fish (1–2 fish servings per day, including species high in mercury, for >10 years)[54]. Such symptoms are typically reversible when mercury exposure is reduced. Evidence suggests that fish consumption may favorably affect clinical neurologic outcomes in adults, including ischemic stroke[118], cognitive decline and dementia[119], and depression and other neuropsychiatric disorders[120,121].

Other potential contaminants in fish such as dioxins and polychlorinated biphenyls could potentially increase the risk of cancer. An analysis of the potential harmful effects of these contaminants in fish versus the benefits of omega-3 fatty acids has, however, concluded that the levels of dioxins and polychlorinated biphenyls in fish are low, and potential carcinogenic and other effects are outweighed by potential benefits of fish intake[89,122].

To sum up, the balance of benefit vs. risk is most favourable for oily fish species which contain higher amounts of *n*-3 LC-PUFAs, compared with lean fish, which are generally lower in *n*-3 LC-PUFAs.

Plant omega-3 fatty acids

To achieve recommended alpha-linoleic acid (ALA) intakes, food sources including flaxseed and flaxseed oil, walnuts and walnut oil, and canola oil are recommended. Short-term trials (6–12 wk) in healthy participants mostly showed no or inconsistent effects of ALA intake (1·2–3·6 g/d) on blood lipids, LDL oxidation, lipoprotein A, and apolipoproteins A-I and B. There was a protective effect against nonfatal myocardial infarction[123–128]. However, no protective associations were observed between ALA status and risk of heart failure, atrial fibrillation, and sudden death[129–134]. Dietary ALA and EPA + DHA had different physiologic effects on fasting TAG concentrations, and susceptibility of LDL to oxidation[135]. Findings from long-term trials of ALA supplementation were awaited to answer the question whether food-based or higher doses of ALA could be important for cardiovascular health in cardiac patients and the general population. ALA derived from plant sources decreased the risk for mild dementia among elderly people[136]. Plant sources of dietary *n*-3 LC-PUFAs may have a protective effect on bone metabolism via a decrease in bone resorption in the presence of consistent levels of bone formation[137].

Flaxseed is a rich source of ALA (35 % of its mass as oil, of which 55 % is ALA), fibre and lignans, making it a potentially attractive functional food for modulating cardiovascular risk. Flaxseed oil intake increases ALA and EPA plasma levels, but not DHA, did not affect glycaemia[138], had an hypotensive effect[139], a modest but short lived LDL-cholesterol lowering effect, yet reduced lipoprotein A, improved insulin sensitivity in hyperlipidemic adults[127], had no effect on plasma adiponectin concentration in dyslipidemic men[140], did not affect serum lipids, except for a slight reduction in serum TAG, did not decrease CVD risk by altering lipoprotein particle size or plasma concentrations, and did not compromise antioxidant status[141,142]. Flaxseed oil did not have antioxidant activity except they suppressed oxygen radical production by white blood cells. An intake of ≤9·5 g/d flaxseed oil ALA did not alter the functional activity of neutrophils, monocytes, or lymphocytes, but it changed the fatty acid composition of

mononuclear cells. Flaxseed oil ALA doses ≤14 g/d did not affect inflammatory mediators/markers, but ≥14 g/d reduced inflammatory mediators/markers and platelet aggregation, and increased platelet activating inhibitor-1 and bleeding time[143]. Therefore, flaxseed and its components improve cardiovascular health. Fibre contents of flaxseed increased bowel movements per week[142], and suppression of atherosclerosis wa just due to its lignan content[143].

Feeding healthy term infants' soy-based formula DHA and ARA supplemented at concentrations similar to human milk significantly increased circulating levels of DHA and ARA in total red blood cells and plasma phospholipids. Supplementation did not affect the tolerance of formula or the incidence of adverse events[144].

Dietary intake of rapeseed ALA, EPA or DHA for 3 weeks led to a significant enrichment these fatty acids in the LDL particles, with dietary EPA preferentially incorporated. ALA enrichment did not enhance LDL oxidizability, whereas the effects of EPA and DHA on LDL oxidation were inconsistent, possibly in part due to further changes in LDL fatty acid composition[145].

Omega-3 fatty acids enriched dairy products

The consumption of 500 mL/d for 6 wk of an enriched semi-skimmed milk (400 mg of EPA and DHA) decreased TAG and increased HDL-cholesterol serum levels[146]. An 8-wk supplementation of 500 mL/d enriched semi-skimmed dairy products (60 mg/100 mL EPA and DHA) decreased LDL-cholesterol and TC serum levels[147,148]. The consumption of 3 g/d *n*-3 LC-PUFAs-supplemented dairy products for fifteen weeks decreased cardiovascular risk factors (TC, TAG, high HDL-cholesterol, low LDL/HDL ratio)[149]. The consumption of *n*-3 LC-PUFAs milkshake providing 2·0 g EPA and 2·7 g DHA (ratio 2:3) had an attenuating effect on augmentation index and stiffness index[150]. Seven-month consumption of 500 mL/d of a PUFA enriched dairy drink (60 % olive oil, 20 % peanut, and 20 % sunflower), containing a quarter of the saturated fat present in standard whole milk, decreased serum levels of total cholesterol and LDL-cholesterol, without reducing caloric intake, in 3–9 year-old children[151]. These effects were not observed after administration of EPA and DHA capsules[152], showing that the vehicle of administration (milk) also plays a role in the produced effects.

The consumption of a PUFA enriched dairy 500 mL/d of the test milk for 1 year in 297 25–65 y-o subjects with moderate CV risk increased serum HDL-cholesterol levels, and decreased TG, TC, and LDL-cholesterol[153]. When this intervention was carried out in patients with peripheral vascular disease, TC apolipoprotein B levels decreased, mainly in patients with high cholesterol values, but also increased the walking distance before the onset of pain, a method to measure the intensity of this illness[154]. Similar results were obtained in patients with history of myocardial infarction[155].

Finally, 3-month consumption of 186 mg/d EPA and DHA in skimmed milk reduced TC, LDL-cholesterol, and TAG serum levels[156]. The average inclusion of 300 mg of EPA and DHA in the milk produced 25–50 % enrichment in the plasma levels of the fatty acids after a minimum period of 6 weeks, because milk is a very efficient carrier for fat absorption, enhancing the bioavailability of *n*-3 LC-PUFAs[7,142,143,156]. The intake of ALA, EPA or DHA-supplemented margarine led to a significant enrichment of the LDL with the respective *n*-3 LC-PUFAs. ALA, EPA, or DHA intake did not affect fasting serum concentrations of total and LDL-cholesterol, but fasting serum TAG concentrations significantly decreased. DHA intake significantly increased serum HDL cholesterol, whereas no changes were found with ALA or EPA intake[124].

These intervention studies in patients show that the inclusion of *n*-3 LC-PUFAs enriched dairy products in the usual dietary pattern increases the ability to control the CVD risk factors, and also improve clinical outcomes.

Animal-derived food omega-3 fatty acids

Poultry meat contributes small but worthwhile amounts of EPA and DHA. Studies on EPA and DHA contents of animal-derived foods mainly use fish oil to enrich these diets. This enrichment has the potential to provide a daily intake of EPA and DHA of about 230 mg to the Western adult diet, with poultry meat providing the largest amount (74 mg)[157]. A significant increase in *n*-3 LC-PUFAs levels in beef from cattle fed rations supplemented with flaxseed has been demonstrated[158].

Available literature indicates that the levels of EPA and DHA in food products may be increased more, if the animals' diet was supplemented with fish products rather than seed products. Sometimes, organoleptic properties of food products may be compromised. It has been suggested that omega-3 fatty acids may be enriched in pork by feeding swine with tuna oil, but sensory properties and shelf life decreased[159,160]. However, adverse effects could not appear, i.e. addition of fish oils to Bruehwurst sausages increased the *n*-3 LC-PUFAs contents without changes on sensory properties, and just showed off-flavours, not always described as 'fishy'[161].

A standard egg contains a ratio of *n*-3 LC-PUFAs to total fat less than 1 %. By feeding laying hens with grains, soybean and ?axseed rich in ALA, *n*-3 LC-PUFAs content per egg can be increased to 6 times than the standard eggs. Three *n*-3 LC-PUFAs-enriched eggs provided approximately the same amount of *n*-3 PUFA as one meal with fish[162]. Consumption of *n*-3 LC-PUFAs-enriched eggs reduced systolic blood pressure, but had no effect on BMI, WHR, waist circumference and diastolic blood pressure, with no change in the daily intake of energy, protein, carbohydrate, total fat, SFA and MUFA, but increased PUFA and TC blood levels, and decreased plasma fasting insulin and CRP levels. Reasonable consumption of *n*-3 LC-PUFAs enriched eggs (hen feed supplemented at 5 % tuna oil, and enriched eggs contained nine times more *n*-3 PUFA than usual eggs, mainly DHA) was associated with a significant decrease in 16–18 % decrease in serum triglycerides, but with no significant difference in serum LDL- and HDL-cholesterol. These eggs could be a palatably acceptable source of *n*-3 LC-PUFAs[163]. Feeding hens with

British Journal of Nutrition

microalgae-rich diet, an improvement in DHA contents was obtained, avoiding unpleasant flavours associated with fish oil supplementation[164].

It is interesting, however, to know the impact of the chow formulation used on farms and breeding centres on the nutritional value of the animal products, and their effect on the health of consumers. The consequences of modifications in the composition of animal foods on the value of derived products consumed by humans are more marked when single-stomach animals are concerned than multi-stomach animals, because hydrogenating intestinal bacteria of the latter group transform a large proportion of PUFA in their food into SFA, among others, thus depriving them of any biological interest[165].

Krill oil omega-3 fatty acids

Antarctic krill, *Euphausia superba*, is a marine crustacean that has not been a traditional food in the human diet. Krill is a rich source of high-quality protein, with the advantage over other animal proteins of being low in fat and a rich source of EPA and DHA. Antioxidant levels in krill are higher than in fish, suggesting benefits against oxidative damage. Finally, the waste generated by the processing of krill into edible products can be developed into value-added products[166].

Plasma EPA and DHA concentrations increased significantly, and blood urea decreased after overweight and obese men and women received capsules containing 2 g/d of krill oil for 4 weeks. Nor other changes, neither adverse effects were detected[167]. Patients treated 3 mo with 1 g/d and 1·5 g/d krill oil demonstrated that krill oil is effective for the management of hyperlipidemia by significantly reducing total cholesterol, LDL, and triglycerides, and increasing HDL levels. At lower and equal doses, krill oil was significantly more effective than fish oil for the reduction of glucose, triglycerides, and LDL levels[168]. Neptune Krill Oil may significantly reduced dysmenorrhea and the emotional symptoms of premenstrual syndrome and showed to be significantly more effective than omega-3 fish oil[169].

Seal oil omega-3 fatty acids

Seal oil supplementation in healthy, normocholesterolemic subjects decreased the *n*-6/*n*-3 ratio and increased EPA, DHA, and DPA and the ratio of EPA/AA and DHA/AA in the serum, while exhibited a modest beneficial effect on fibrinogen and CRP levels[170]. No change was observed in body weight, fasting blood glucose, renal function and blood cells of patients with nonalcoholic fatty liver disease associated with hyperlipidemia after an intervention with 2 g *n*-3 LC-PUFAs from seal oils, three times a day, 24 wk. Liver alanine aminotransferase and TAG blood levels decreased after the intervention. Fatty liver regression was observed in 19·7 % of the patients, and an overall reduction was found in 53·0 %. No serious adverse events occurred in all the patients who completed the treatment[171].

Discussion

In this review, findings were classified according to the dietary source of the omega-3 fatty acids, and their benefits and the risks for the public health.

Algal omega-3 fatty acids are DHA and DPA, and their main effects are a decrease of TAG and VLDL and a slightly increase of HDL and LDL-cholesterol plasma levels, as well as Factor VII coagulant activity. Up to date, no adverse effects have been observed.

Fish oils are the most common source of source of omega-3 fatty acids, mainly EPA and DHA. It has been pointed out protective and beneficial effects of these fatty acids on hearth health, CVD, blood lipid profile, T2DM, inflammatory and renal diseases, maternal and child health, CNS function, elderly, psychiatric disorders, several cancers, and other illnesses. Several studies suggested an increased risk of T2DM with the intake of marine *n*-3 LC-PUFAs, especially with higher intakes. Another potential health risk derived from the environmental contaminants found in fish.

Plant omega-3 fatty acids are the main source of ALA, which increases blood DHA and ARA levels, improves insulin sensitivity, has a very small hypotensive effect, and a protective effect on bone metabolism. Other benefits are still inconsistent. The main question is whether dietary intake of ALA can provide enough EPA and DHA amounts.

Enriched dairy products are a good vehicle to provide omega-3 fatty acids. The benefits are addressed to improve the blood lipid profile, arterial stiffness, inflammation, and oxidative stress markers, and to decrease CVD risks. No adverse effects have been yet described.

Animal-derived food omega-3 fatty acids contribute to EPA and DHA levels. Enriched eggs are one of the most common sources of animal-derived food omega-3 fatty acids. The benefits and risks on the public health depend on the chow formulation used in farms, and the type of fats fed by the animals. The only adverse effects may be decreased meat sensory properties and shelf life.

Krill is a rich source of high-quality protein, also low in fat and a rich source of EPA and DHA. The benefits are effects against oxidative damage, increase of HDL, EPA and DHA blood levels, decrease of LDL, TAG, and urea levels, as well as dysmenorrhea and premenstrual symptoms, and the waste generated by its processing into edible products can be developed into value-added products. No adverse effects have been described.

Seal oil contributes to increase EPA, DHA, DPA, and TAG blood levels. No adverse effects have been described. and disclosures

Acknowledgements and disclosures

The preparatory meetings for this series of reviews on fat and health were funded by Puleva Food. Neither Josep A. Tur nor Maria del Mar Bibiloni, Antoni Sureda or Antoni Pons have conflicts of interest to disclose. Josep A. Tur and Maria del Mar Bibiloni contributed to the design of the strategy for the literature search, double screened and selected the retrieved

British Journal of Nutrition

documents. Authors acknowledge Angel Gil from the University of Granada the support provided to select and retrieve several documents. Antoni Sureda and Antoni Pons provided previous literature searches and analysis. Josep A. Tur prepared the main outline of the manuscript and all authors contributed to the preparation of the manuscript.

References

1. EFSA (2009) Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the Commission related to labeling reference intake values for n-3 and n-6 polyunsaturated fatty acids. *EFSA J* **1176**, 1–11.
2. Kris-Etherton PM, Harris WS, Appel LJ, *et al.* (2002) Nutrition Committee, Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* **106**, 2747–2757.
3. Kris-Etherton PM, Harris WS, Appel LJ, *et al.* (2003) Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. *Arterioscler Thromb Vasc Biol* **23**, 1, 51–152.
4. The World Health Organisation (2003) *Diet nutrition and the prevention of chronic diseases*. Report of the WHO/FAO Joint Expert Consultation, WHO, Technical Report Series 916
5. Pawlosky RJ, Hibbeln JR, Novotny JA, *et al.* (2001) Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. *J Lipid Res* **42**, 1257–1265.
6. Arterburn LM, Hall EB & Oken H (2006) Distribution, interconversion, and dose response of n-3 fatty acids in humans. *Am J Clin Nutr* **83**, 1467S–1476S.
7. Lopez-Huertas E (2010) Health effects of oleic acid and long chain omega-3 fatty acids (EPA and DHA) enriched milks. A review of intervention studies. *Pharmacol Res* **61**, 200–207.
8. Neff LM, Culiner J, Cunningham-Rundles S, *et al.* (2011) Algal docosahexaenoic acid affects plasma lipoprotein particle size distribution in overweight and obese adults. *J Nutr* **141**, 207–213.
9. Geppert J, Kraft V, Demmelmair H, *et al.* (2006) Microalgal docosahexaenoic acid decreases plasma triacylglycerol in normolipidaemic vegetarians: a randomised trial. *Br J Nutr* **95**, 779–786.
10. Sanders TA, Gleason K, Griffin B, *et al.* (2006) Influence of an algal triacylglycerol containing docosahexaenoic acid (22 : 6n-3) and docosapentaenoic acid (22 : 5n-6) on cardiovascular risk factors in healthy men and women. *Br J Nutr* **95**, 525–531.
11. Harris WS, Pottala JV, Sands SA, *et al.* (2007) Comparison of the effects of fish and fish-oil capsules on the n 3 fatty acid content of blood cells and plasma phospholipids. *Am J Clin Nutr* **86**, 1621–1625.
12. Milte CM, Coates AM, Buckley JD, *et al.* (2008) Dose-dependent effects of docosahexaenoic acid-rich fish oil on erythrocyte docosahexaenoic acid and blood lipid levels. *Br J Nutr* **99**, 1083–1088.
13. Peoples GE, McLennan PL, Howe PR, *et al.* (2008) Fish oil reduces heart rate and oxygen consumption during exercise. *J Cardiovasc Pharmacol* **52**, 540–547.
14. Harrison RA, Sagara M, Rajpura A, *et al.* (2004) Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. *Nutr Metab Cardiovasc Dis* **14**, 344–350.
15. Singer P, Melzer S, Goschel M, *et al.* (1990) Fish oil amplifies the effect of propranolol in mild essential hypertension. *Hypertension* **16**, 682–691.
16. Din JN, Harding SA, Valerio CJ, *et al.* (2008) Dietary intervention with oil rich fish reduces platelet–monocyte aggregation in man. *Atherosclerosis* **197**, 290–296.
17. Pirich C, Gaszo A, Granegger S, *et al.* (1999) Effects of fish oil supplementation on platelet survival and *ex vivo* platelet function in hypercholesterolemic patients. *Thromb Res* **96**, 219–227.
18. Metcalf RG, James MJ, Gibson RA, *et al.* (2007) Effects of fish-oil supplementation on myocardial fatty acids in humans. *Am J Clin Nutr* **85**, 1222–1228.
19. Mehra MR, Lavie CJ, Ventura HO, *et al.* (2006) Fish oils produce anti-inflammatory effects and improve body weight in severe heart failure. *J Heart Lung Transplant* **25**, 834–838.
20. Kaul U, Sanghvi S, Bahl VK, *et al.* (1992) Fish oil supplements for prevention of restenosis after coronary angioplasty. *Int J Cardiol* **35**, 87–93.
21. Erkkilä AT, Lichtenstein AH, Mozaffarian D, *et al.* (2004) Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr* **80**, 626–632.
22. Seierstad SL, Seljeflot I, Johansen O, *et al.* (2005) Dietary intake of differently fed salmon; the influence on markers of human atherosclerosis. *Eur J Clin Invest* **35**, 52–59.
23. Ueshima H, Stamler J, Elliott P, *et al.* (2007) Food omega-3 fatty acid intake of individuals (total, linolenic acid, long-chain) and their blood pressure: INTERMAP study. *Hypertension* **50**, 313–319.
24. Berry JD, Prineas RJ, van Horn L, *et al.* (2010) Dietary fish intake and incident atrial fibrillation (from the Women's Health Initiative). *Am J Cardiol* **105**, 844–848.
25. Brouwer IA, Zock PL, Camm AJ, *et al.* (2006) Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA* **295**, 2613–2619.
26. Fahs CA, Yan H, Ranadive S, *et al.* (2010) The effect of acute fish-oil supplementation on endothelial function and arterial stiffness following a high-fat meal. *Appl Physiol Nutr Metab* **35**, 294–302.
27. Poppitt SD, Howe CA, Lithander FE, *et al.* (2009) Effects of moderate-dose omega-3 fish oil on cardiovascular risk factors and mood after ischemic stroke: a randomized, controlled trial. *Stroke* **40**, 3485–3492.
28. DeGiorgio CM, Miller P, Meymandi S, *et al.* (2008) n-3 fatty acids (fish oil) for epilepsy, cardiac risk factors, and risk of SUDEP: clues from a pilot, double-blind, exploratory study. *Epilepsy Behav* **13**, 681–684.
29. Watanabe N, Watanabe Y, Kumagai M, *et al.* (2009) Administration of dietary fish oil capsules in healthy middle-aged Japanese men with a high level of fish consumption. *Int J Food Sci Nutr* **60**, Suppl 5, 136–142.
30. Piolot A, Blache D, Boulet L, *et al.* (2003) Effect of fish oil on LDL oxidation and plasma homocysteine concentrations in health. *J Lab Clin Med* **141**, 41–49.
31. Mostad IL, Bjerve KS, Lydersen S, *et al.* (2008) Effects of marine n-3 fatty acid supplementation on lipoprotein subclasses measured by nuclear magnetic resonance in subjects with type II diabetes. *Eur J Clin Nutr* **62**, 419–429.
32. Khandelwal S, Demonty I, Jeemon P, *et al.* (2009) Independent and interactive effects of plant sterols and fish oil n-3 long-chain polyunsaturated fatty acids on the plasma lipid

British Journal of Nutrition

profile of mildly hyperlipidaemic Indian adults. *Br J Nutr* **102**, 722–732.
33. Feskens EJ, Virtanen SM, Rasanen L, *et al.* (1995) Dietary factors determining diabetes and impaired glucose tolerance. A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetes Care* **18**, 1104–1112.
34. Patel PS, Sharp SJ, Luben RN, *et al.* (2009) Association between type of dietary fish and seafood intake and the risk of incident type 2 diabetes: the European prospective investigation of cancer (EPIC)-Norfolk cohort study. *Diabetes Care* **32**, 1857–1863.
35. Feskens EJ, Bowles CH & Kromhout D (1991) Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. *Diabetes Care* **14**, 935–941.
36. Kaushik M, Mozaffarian D, Spiegelman D, *et al.* (2009) Long chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. *Am J Clin Nutr* **90**, 613–620.
37. Friday KE, Childs MT, Tsunehara CH, *et al.* (1989) Elevated plasma glucose and lowered triglyceride levels from omega-3 fatty acid supplementation in type II diabetes. *Diabetes Care* **12**, 276–281.
38. Rivellese AA, Maffettone A, Iovine C, *et al.* (1996) Long-term effects of fish oil on insulin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. *Diabetes Care* **19**, 1207–1213.
39. Luo J, Rizkalla SW, Vidal H, *et al.* (1998) Moderate intake of n-3 fatty acids for 2 months has no detrimental effect on glucose metabolism and could ameliorate the lipid profile in type 2 diabetic men. Results of a controlled study. *Diabetes Care* **21**, 717–724.
40. Borkman M, Chisholm DJ, Furler SM, *et al.* (1989) Effects of fish oil supplementation on glucose and lipid metabolism in NIDDM. *Diabetes* **38**, 1314–1319.
41. Djoussé L, Gaziano JM, Buring JE, *et al.* (2011) Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. *Am J Clin Nutr* **93**, 143–150.
42. Belalcazar LM, Reboussin DM, Haffner SM, *et al.* (2010) Marine omega-3 fatty acid intake: associations with cardiometabolic risk and response to weight loss intervention in the Look AHEAD Study. *Diabetes Care* **33**, 197–199.
43. Giacco R, Cuomo V, Vessby B, *et al.* (2007) Fish oil, insulin sensitivity, insulin secretion and glucose tolerance in healthy people: is there any effect of fish oil supplementation in relation to the type of background diet and habitual dietary intake of n-6 and n-3 fatty acids? *Nutr Metab Cardiovasc Dis* **17**, 572–580.
44. Mostad IL, Bjerve KS, Basu S, *et al.* (2009) Addition of n-3 fatty acids to a 4-hour lipid infusion does not affect insulin sensitivity, insulin secretion, or markers of oxidative stress in subjects with type 2 diabetes mellitus. *Metabolism* **58**, 1753–1761.
45. Navas-Carretero S, Pérez-Granados AM, Schoppen S, *et al.* (2009) An oily fish diet increases insulin sensitivity compared to a red meat diet in young iron-deficient women. *Br J Nutr* **102**, 546–553.
46. Kew S, Mesa MD, Tricon S, *et al.* (2004) Effects of oils rich in eicosapentaenoic and docosahexaenoic acids on immune cell composition and function in healthy humans. *Am J Clin Nutr* **79**, 674–681.
47. Ramel A, Martinez JA, Kiely M, *et al.* (2010) Effects of weight loss and seafood consumption on inflammation parameters in young, overweight and obese European men and women during 8 weeks of energy restriction. *Eur J Clin Nutr* **64**, 987–993.
48. Ramel A, Martinez JA, Kiely M, *et al.* (2010) Moderate consumption of fatty fish reduces diastolic blood pressure in overweight and obese European young adults during energy restriction. *Nutrition* **26**, 168–174.
49. Zhang J, Wang C, Li L, *et al.* (2010) Inclusion of Atlantic salmon in the Chinese diet reduces cardiovascular disease risk markers in dyslipidemic adult men. *Nutr Res* **30**, 447–454.
50. Mickleborough TD, Murray RL, Ionescu AA, *et al.* (2003) Fish oil supplementation reduces severity of exercise-induced bronchoconstriction in elite athletes. *Am J Respir Crit Care Med* **168**, 1181–1189.
51. Bowden RG, Wilson RL, Deike E, *et al.* (2009) Fish oil supplementation lowers C-reactive protein levels independent of triglyceride reduction in patients with end-stage renal disease. *Nutr Clin Prac* **24**, 508–512.
52. Lankinen M, Schwab U, Erkkilä A, *et al.* (2009) Fatty fish intake decreases lipids related to inflammation and insulin signalling: a lipidomics approach. *PLoS One* **4**, e5258.
53. Lopez-Garcia E, Schulze MB, Manson JE, *et al.* (2004) Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. *J Nutr* **134**, 1806–1811.
54. Xiong J, Zhu S, Zhou Y, *et al.* (2009) Regulation of omega-3 fish oil emulsion on the SIRS during the initial stage of severe acute pancreatitis. *J Huazhong Univ Sci Technolog Med Sci* **29**, 35–38.
55. Lau CS, Morley KD & Belch JJ (1993) Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis – a double-blind placebo controlled study. *Br J Rheumatol* **32**, 982–989.
56. Maroon JC & Bost JW (2006) Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. *Surg Neurol* **65**, 326–331.
57. Galarraga B, Ho M, Youssef HM, *et al.* (2008) Cod liver oil (n-3 fatty acids) as an non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. *Rheumatology (Oxford)* **47**, 665–669.
58. Caughey GE, James MJ, Proudman SM, *et al.* (2010) Fish oil supplementation increases the cyclooxygenase inhibitory activity of paracetamol in rheumatoid arthritis patients. *Complement Ther Med* **18**, 171–174.
59. Dry J & Vincent D (1991) Effect of a fish oil diet on asthma: results of a 1-year double-blind study. *Int Arch Allergy Appl Immunol* **95**, 156–157.
60. Pot GK, Brouwer IA, Enneman A, *et al.* (2009) No effect of fish oil supplementation on serum inflammatory markers and their interrelationships: a randomized controlled trial in healthy, middle-aged individuals. *Eur J Clin Nutr* **63**, 1353–1359.
61. Michaeli B, Berger MM, Revelly JP, *et al.* (2007) Effects of fish oil on the neuro-endocrine responses to an endotoxin challenge in healthy volunteers. *Clin Nutr* **26**, 70–77.
62. Bouwens M, van de Rest O, Dellschaft N, *et al.* (2009) Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. *Am J Clin Nutr* **90**, 415–424.
63. Moghadamnia AA, Mirhosseini N, Abadi MH, *et al.* (2010) Effect of *Clupeonella grimmi* (anchovy/kilka) fish oil on dysmenorrhoea. *East Mediterr Health J* **16**, 408–413.
64. Franke C, Demmelmair H, Decsi T, *et al.* (2010) Influence of fish oil or folate supplementation on the time course of plasma redox markers during pregnancy. *Br J Nutr* **103**, 1648–1656.

British Journal of Nutrition

65. Dunstan JA, Simmer K, Dixon G, *et al.* (2008) Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed* **93**, F45–F50.
66. Schnappinger M, Sausenthaler S, Linseisen J, *et al.* (2009) Fish consumption, allergic sensitization and allergic diseases in adults. *Ann Nutr Metab* **54**, 67–74.
67. Prescott SL, Barden AE, Mori TA, *et al.* (2007) Maternal fish oil supplementation in pregnancy modifies neonatal leukotriene production by cord-blood-derived neutrophils. *Clin Sci (Lond)* **113**, 409–416.
68. Smithers LG, Markrides M & Gibson RA (2010) Human milk fatty acids from lactating mothers of preterm infants: a study revealing wide intra- and inter-individual variation. *Prostaglandins Leukot Essent Fatty Acids* **83**, 9–13.
69. Furuhjelm C, Warstedt K, Larsson J, *et al.* (2009) Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. *Acta Paediatr* **98**, 1461–1467.
70. Lauritzen L, Christensen JH, Damsgaard CT, *et al.* (2008) The effect of fish oil supplementation on heart rate in healthy Danish infants. *Pediatr Res* **64**, 610–614.
71. Fortier M, Tremblay-Mercier J, Plourde M, *et al.* (2010) Higher plasma n-3 fatty acid status in the moderately healthy elderly in southern Québec: higher fish intake or aging-related change in n-3 fatty acid metabolism? *Prostaglandins Leukot Essent Fatty Acids* **82**, 277–280.
72. van de Rest O, Geleijnse JM, Kok FJ, *et al.* (2008) Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. *Neurology* **71**, 430–438.
73. van de Rest O, Geleijnse JM, Kok FJ, *et al.* (2009) Effect of fish oil supplementation on quality of life in a general population of older Dutch subjects: a randomized, double-blind, placebo-controlled trial. *J Am Geriatr Soc* **57**, 1481–1486.
74. Astorg P, Couthouis A, Bertrais S, *et al.* (2008) Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women. *Prostaglandins Leukot Essent Fatty Acids* **78**, 171–182.
75. Ramel A, Parra D, Martinez JA, *et al.* (2009) Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr* **48**, 107–114.
76. van de Rest O, Geleijnse JM, Kok FJ, *et al.* (2008) Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* **88**, 706–713.
77. Augood C, Chakravarthy U, Young I, *et al.* (2008) Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. *Am J Clin Nutr* **88**, 398–406.
78. Mori TA, Bao DQ, Burke V, *et al.* (1999) Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects. *Am J Clin Nutr* **70**, 817–825.
79. Gunnarsdottir I, Tomasson H, Kiely M, *et al.* (2008) Inclusion of fish or fish oil in weight-loss diets for young adults: effects on blood lipids. *Int J Obes (Lond)* **32**, 1105–1112.
80. Parra D, Ramel A, Bandarra N, *et al.* (2008) A diet rich in long chain omega-3 fatty acids modulates satiety in overweight and obese volunteers during weight loss. *Appetite* **51**, 676–680.
81. Kratz M, Callahan HS, Yang PY, *et al.* (2009) Dietary n-3-polyunsaturated fatty acids and energy balance in overweight or moderately obese men and women: a randomized controlled trial. *Nutr Metabol* **6**, 7.
82. Rhodes LE, Durham BH, Fraser WD, *et al.* (1995) Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. *J Invest Dermatol* **105**, 532–535.
83. Thusgaard M, Christensen JH, Mørn B, *et al.* (2009) Effect of fish oil (n-3 polyunsaturated fatty acids) on plasma lipids, lipoproteins and inflammatory markers in HIV-infected patients treated with antiretroviral therapy: a randomized, double-blind, placebo-controlled study. *Scand J Infect Dis* **41**, 760–766.
84. Engeset D, Alsaker E, Lund E, *et al.* (2006) Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer* **119**, 175–182.
85. van der Meij BS, Langius JA, Smit EF, *et al.* (2010) Oral nutritional supplements containing (n-3) polyunsaturated fatty acids affect the nutritional status of patients with stage III non-small cell lung cancer during multimodality treatment. *J Nutr* **140**, 1774–1780.
86. Cerchietti LC, Navigante AH & Castro MA (2007) Effects of eicosapentaenoic and docosahexaenoic n-3 fatty acids from fish oil and preferential Cox-2 inhibition on systemic syndromes in patients with advanced lung cancer. *Nutr Cancer* **59**, 14–20.
87. Barber MD, Ross JA, Voss AC, *et al.* (1999) The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. *Br J Cancer* **81**, 80–86.
88. Leitzmann MF, Stampfer MJ, Michaud DS, *et al.* (2004) Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. *Am J Clin Nutr* **80**, 204–216.
89. Mozaffarian D (2006) Fish Intake, Contaminants, and Human Health: Evaluating the Risks and the Benefits Part 2 – Health Risks and Optimal Intakes. *Cardiol Rounds* **10**, 1–6.
90. U.S. Environmental Protection AgencyMercury Study Report to Congress Available: http://www.epa.gov/mercury/report.htm (accessed May 2011)
91. Jeejeebhoy KN (2008) Benefits and risks of a fish diet – should we be eating more or less? *Nature Clin Pract* **5**, 178–179.
92. Harris HH, Pickering IJ & George GN (2003) The chemical form of mercury in fish. *Science* **302**, 1203.
93. Committee on the Toxicological Effects of Methylmercury (2000) Board on Environmental Studies and Toxicology; Commission on Life Sciences; National Research Council. Toxicological Effects of Methylmercury. Washington, DC: National Academy Press.
94. Gochfeld M (2003) Cases of mercury exposure, bioavailability, and absorption. *Ecotoxicol Environ Saf* **56**, 174–179.
95. U.S. EPA (U.S. Environmental Protection Agency) (2001) Methylmercury (MeHg) (CASRN 22967-92-6). Available: http://www.epa.gov/iris/subst/0073.htm (accessed May 2011)
96. Ginsberg GL & Toal BF (2009) Quantitative approach for incorporating methylmercury risks and omega-3 fatty acid benefits in developing species-specific fish consumption advice. *Environ Health Persp* **117**, 267–275.
97. McDowell MA, Dillon CF, Osterloh J, *et al.* (2004) Hair mercury levels in U.S. children and women of childbearing age: reference range data from NHANES 1999–2000. *Environ Health Perspect* **112**, 1165–1171.

British Journal of Nutrition

98. Grandjean P, Weihe P, White RF, *et al.* (1997) Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol* **19**, 417–428.
99. Grandjean P, Weihe P, White RF & Debes F (1998) Cognitive performance of children prenatally exposed to "safe" levels of methylmercury. *Environ Res* **77**, 165–172.
100. Kjellstrom T (1989) Physical and mental development of children with prenatal exposure to mercury from fish. Stage II: interviews and psychological tests at age 6. Stockholm, Sweden: National Swedish Environmental Protection Board; Report 3642. Solna, Sweden: National Swedish Environmental Protection Board.
101. Crump KS, Kjellstrom T, Shipp AM, *et al.* (1998) Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. *Risk Anal* **18**, 701–713.
102. Jedrychowski W, Jankowski J, Flak E, *et al.* (2006) Effects of prenatal exposure to mercury on cognitive and psychomotor function in one-year-old infants: Epidemiologic Cohort Study in Poland. *Ann Epidemiol* **16**, 439–447.
103. Davidson PW, Palumbo D, Myers GJ, *et al.* (2000) Neurodevelopmental outcomes of Seychellois children from the pilot cohort at 108 months following prenatal exposure to methylmercury from a maternal fish diet. *Environ Res* **84**, 1–11.
104. Palumbo DR, Cox C, Davidson PW, *et al.* (2000) Association between prenatal exposure to methylmercury and cognitive functioning in Seychellois children: a reanalysis of the McCarthy Scales of Children's Ability from the main cohort study. *Environ Res* **84**, 81–88.
105. Oken E, Wright RO, Kleinman KP, *et al.* (2005) Maternal fish consumption, hair mercury, and infant cognition in a U.S. Cohort. *Environ Health Perspect* **113**, 1376–1380.
106. Daniels JL, Longnecker MP, Rowland AS, *et al.* (2004) Fish intake during pregnancy and early cognitive development of offspring. *Epidemiology* **15**, 394–402.
107. FDA (Food and Drug Administration) (2004) Press Release: FDA and EPA Announce the Revised Consumer Advisory on Methylmercury in Fish, March 19, 2004. Available: http://www.fda.gov/bbs/topics/news/2004/NEW01038.html (accessed May 2011)
108. FDA (2005) Letter Regarding Eggs with Enhanced Omega-3 Fatty Acid Content and a Balanced Ratio of Omega-3/Omega-6 Fatty Acids and Reduced Risk of Heart Disease and Sudden Fatal Heart Attack (Docket No. 2004Q-0072). Available: http://www.cfsan.fda.gov/~dms/qhceggs.html (accessed May 2011)
109. FDA (2006) Mercury Levels in Commercial Fish and Shellfish. Available: http://www.cfsan.fda.gov/~frf/sea-mehg.html (accessed May 2011).
110. USDA (2005) Addendum A: EPA and DHA Content of Fish Species. Available: http://www.health.gov/dietaryguidelines/dga2005/report/HTML/table_g2_adda2.htm (accessed May 2011).
111. U.S. EPA (U.S. Environmental Protection Agency) (1995) IRIS file for Mercuric Chloride. Available: http://www.epa.gov/ncea/iris/subst/0692.htm (accessed May 2011).
112. U.S. EPA (U.S. Environmental Protection Agency) (2004) What You Need to Know about Mercury in Fish and Shellfish. Available: http://www.epa.gov/waterscience/fishadvice/advice.html (accessed May 2011).
113. Rice DC (2004) The US EPA reference dose for methylmercury: sources of uncertainty. *Environ Res* **95**, 406–413.
114. Rissanen T, Voutilainen S, Nyyssonen K, *et al.* (2000) Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study. *Circulation* **102**, 2677–2679.
115. Guallar E, Sanz-Gallardo MI, van't Veer P, *et al.* (2002) Mercury, fish oils, and the risk of myocardial infarction. *N Engl J Med* **347**, 1747–1754.
116. Virtanen JK, Voutilainen S, Rissanen TH, *et al.* (2005) Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. *Arterioscler Thromb Vasc Biol* **25**, 228–233.
117. Risher JF, Murray HE & Prince GR (2002) Organic mercury compounds: human exposure and its relevance to public health. *Toxicol Ind Health* **18**, 109–160.
118. He K, Song Y, Daviglus ML, *et al.* (2004) Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke* **35**, 1538–1542.
119. Morris MC, Evans DA, Tangney CC, *et al.* (2005) Fish consumption and cognitive decline with age in a large community study. *Arch Neurol* **62**, 1849–1853.
120. Peet M & Stokes C (2005) Omega-3 fatty acids in the treatment of psychiatric disorders. *Drugs* **65**, 1051–1059.
121. Young G & Conquer J (2005) Omega-3 fatty acids and neuropsychiatric disorders. *Reprod Nutr Dev* **45**, 1–28.
122. Mozaffarian D & Rimm EB (2006) Fish intake, contaminants, and human health evaluating the risks and the benefits. *JAMA* **296**, 1885–1899.
123. Kaul N, Kreml R, Austria JA, *et al.* (2008) A comparison of fish oil, flaxseed oil and hempseed oil supplementation on selected parameters of cardiovascular health in healthy volunteers. *J Am Coll Nutr* **27**, 51–58.
124. Egert S, Kannenberg F, Somoza V, *et al.* (2009) Dietary alpha-linolenic acid, EPA, and DHA have differential effects on LDL fatty acid composition but similar effects on serum lipid profiles in normolipidemic humans. *J Nutr* **139**, 861–868.
125. Barceló-Coblijn G, Murphy EJ, Othman R, *et al.* (2008) Flaxseed oil and fish-oil capsule consumption alters human red blood cell n-3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n-3 fatty acid. *Am J Clin Nutr* **88**, 801–809.
126. Sioen I, Hacquebard M, Hick G, *et al.* (2009) Effect of ALA-enriched food supply on cardiovascular risk factors in males. *Lipids* **44**, 603–611.
127. Bloedon LT, Balikai S, Chittams J, *et al.* (2008) Flaxseed and cardiovascular risk factors: results from a double blind, randomized, controlled clinical trial. *J Am Coll Nutr* **27**, 65–74.
128. Dodin S, Cunnane SC, Mâsse B, *et al.* (2008) Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. *Nutrition* **24**, 23–30.
129. Campos H, Baylin A & Willett WC (2008) Alpha-linolenic acid and risk of nonfatal acute myocardial infarction. *Circulation* **118**, 339–345.
130. Yamagishi K, Nettleton JA, Folsom AR & ARIC Study Investigators (2008) Plasma fatty acid composition and incident heart failure in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* **156**, 965–974.
131. Warensjö E, Sundström J, Vessby B, *et al.* (2008) Markers of dietary fat quality and fatty acid desaturation as predictors of total and cardiovascular mortality: a population-based prospective study. *Am J Clin Nutr* **88**, 203–209.
132. Park Y, Park S, Yi H, *et al.* (2009) Low level of n-3 polyunsaturated fatty acids in erythrocytes is a risk factor for

British Journal of Nutrition

both acute ischemic and hemorrhagic stroke in Koreans. *Nutr Res* **29**, 825–830.
133. Virtanen JK, Mursu J, Voutilainen S, *et al.* (2009) Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men. *Circulation* **120**, 2315–2321.
134. Lemaitre RN, King IB, Sotoodehnia N, *et al.* (2009) Red blood cell membrane alpha-linolenic acid and the risk of sudden cardiac arrest. *Metabolism* **58**, 534–540.
135. Finnegan YE, Minihane AM, Leigh-Firbank EC, *et al.* (2003) Plant- and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects. *Am J Clin Nutr* **77**, 783–795.
136. Malgeunsinae Kim, Jung Hyun Nam, Dong Hoon Oh, *et al.* (2010) Erythrocyte alpha-linolenic acid is associated with the risk for mild dementia in Korean elderly. *Nutr Res* **30**, 756–761.
137. Griel AE, Kris-Etherton PM, Hilpert KF, *et al.* (2007) An increase in dietary n-3 fatty acids decreases a marker of bone resorption in humans. *Nutr J* **6**, 2.
138. Taylor CG, Noto AD, Stringer DM, *et al.* (2010) Dietary milled flaxseed and flaxseed oil improve *N*-3 fatty acid status and do not affect glycemic control in individuals with well-controlled type 2 diabetes. *J Am Coll Nutr* **29**, 72–80.
139. Paschos GK, Magkos F, Panagiotakos DB, *et al.* (2007) Dietary supplementation with flaxseed oil lowers blood pressure in dyslipidaemic patients. *Eur J Clin Nutr* **61**, 1201–1206.
140. Paschos GK, Zampelas A, Panagiotakos DB, *et al.* (2007) Effects of flaxseed oil supplementation on plasma adiponectin levels in dyslipidemic men. *Eur J Clin Nutr* **46**, 315–320.
141. Harper CR, Edwards MC & Jacobson TA (2007) Flaxseed oil supplementation does not affect plasma lipoprotein concentration or particle size in human subjects. *J Nutr* **136**, 2844–2848.
142. Cunnane SC, Hamadeh MJ, Liede AC, *et al.* (1995) Nutritional attributes of traditional flaxseed in healthy young adults. *Am J Clin Nutr* **61**, 62–68.
143. Kew S, Banerjee T, Minihane AM, *et al.* (2003) Lack of effect of foods enriched with plant- or marine-derived n-3 fatty acids on human immune function. *Am J Clin Nutr* **77**, 1287–1295.
144. Hoffman D, Ziegler E, Mitmesser SH, *et al.* (2008) Soy-based infant formula supplemented with DHA and ARA supports growth and increases circulating levels of these fatty acids in infants. *Lipids* **43**, 29–35.
145. Egert S, Somoza V, Kannenberg F, *et al.* (2007) Influence of three rapeseed oil-rich diets, fortified with alpha-linolenic acid, eicosapentaenoic acid or docosahexaenoic acid on the composition and oxidizability of low-density lipoproteins: results of a controlled study in healthy volunteers. *Eur J Clin Nutr* **61**, 314–325.
146. Visioli F, Rise P, Plasmati E, *et al.* (2000) Very low intakes of n-3 fatty acids incorporated into bovine milk reduce plasma triacylglycerols and increase HDL-cholesterol concentrations in healthy subjects. *Pharmacol Res* **41**, 571–576.
147. Baró L, Fonollá J, Peña JL, *et al.* (2003) n-3 fatty acids plus oleic acid supplemented milk reduces total and LDL cholesterol, homocysteine and levels of endothelial adhesion molecules in healthy humans. *Clin Nutr* **22**, 175–182.
148. Carrero JJ, Baró L, Fonollá J, *et al.* (2004) Cardiovascular effects of milk enriched with n-3 polyunsaturated fatty acids, oleic acid folic acid and vitamins E, B6 and B12 in volunteers with mild hyperlipidaemia. *Nutrition* **20**, 521–527.
149. Dawczynski C, Martin L, Wagner A, *et al.* (2010) n-3 LC-PUFAs-enriched dairy products are able to reduce cardiovascular risk factors: a double-blind, cross-over study. *Clin Nutr* **29**, 592–599.
150. Chong MF, Lockyer S, Saunders CJ, *et al.* (2010) Long chain n-3 PUFA-rich meal reduced postprandial measures of arterial stiffness. *Clin Nutr* **29**, 678–681.
151. Estévez-González MD, Saavedra-Santana P & Betancor-León P (1998) Reduction of serum cholesterol and low-density lipoprotein cholesterol levels in a juvenile population after isocaloric substitution of whole milk with a milk preparation (skimmed milk enriched with oleic acid). *J Pediatr* **132**, 85–89.
152. Cobiac L, Clifton PM, Abbey M, *et al.* (1991) Lipid, lipoprotein, and hemostatic effects of fish vs fish-oil n-3 fatty acids in mildly hyperlipidemic males. *Am J Clin Nutr* **53**, 1210–1216.
153. Fonollá J, López-Huertas E, Machado FJ, *et al.* (2009) Milk enriched with "healthy fatty acids" improves cardiovascular risk markers and nutritional status in human volunteers. *Nutrition* **25**, 408–414.
154. Carrero JJ, López-Huertas E, Salmerón LM, *et al.* (2005) Daily supplementation with (n-3) PUFAs, oleic acid, folic acid, and vitamins B-6 and E increases pain free walking distance and improves risk factors in men with peripheral vascular disease. *J Nutr* **135**, 1393–1399.
155. Carrero JJ, Fonollá J, Marti JL, *et al.* (2007) Intake of fish oil, oleic acid, folic acid, and vitamins B-6 and E for 1 year decreases plasma C reactive protein and reduces coronary heart disease risk factors in male patients in a cardiac rehabilitation program. *J Nutr* **137**, 384–390.
156. Benito P, Caballero J, Moreno J, *et al.* (2006) Effects of milk enriched with omega-3 fatty acid, oleic acid and folic acid in patients with metabolic syndrome. *Clin Nutr* **25**, 581–587.
157. Givens DI & Gibbs RA (2008) Current intakes of EPA and DHA in European populations and the potential of animal-derived foods to increase them. *Proc Nutr Soc* **67**, 273–280.
158. Kronberg SL, Barcelo-Coblijn G, Shin J, *et al.* (2006) Bovine muscle n-3 fatty acid content is increased with flaxseed feeding. *Lipids* **41**, 1059–1068.
159. Kjos NP, Skrede A & Overland M (1999) Effects of dietary fish silage and fish fat on growth performance and sensory quality of growing-finishing pigs. *Can J Anim Sci* **79**, 139–147.
160. Jatuasitha S, Khiaosa-ard R, Pongpiachan P, *et al.* (2009) Early deposition of n-3 fatty acids from tuna oil in lean and adipose tissue of fattening pigs is mainly permanent. *J Anim Sci* **87**, 693–703.
161. Muench S & Watzl B (2010) Incorporation of ingredients rich in omega-3 fatty acids into functional meat products. *Mitteil Fleischf Kulmb* **49**, 39–48.
162. Cachaldora P, Garcia-Rebollar P & Alvarez C (2009) Double enrichment of chicken eggs with conjugated linoleic acid and n-3 fatty acids through dietary fat supplementation. *Animal Feed Sci Tech* **144**, 315–326.
163. Bovet P, Faeh D, Madeleine G, *et al.* (2007) Decrease in blood triglycerides associated with the consumption of eggs of hens fed with food supplemented with fish oil. *Nutr Metab Cardiovasc Dis* **17**, 280–287.
164. Rizzi L, Bochicchio D & Bargellini A (2009) Effects of dietary microalgae, other lipid sources, inorganic selenium

British Journal of Nutrition

and iodine on yolk n-3 fatty acid composition, selenium content and quality of eggs in laying hens. *J Sci Food Agric* **89**, 1775–1781.
165. Bourre JM (2005) Where to find omega-3 fatty acids and how feeding animals with diet enriched in omega-3 fatty acids to increase nutritional value of derived products for human: what is actually useful? *J Nutr Health Aging* **9**, 232–242.
166. Tou JC, Jaczynski J & Chen YC (2007) Krill for human consumption: nutritional value and potential health benefits. *Nutr Rev* **65**, 63–77.
167. Maki KC, Reeves MS, Farmer M, *et al.* (2009) Krill oil supplementation increases plasma concentrations of eicosapentaenoic and docosahexaenoic acids in overweight and obese men and women. *Nutr Res* **29**, 609–615.
168. Bunea R, El Farrah K & Deutsch L (2004) Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. *Altern Med Rev* **9**, 420–428.
169. Sampalis F, Bunea R, Pelland MF, *et al.* (2003) Evaluation of the effects of Neptune Krill Oil on the management of premenstrual syndrome and dysmenorrheal. *Altern Med Rev* **8**, 171–179.
170. Conquer JA, Cheryk LA, Chan E, *et al.* (1999) Effect of supplementation with dietary seal oil on selected cardiovascular risk factors and hemostatic variables in healthy male subjects. *Thromb Res* **96**, 239–250.
171. Zhu FS, Liu S, Chen XM, *et al.* (2008) Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease associated with hyperlipidemia. *World J Gastroenterol* **14**, 6395–6400.

British Journal of Nutrition