

Review Article

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Sustainable and available sources of omega-3 fatty acids for health: are the current dietary recommendations, food sources and legislation fit for purpose?

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Abstract

The health benefits of the long-chain omega-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been known for over 50 years and underpin the UK population recommendation to consume >450 mg EPA + DHA per day. These recommendations, last revised in 2004, are based mainly on epidemiological evidence. Much research has been conducted in the interim. Most randomised controlled trials (RCT) use doses of EPA + DHA of 840 mg/d or more. For anti-inflammatory, triacylglycerol-lowering and anti-hypertensive effects, >1.5 g EPA + DHA per day is needed. Cognitive benefits are also likely to require these higher intakes. Farmed salmon now contains considerably less EPA + DHA relative to farmed fish of 20 years ago, meaning one portion per week will no longer provide the equivalent of 450 mg EPA + DHA per day. Oily fish alone can only provide a fraction of the EPA + DHA required to meet global needs. Furthermore, there is low global oily fish consumption, with typical intakes of <200 mg EPA + DHA per day, and limited intakes in vegans and vegetarians. Therefore, there is an urgent need for affordable, acceptable, alternative EPA + DHA sources, including vegan/vegetarian friendly options, such as bio-enriched poultry, red meat and milk products; fortified foods; enriched oilseeds (for example, genetically modified *Camelina sativa*); algae and algal oils; and approaches which enhance endogenous EPA/DHA synthesis. In this narrative review, we suggest that current EPA + DHA intake recommendations are too low, consider EPA/DHA from a holistic health-sustainability perspective and identify research, policy and knowledge mobilisation areas which need attention.

Introduction

A high consumption and tissue status of the long-chain omega-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are associated with lower total mortality and cardiovascular disease (CVD) incidence and mortality⁽¹⁾. EPA and DHA intake is associated with improved cognitive health into older age and lower lifetime risk of dementia⁽²⁾. Moreover, demonstrable benefits for diabetes risk, liver health and the risk of comorbidities associated with excess body weight are also evident^(3–5). In a Global Burden of Disease analysis, dietary risk factors were responsible for 22% of deaths and 15% of overall disease burden, with a 'diet low in seafood omega-3 fatty acids' being the sixth most important dietary attribute to risk⁽⁶⁾. EPA and DHA intake and status are recognised to be important to health throughout the life course, from conception into older age⁽⁷⁾.

Although, strictly speaking, EPA and DHA are not essential nutrients, within the human body the conversion to EPA and DHA from their essential PUFA precursor, alpha linolenic acid (ALA), is considered to be low (Figure 1)⁽⁸⁾, and therefore consumption of pre-formed EPA + DHA is recommended. In the UK, the advice is to eat two portions (140 g each) of fish per week,

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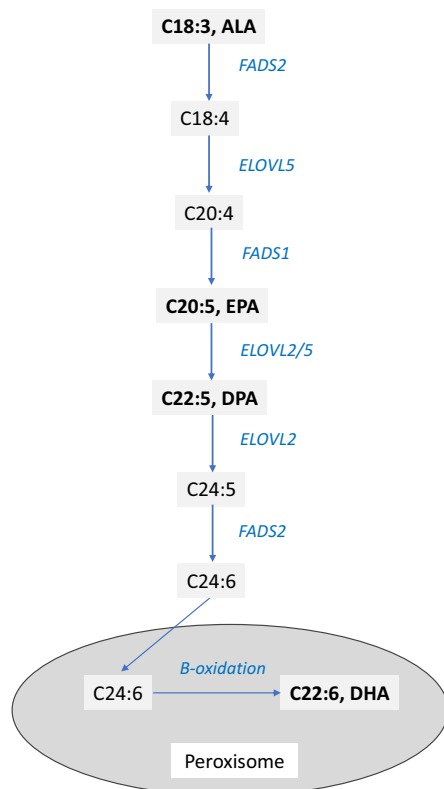


Fig. 1. The pathway of conversion of α -linolenic acid (ALA) to EPA and DHA. ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid; FADS1, fatty acid desaturase 1/delta-5 desaturase/ Δ 5-desaturase; FADS2, fatty acid desaturase 2/delta-6 desaturase/ Δ 6-desaturase; ELOVL, fatty acid elongase.

one of which should be oily. This intake was estimated to equate to 450–500 mg EPA + DHA per day, which is in line with international recommendations (see the ‘Current guideline intakes’ section). Despite their importance to human health, intakes of EPA + DHA are substantially lower than recommendations, with the majority of the UK population consuming <50 mg EPA + DHA per day and an average population intake of less than 250 mg/d⁽⁹⁾, as will be discussed later.

Low EPA + DHA intake and status have undoubted negative health consequences for individuals and populations and contribute to health inequalities. Therefore, there is an urgent need to identify accessible, acceptable, sustainable and affordable non-fish EPA + DHA sources to increase intake in order to contribute to improved population health across the life course. In a symposium (June 2023) held at the University of East Anglia (Norwich, UK), entitled ‘Sustainable and available sources of omega-3 fatty acids for healthy living and ageing’, we sought to discuss and gain consensus on the physiological, health and disease risk impacts of omega-3 PUFA and innovation in omega-3 PUFA enrichment of foods. The symposium was attended by a cross-section of disciplines including animal science and nutrition, plant metabolic engineering, human nutrition, public health nutrition, medicine and health inequalities. As critiqued throughout the review, and as summarised in Table 2, we furthermore aimed to define priority research areas and important next steps for the translation of research into awareness, policy and further product innovation.

Table 1. Oily fish consumption in the UK⁽⁷³⁾

Age range	Oily fish consumers (%)	Meeting oily fish recommendation (%)
4–11 years	12.7	4.4
12–19 years	13.2	6.3
20–29 years	16.4	8.8
30–39 years	26.5	16.2
40–49 years	23.0	14.0
50–59 years	30.3	20.4
60–69 years	38.2	28.6
70 years +	38.5	26.1
All	25.2	15.9

Importance of EPA + DHA for human health

Rather than be exhaustive, in this review we summarise a selection of health benefits of EPA + DHA with a focus on dose–response relationships.

Cardiovascular health

The most widely investigated health effect of EPA + DHA is their impact on cardiovascular phenotypes and primary and secondary CVD prevention. A significant body of prospective cohort evidence consistently supports an inverse association between EPA + DHA intake and status and CVD incidence and mortality, with typical effect sizes of 10–40% reduced risk^(1,10,11). Underlying mechanisms include beneficial impacts on plasma lipids, lipoprotein composition and metabolism; blood pressure, inflammation and atherosclerotic plaque stability; vascular function; and cardiac function and arrhythmias^(12–14).

Existing RCT evidence is less consistent but is overall supportive of cardiovascular benefits at intakes of 840 mg EPA + DHA per day or greater. Earlier RCT reported a 20–30% reduced risk of cardiovascular death⁽¹⁰⁾. However, subsequent RCT, which typically supplemented with 840 mg of EPA + DHA (EPA:DHA, 1:2) per day, given as Omacor capsules, often observed no effect on CVD incidence or deaths^(10,14). In the ASCEND⁽¹⁵⁾ (900 mg EPA + DHA per day, ratio, 1:2) and VITAL⁽¹⁶⁾ (Omacor) primary prevention trials, no impact of supplementation on the primary composite cardiovascular outcome was evident, following 5.3 years and 7.4 years of supplementation, respectively, although in VITAL, a significant effect of intervention on incident myocardial infarction (MI) was observed (hazard ratio (HR) (95% CI) of 0.72 (0.59–0.90)). In VITAL, a secondary analysis provided insight into the likely impact of baseline EPA + DHA status. A HR of 0.81 (0.67–0.98) for the primary endpoint, and of 0.60 (0.45–0.81) for MI was observed in those with total fish intakes of less than 1.5 servings per week, and no effect was detected in participants with fish intakes of at least 1.5 servings per week (HR, 1.08 and 0.94, respectively)⁽¹⁶⁾. The REDUCE-IT secondary prevention trial saw a 25% lower risk of incident or fatal CVD and a nonsignificant reduction in total mortality (HR (95% CI) of 0.87 (0.74–1.02)) with a high dose (4 g/d) of icosapent ethyl EPA (a highly purified and stable EPA ethyl ester) among patients with established CVD or risk factors⁽¹⁷⁾.

These RCT were included in two meta-analyses published in 2019 and 2020^(18,19). Including thirteen RCT and 127 000 participants, and with a mean follow-up of 5 years (excluding REDUCE-IT), EPA + DHA supplementation resulted in a lower risk of MI (0.92 (0.86–0.99)), coronary heart disease (CHD) death (0.92 (0.86–0.98)), total CHD (0.95 (0.91–0.99)), CVD death (0.93 (0.88–0.99)) and total CVD (0.97 (0.94–0.99))⁽¹⁸⁾. The inclusion of REDUCE-IT substantially strengthened the inverse dose-dependent associations to 0.88 (0.83–0.94) for MI and 0.93 (0.89–0.96) for total CHD. According to the latest (2020) Cochrane meta-analysis, supplementation with EPA + DHA reduces CHD mortality and CHD events by approximately 10%, although no significant effect was shown for total CVD events or stroke⁽¹⁹⁾.

Brain health

Despite rapidly rising incident dementia (of which Alzheimer's disease is the main form)⁽²⁰⁾, there are currently no pharmacological interventions to prevent dementia, with current UK National Institute for Health and Care Excellence (NICE)-approved medications treating only symptomatology. Upcoming β -amyloid immunotherapies, not approved for use by NICE, are promising but only suitable for β -amyloid positive, early Alzheimer's disease (<20% of total dementia) and are associated with significant side effects⁽²¹⁾. With such limited medication options, there is a great need for inclusive, affordable, effective interventions which can prevent or delay dementia, with increased oily fish and omega-3 PUFA intake showing promise. Cardiovascular health, neurophysiology and neuropathology are intimately linked^(22,23) via processes such as blood–brain barrier function, brain perfusion and inflammation. Furthermore, brain tissue is highly enriched in DHA⁽²⁴⁾, which constitutes up to 40% of synaptic membrane lipids. Preclinical studies have demonstrated numerous potentially beneficial structural and functional roles for DHA, including on neurogenesis, dendrite outgrowth, neuronal survival, neurotransmission/synaptic function, β -amyloid processing and clearance, brain perfusion and neuroinflammation⁽²⁵⁾. Although levels of EPA in the brain are ten to twenty times lower than those of DHA, recent evidence has highlighted the importance of EPA to brain function and, in particular, the microglial cells which are enriched in EPA relative to neurons⁽²⁶⁾.

Prospective epidemiological studies consistently associate higher fish, oily fish and EPA + DHA intake with increased brain volume, improved cognition and lower dementia risk and mortality^(1,27,28). For example, in the NIH-AARP Diet and Health Study, being in quintile 5 v. 1 of EPA + DHA intake was associated with a 30% and 41% reduced risk of Alzheimer's disease death in males and females, respectively⁽¹⁾. Wei *et al.* reported that increased intakes of 0.1 g/d of DHA and EPA were associated with 8.0% and 9.9% lower risk of cognitive decline respectively⁽²⁸⁾.

Results from RCT supplementing with EPA + DHA are more mixed and often show no benefit^(29,30). Most are secondary prevention trials, conducted in individuals with incident dementia or cognitive impairment⁽²⁾. For example, the Multidomain Alzheimer Preventive Trial (MAPT)⁽³¹⁾ which supplemented with 1.1 g EPA + DHA (ratio 0.23:1) per day for 3 years in older adults with memory complaints, and the Alzheimer's Disease Cooperative study (ADCS)⁽³²⁾ which supplemented with 2.0 g DHA per day for 18 months in participants with mild-to-moderate dementia, did not show any effect on cognition. In a 2016 Cochrane systematic review of omega-3 supplementation in dementia, only three trials were considered, with no evidence of cognitive or quality of life benefits observed⁽³³⁾. Similarly in a more

recent meta-analysis in participants without dementia, no effect of EPA + DHA supplementation on global cognition or several cognitive domains including episodic memory was evident, although there was some evidence of beneficial effects for executive function⁽³⁴⁾.

In many RCT which report on cognition, the design is often not appropriate, with small sample sizes, short intervention periods, brain health as a secondary rather than primary outcome, and little consideration given to baseline EPA + DHA status. By contrast, in a study in young healthy adults with low habitual fish intake, the consumption of 1.4 g EPA + DHA per day (of which 1.2 g was DHA) over 6 months improved both episodic and working memory⁽³⁵⁾. Traditionally, RCT focused on brain health have intervened with DHA-rich supplements, on the basis that brain tissue is highly enriched in DHA relative to EPA⁽²⁴⁾. The role of EPA in brain, and in particular glial function, is being increasingly recognised⁽²⁶⁾, with Patan and colleagues demonstrating that EPA, but not DHA, improved global cognition over 6 months in healthy adults⁽³⁶⁾.

Eye health

Omega-3 PUFA play an important role in eye health, with the retina particularly enriched in DHA. DHA appears to be conserved in the retina even in situations of low omega-3 PUFA intake. Patients with retinitis pigmentosa (RP) were reported to have significantly lower plasma DHA levels, suggesting an inverse association between DHA availability and higher risk of RP^(37,38). Treatment with omega-3 PUFA has been associated with improvement in some clinical outcomes in patients with RP⁽³⁹⁾. A meta-analysis of pooled data from nine studies showed that high dietary intake of omega-3 PUFA and fish twice a week was associated with a 38% and 33% reduction in the risk of late age-related macular degeneration (AMD)⁽⁴⁰⁾. The incidence of dry eye syndrome was lower among women who consumed higher amounts of omega-3 PUFA⁽⁴¹⁾.

Emerging health benefits

Two recent meta-analyses support a role for omega-3 PUFA in preventing and treating non-alcoholic fatty liver disease (NAFLD), with significant effects of EPA + DHA supplementation on liver fat and liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT)) in both adult and paediatric patients^(4,42). In a 2024 meta-analysis which included six RCT that focused on either ALA from flaxseed or DHA from algal oil, all reported a benefit of supplementation on either ALT or liver steatosis/fibrosis⁽⁴³⁾. The effects of EPA + DHA are likely to be mediated by a host of pathological processes which affect the transition from a normal liver phenotype through to cirrhosis, including liver triacylglycerol load, insulin action, mitochondrial function, oxidative stress and inflammatory status⁽⁴⁴⁾. The anti-inflammatory actions of EPA + DHA are typically reported at intakes of EPA + DHA of 1.5 g/d and above⁽⁴⁵⁾.

The potential of EPA + DHA to mitigate the metabolic consequences of excess adipose tissue and obesity is an emerging area with great public health potential. Obesity is associated with increased adipose tissue macrophage infiltration and higher concentrations of circulating and adipose tissue inflammatory cytokines^(46,47). There is some evidence of a reversal of this phenotype following EPA + DHA supplementation, but higher doses are likely to be needed relative to normal-weight individuals^(3,47).

Research inconsistencies and recommendations for future intervention studies

EPA and DHA from foods v. capsules

Available data indicate larger cardioprotective and other health outcome effect sizes in prospective cohort studies (where EPA + DHA is predominantly consumed as oily fish) rather than RCT (where EPA + DHA is exclusively supplemented in capsule form)⁽¹⁰⁾. This is likely to be in part due to residual confounding, with oily fish intake acting as a biomarker for a higher socioeconomic status and better lifestyle behaviours including eating behaviour, with oily fish itself rich in other important nutrients such as selenium, vitamin D and vitamin B₁₂, which may not be fully corrected for in the statistical models, therefore overestimating the health benefits of EPA and DHA from fish.

The EPA and DHA oxidation status and the chemical form of EPA + DHA consumed are also important considerations. PUFA are prone to oxidation, and sources used in trials should be analysed for the amount of EPA + DHA in the consumed capsules (v. percentage claimed), as well as the oxidative profile, as certain oxidised omega-3 PUFA are deleterious for human health⁽⁴⁸⁾. EPA and DHA in supplements are in the form of triacylglycerols (TG), re-esterified TG, phospholipids (PL), ethyl esters or free fatty acids, which may impact on bioavailability^(10,49,50), with the PL and TG form of EPA and DHA typically found in fish, meat and eggs more bioavailable than the other forms. Even within a complex lipid class there may be a further implication of the specific molecular arrangement (*sn* position) occupied by EPA and DHA within TG. Research suggests that bioavailability may be improved by the omega-3 PUFA occupying the *sn*-2 position of TG⁽⁵¹⁾. Furthermore, capsules are often consumed under fasting conditions, which results in lower EPA + DHA absorption v. consumption with a fat-containing meal⁽⁵²⁾.

Study participants

Experimental design should carefully consider the study participants, with lack of response to intervention in RCT often likely attributable to participants being EPA + DHA replete at baseline, which is not representative of the general population. This is clearly demonstrated in the above-mentioned VITAL trial, where a significant effect on the composite CVD primary endpoint was evident only in those having a fish intake <1.5 servings per week⁽¹⁶⁾.

The stage of disease progression and age of RCT participants are also likely to be important. RCT are often secondary prevention trials where the participants have already experienced a cardiovascular event or significant neuropathology and cognitive decline, with secondary prevention potentially harder to mediate than the primary prevention measured in prospective cohort analysis. Often in brain health research, supplementation studies are conducted in older adults with evidence of existing cognitive decline, where possible reduced brain omega-3 PUFA uptake⁽⁵³⁾ may blunt any potential cognitive benefits of increased EPA + DHA intake. Recent evidence suggests that carriers of the *APOE4* allele (25% of the UK population), which is the most important common genetic determinant of dementia risk, have particularly compromised brain DHA uptake with age⁽⁵⁴⁾, which may be exacerbated by female sex and menopause^(55,56), and may partly explain the higher overall dementia risk in females. Therefore, supplementation in older age may have limited impact on brain DHA and cognition, relative to intervention in mid-life.

EPA:DHA ratio and supplementation with other nutrient or non-nutrient bioactives

Based on the high content of DHA in brain tissue relative to EPA, trials focusing on brain function tend to have used a supplement of DHA only or with a high DHA:EPA ratio^(29,32). One relatively recent trial compared the effect of EPA v. DHA on cognitive outcomes over a 6-month period and noted a significant effect on global cognition accuracy and speed with an EPA-rich, but not DHA-rich supplement⁽³⁶⁾. REDUCE-IT⁽¹⁷⁾ and EVAPORATE⁽⁵⁷⁾ report a 25% reduced incident CVD and 17% reduced coronary plaque volume with high dose EPA (3.6 g/d), with no comparable DHA trials allowing a comparison of the relative efficacy of EPA and DHA. The LipiDiDiet study, intervening with a commercial formulation, highlights the benefits of co-supplementing with other nutrients (for example, choline, antioxidant vitamins, B-vitamins and selenium) in addition to DHA and EPA to affect brain health in the short-to-medium term (that is, 6 months to 5 years)⁽⁵⁸⁾. New fortification or supplement innovation should consider the EPA:DHA ratio and a multi-nutrient/bioactive approach when targeting specific health outcomes.

Study duration

RCT often do not adequately consider length of intervention to establish efficacy. In cardiovascular research, cardiovascular risk factors such as plasma lipids and vascular/endothelial function, can be modulated by EPA + DHA supplementation within weeks to months^(59,60). By contrast, incident disease as the primary outcome requires several years of follow-up, particularly for primary prevention studies to have sufficient case numbers⁽¹⁰⁾. Length of intervention is particularly pertinent, but often not adequately considered, in brain health research. Often, trial durations are less than 1 year, but given that the half-life of brain DHA is more than 2 years⁽⁶¹⁾, cognitive benefits which rely on DHA enrichment of brain tissue are likely to require at least a year to manifest. This was evident in the LipiDiDiet study where no significant impact of the intervention on the primary outcome, global cognition, was evident at 2 years, but significant effects of intervention on both global cognition and brain volumes emerged at the 3-year follow-up^(58,62).

Sample size

A robust and clearly reported sample size estimate is a defining feature of well-executed RCT⁽⁶³⁾. However, such estimates are often absent, with a 2019 analysis of RCT in macular degeneration reporting that 52% did not provide any justification of the number of patients included, and only 8% reported a correct and complete sample size⁽⁶⁴⁾. In combination with a short study duration, an absent or sub-optimal and poorly derived sample size estimate can result in a false negative result and the inability to detect a statistically or clinically meaningful change in primary and secondary outcomes in response to intervention^(30,65). This is particularly problematic with incident disease with long prodromal periods such as Alzheimer's disease (AD)⁽⁶⁶⁾. Overly ambitious effect size estimates or lower than realistic estimates of the inter-individual heterogeneity in response, both contribute to inadequately low sample size estimates⁽⁶⁷⁾.

Inclusive RCT

RCT to date are dominated by white participants, often of higher socioeconomic and dietary status, with research not attractive to, or inclusive of, many demographic groups, and often of communities who would most benefit from the research findings.

In the VITAL trial, greater responsiveness to intervention was evident in African American participants, with the authors concluding: 'Finally, there were few Black participants in the secondary prevention trials, and our trial suggests that there is a greater coronary benefit of supplemental *n*-3 fatty acids in this racial group than in others'⁽¹⁶⁾. In a recent project focused on engaging UK ethnic minority groups in research⁽⁶⁸⁾, six main strategies were identified that build trust and inclusion: (1) early involvement of patient and public involvement and engagement (PPIE) partners; (2) relationship-focused activities; (3) co-production and consultation activities; (4) open communication; (5) co-production of project closure activities; and (6) diverse research teams. Much can also be learned from a recent public engagement exercise exploring how a nationwide nutrition study, MedEx-UK, could be made more inclusive (<https://cdn.sanity.io/files/87v9614m/production/bfb8f61e77055b25b0856f3ac45164b01d020253.pdf>). In terms of wider implications for ensuring that nutrition research and recommendations are inclusive, there are four key learnings. Firstly, there is a desire amongst communities not currently engaging in research, to learn more about nutrition and to improve their diet, alongside a willingness to take part in studies with appropriate adjustments. Secondly, community engagement is key to building rapport and trust. Research teams need to go to the participant in their setting and not expect people to attend university or hospital sites. Thirdly, interventions should be tailored to limit the use of jargon. Lastly, research teams must not assume all participants have resources, whether these be access to a computer and IT, transport or funds for intervention elements, and the intervention design needs to ensure that resources are not a barrier to participation.

Current guideline intakes

Globally there is no daily recommended intake (DRI) for EPA + DHA, but guideline intakes do exist. In the UK, the advice is to eat two portions of fish per week (140 g each), one of which should be oily, with a recommended EPA + DHA intake greater than 450 mg/d⁽⁶⁹⁾. This is in line with the International Society for the Study of Fatty Acid and Lipids (ISSFAL)⁽⁷⁰⁾ and the American Heart Association (AHA)⁽⁷¹⁾ recommendations of at least 500 mg/d for the general population, and higher than the European Food Safety Authority (EFSA) recommendation of 250 mg EPA + DHA per day⁽⁷²⁾. The AHA recommend at least 1 g of EPA + DHA per day for secondary prevention. Typically, an additional 200–300 mg of DHA or EPA + DHA is recommended during pregnancy and lactation⁽⁷²⁾.

Current intakes and status

Despite their importance to human health, consumption of EPA and DHA is substantially lower than recommended intakes. Much of the UK population consumes < 50 mg EPA + DHA per day with an average population intake of less than 250 mg/d⁽⁹⁾, heavily skewed by the approximate 25% of the UK population who are oily fish consumers⁽⁷³⁾ (Table 1). Only 16–17% of the UK population meet the oily fish recommendation of at least one 140 g portion per week^(73,74). This problem is not limited to the UK, with most global populations consuming on average <200 mg EPA + DHA per day⁽⁷⁵⁾. In Australia, Meyer and colleagues using data from the 2011–2012 National Nutrition and Physical Activity Survey found median EPA + DHA + DPA intakes of less than 50% of the mean

of ~340 mg/d intake, which again illustrates highly-skewed omega-3 PUFA intakes⁽⁷⁶⁾.

Oily fish consumption demonstrates a strong socio-economic gradient with affluent groups 2.4–4.0 times more likely to eat oily fish than the least affluent groups in the UK⁽⁷⁷⁾. Affordability of products containing EPA and DHA is likely to be a contributor to low intakes in many communities.

Given that oily fish is almost exclusively the current dietary source of EPA and DHA, vegetarians and vegans would be expected to have negligible intakes relative to fish consumers; however, data on this are limited. In the EPIC-Norfolk cohort, EPA/DHA intakes of 0.13/0.19, 0.02/0.02 and 0.01/0.00 g/d were evident in male fish eaters, vegetarians and vegans, respectively, with equivalent intakes in females of 0.11/0.15, 0.02/0.01 and 0.02/0.00 g/d⁽⁷⁸⁾.

In addition to intake, it is important to have an accurate objective measurement of status. The omega-3 index (OM3I), which is the percentage contribution of EPA + DHA to total fatty acids in erythrocytes, is becoming widely used in research and clinical practice as a standardised measurement of omega-3 fatty acid status and prognostic measure of future chronic disease risk⁽⁷⁹⁾. It is proposed that an OM3I of >8% is desirable ('green zone'), 4–8% is intermediate ('yellow zone') and <4% is undesirable ('red zone'). Much of the UK and global populations have a sub-optimal OM3I of <4%. In a recent analysis, which included forty-eight countries/regions, the average OM3I in most countries was <6%, with only Iceland, Norway, Finland, South Korea, Japan, Alaska and Greenland having an average OM3I >8%⁽⁸⁰⁾. In the UK BIOBANK the mean OM3I is 5.58% with just 36% of participants presenting with a value of ≥8%⁽⁸¹⁾. Wider screening for OM3I could inform policy and the targeting of research and intervention according to habitual status.

Despite a tenfold lower EPA + DHA intake, blood EPA + DHA status, including OM3I, are typically <25% lower in vegetarians and vegans^(78,82,83), potentially reflecting efficient endogenous synthesis or retention in these groups (see 'Approaches to increase endogenous EPA + DHA biosynthesis' section).

Sustainability challenges

Seafood not only provides EPA and DHA but also other essential nutrients, including iron, vitamin D and iodine⁽⁸⁴⁾, and over half (58%) of food-based dietary guidelines globally include a mention of fish⁽⁸⁵⁾. However, the seafood sector faces many challenges as a sustainable source of long-chain omega-3 fatty acids (and other nutrients), including the influence of climate change. It is estimated that the oceans have absorbed over a quarter of CO₂ entering the atmosphere since the start of the industrial revolution⁽⁸⁶⁾. This leads to acidification and, alongside rising ocean temperatures, has negatively impacted fish stocks within economic exclusion zones (areas within which a country retains fishing rights), due to migration to cooler/deeper waters. In addition, acidification can affect calcification of shells in some species⁽⁸⁷⁾ and possibly wild fish growth rates⁽⁸⁸⁾.

Overfishing poses another challenge to the seafood sector; about one-third of global fish stocks are overfished⁽⁸⁹⁾. While the remaining two-thirds are fished within biologically sustainable levels, meeting the rising global demand for fish in a sustainable way will require concerted efforts to protect and restore global fish stocks⁽⁹⁰⁾. The growth of aquaculture to meet increased demand has also led to environmental and animal welfare issues. The use of smaller oily fish species (for example, sardines) in fish feed has led

to an increased demand to provide for farmed species (for example, salmon), with poorly managed fish farming facilitating the growth of pathogens, pests and parasites, and habitat damage, which may also contribute to climate change effects⁽⁹¹⁾.

Based on the most commonly used recommendation of 500 mg EPA + DHA per day and a current global population of 8.2 billion, 1.5 million tonnes of EPA + DHA would be required per year to meet the demand from fisheries and other marine sources, with deficits between supply and demand of 0.4 million tonnes and 1 million tonnes currently reported, which will be exacerbated by population growth^(92–94). This starkly highlights the need for improved fisheries management and targeting of existing marine EPA and DHA and the development of non-marine sources.

One approach utilised by the aquaculture industry to deal with cost, supply and sustainability issues has been to reduce the use of fishmeal and fish oil in farmed fish diets, with reduced EPA + DHA in the resulting farmed fish for human consumption. The EPA + DHA content of Scottish farmed salmon approximately halved between 2006 and 2015 (Figure 2)⁽⁹⁵⁾. The implication of this reduced omega-3 PUFA content is that oily fish intake recommendations need to increase substantially if farmed salmon is a major dietary source of EPA + DHA. One option for the aquaculture industry is to maintain or return to traditional EPA + DHA concentrations in fish by using approved more sustainable sources of EPA + DHA in the fish feed, such as EPA/DHA-rich microalgae or EPA/DHA-containing oilseeds, which has started to happen in recent years⁽⁹⁶⁾ (see 'Algal oils' and 'Biotechnology-derived sources' section).

Diversity of EPA + DHA sources

Although there are no other foods that contain comparable quantities of EPA + DHA on a per 100 g or per serving basis as oily fish, it has previously been suggested by Givens and Gibbs^(9,97) that a 'supermarket basket' approach with a range of contributing foods, should be considered. However, what foods should we focus on as meaningful contributors to our 'basket' of EPA + DHA and can they be meaningfully bio-enriched?

White meat (chicken, turkey and pork)

In the UK, white meat (poultry) is consumed at 35.7 g/d per capita, with 79% of the population classed as consumers of white meat⁽⁹⁸⁾. This means that consumers eat 45 g per person per day, or 316 g per person per week, which is comparable to a previous figure of 374 g⁽⁹⁷⁾. This high and widespread consumption makes poultry an interesting vehicle for EPA + DHA provision.

Several experiments have been described in which broiler chickens (chickens reared for their meat) were fed diets enriched with DHA-rich microalgae biomass or oil^(99–101). The birds grow as normal, and analysis of the meat shows that the concentration of DHA is proportional to the concentration of DHA in the diet. In practice, 100 g of chicken could provide at least 60 mg of DHA⁽¹⁰²⁾. Although not reaching the concentrations of EPA + DHA found in oily fish, its widespread consumption means that EPA and DHA enriched poultry meat could act as an important population source.

Because of the poor efficiency of converting ALA to EPA, and potentially DHA, due to low $\Delta 6$ -desaturase activity (Figure 1), an alternative could be to supply dietary sources of stearidonic acid (SDA; 18 : 4 *n*-3), a product of $\Delta 6$ -desaturase. Rymer *et al.*⁽¹⁰³⁾ examined the effect of feeding poultry a diet containing oil from

genetically modified soya beans providing SDA (240 mg/g oil), relative to an oil with no SDA from near-isogenic soya beans. Whilst small increases in EPA and Docosapentaenoic acid (DPA) (but not DHA except in skinless breast meat) were seen in the meat from the SDA-fed birds, the major effect was a significant increase in SDA (treatment 231 mg/g fresh tissue *v.* control 3 mg/g). There was therefore no indication that birds converted SDA to EPA and DHA any more efficiently than from ALA. A recent study with sixty male chickens compared diets containing lipid sources from soyabean oil (SO) rich in 18:2 *n*-6, linseed oil (LO) rich in 18:3 *n*-3 and echium oil (EO) which provided a balanced combination of 18:2 *n*-6 and 18:3 *n*-3 and is rich in SDA (mean 3.71 g/100 g total fatty acids)⁽¹⁰⁴⁾. The EO treatment was more efficient than LO at enhancing chicken thigh meat with long-chain omega-3 fatty acids (6.0 *v.* 4.2 g/100 g total fatty acids). The long-chain omega-3 fatty acids in the meat from EO-fed birds included SDA 0.30, EPA 0.72, DPA 3.41 and DHA 1.83 g/100 g total fatty acids. The authors concluded that a combination of lowering the 18:2 *n*-6/18:3 *n*-3 ratio and increasing SDA in the diet for chickens would increase the birds' metabolic ability for enhancing their meat with long-chain omega-3 fatty acids.

James *et al.*⁽¹⁰⁵⁾ suggested that, based on EPA enrichment of plasma and erythrocytes, 3 g/d SDA was equivalent to 0.6–1 g/d EPA in human subjects. A review of several human studies concluded that enrichment of EPA in erythrocytes by dietary EPA consumption was about nine-times more per gram consumed than that from dietary SDA⁽¹⁰⁶⁾. Baker and colleagues⁽¹⁰⁷⁾ concluded that, although both dietary ALA and SDA may be an alternative to dietary EPA, they are unlikely to be appropriate for DHA. More recently, in a human intervention study, feeding Ahiflower oil from seeds of *Buglossoides arvensis*, which is rich in ALA and SDA (44.3 and 20.9 g/100 g total fatty acids, respectively), increased circulating EPA but not DHA was evident, although the relative impact of ALA *v.* SDA was not assessed⁽¹⁰⁸⁾.

Although consumed in small quantities, at 6 g/d per capita (with 10 g/d per capita consumption of sausages, which are likely to be predominately pork as the meat source), and by just 24% of consumers⁽⁹⁸⁾, pork has also been shown to have a place in the basket. Experiments show that when pigs are fed a diet enriched with DHA, the resulting meat is enriched in DHA, with 70 mg DHA per 100 g achieved⁽¹⁰⁹⁾. One challenge with larger animals from a retail and consumption perspective is that although the meat fatty acid concentration is proportional to the fatty acid concentration in the animals' diet, the fatty acid concentration in the meat differs according to meat cut⁽¹¹⁰⁾. Interestingly, the higher-fat cuts of meat, which are often lower value but more widely consumed and affordable, are the most highly enriched.

Eggs

Laying hens have proven to be very efficient utilisers of dietary DHA. As with broilers, several experiments have described egg DHA enrichment when laying hens (hens which lay eggs for human consumption) are fed diets enriched with DHA-rich microalgae biomass or oil. The birds consume the feed as normal and produce the same number and quality of eggs as standard-fed birds. Analysis of the eggs shows that the concentration of DHA is proportional to the concentration of DHA in the diet^(111–113).

It is interesting to note that egg-laying hens appear to have a substantial ability to synthesise DHA from ALA, possibly a necessity to provide a supply of DHA to the embryo/chick for

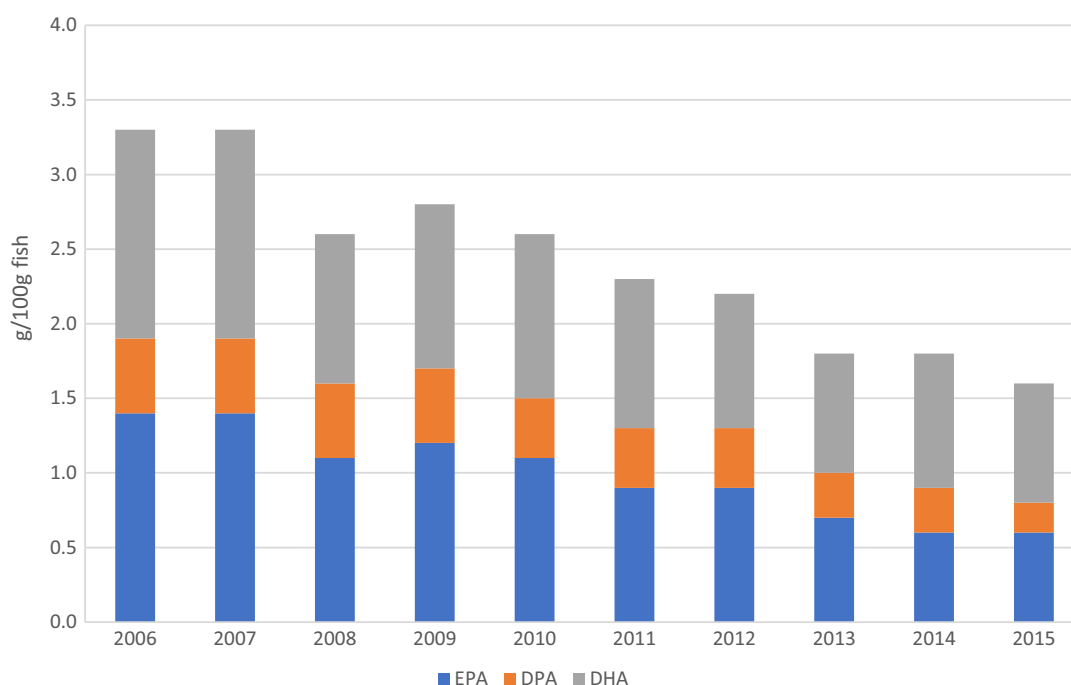


Fig. 2. Fatty acid composition of farmed Scottish Atlantic salmon between 2006 and 2015.⁽⁹⁵⁾

development of the brain and nervous system. In hens, while EPA was not affected, the concentration of DHA was increased significantly from 51 to 81 and 87 mg DHA per egg, respectively, for diets providing, 0, 100 and 200 g linseed/kg, respectively⁽¹¹⁴⁾, which was broadly consistent with a subsequent feeding study⁽¹¹⁵⁾. In a subsequent human intervention, four enriched eggs per day for 2 weeks increased total omega-3 fatty acids and DHA in blood platelet phospholipids⁽¹¹⁴⁾. A study compared diets for laying hens containing a flaxseed-rich supplement (2.6 g/100 g; total omega-3 fatty acids 0.35 g/100 g) with a control diet without the supplement (total omega-3 fatty acids 0.14 g/100 g). This led to egg yolks from the treatment diet having significantly higher DHA concentrations (1.89 g/100 g total fatty acids) than yolks from the control diet (0.87 g/100 g total fatty acids). There were no significant changes in the concentrations of EPA or DPA in the yolks⁽¹¹⁶⁾. Overall, eggs modified by the inclusion of plant sources of ALA in the diet of the laying hen could provide a valuable and sustainable dietary source of DHA for humans without the need to use fish oils.

In 2023, egg consumption in the UK was 175 eggs per person per year, which equates to 23 g/d (assuming an average-sized 'large' egg, which is 68 g)⁽¹¹⁷⁾. As per EU and GB nutrition and health claims regulations, standard eggs are a 'source of' omega-3 EPA + DHA if they contain a minimum of 40 mg EPA + DHA per 100 g and per 100 kcal⁽¹¹⁸⁾. However, the enrichment experiments described above show that laying hens can efficiently deposit additional dietary DHA in their eggs, meaning that eggs can become 'high in' omega-3 EPA + DHA. These enriched eggs contain >105 mg EPA + DHA per 100 g and even >200 mg EPA + DHA per 100 g (that is, >71 mg and >136 mg EPA + DHA per egg, respectively). Therefore, at current rates of egg consumption, enriched eggs would contribute at least 26 mg EPA + DHA daily to a person's intake, and in the case of highly enriched eggs would contribute 46 mg EPA + DHA daily.

Red meat (beef, lamb) and milk

In the UK, on average, 23.7 g of red meat is consumed per day, with 69% of the population red meat consumers, equating to a consumption of 34.3 g meat per person per day in meat eaters⁽⁹⁸⁾. Milk is purchased by 98.5% of UK households at a rate of approximately 1.3 litres per person per week, which equates to almost 190 ml/d. These consumption levels suggest red meat and milk may be possible vehicles for fortification to provide EPA + DHA to consumers.

One aspect which has received particular attention is pasture-fed meat and milk as a source of omega-3 fatty acids. This is because pasture is high in ALA. Increased ALA in milk from pasture-fed compared with total mixed ration-fed (that is, indoors offered silage and concentrate) cows has been reported⁽¹¹⁹⁾. A review of eleven animal feeding studies of pasture- v. concentrate-fed cows showed that pasture feeding leads to a higher EPA + DHA concentration in milk⁽¹²⁰⁾. However, even at concentrations up to 100 mg EPA + DPA + DHA per 100 g fat, because of the low fat content of milk (4%), 250 ml of full-fat milk from a pasture-fed system would provide just 10 mg EPA + DHA. Moreover, most milk consumed in the UK is fat-reduced.

It seems, therefore, that direct supplementation of the dairy cow diet with DHA to effect an increase in DHA in the milk needs to be considered⁽¹²¹⁾. Moran *et al.* reported on studies where microalgal DHA was added to the dairy cow diet and found just 15–16 mg DHA per 250 ml of full-fat milk resulted from the enriched diets, enriched in the region of 25 g DHA per cow per day⁽¹²²⁾. Similar results were seen in milk resulting from fish oil-supplemented diets⁽¹²³⁾. This highlights the poor 'transfer efficiency' when EPA + DHA is ingested by ruminants. Polyunsaturated fatty acids such as EPA and DHA undergo extensive hydrolysis and biohydrogenation in the rumen. This occurs to avoid unsaturated fatty acids in

the rumen as they can have a toxic effect on some of the rumen bacteria. As a result, dietary EPA and DHA are poorly available for deposition in ruminant meat or milk. It also results in the production of fatty acid metabolites which may negatively affect intake and, in the case of dairy cows, negatively affect milk fat concentration and yield. To overcome this problem, 'protecting' or encapsulating the DHA in the diet from the hydrolysis and biohydrogenation processes in the rumen has been considered. For example, the DHA increased from 0.05 to 0.29 mg/g muscle tissue, and EPA from 0.05 to 0.83 mg/g muscle tissue, in a common beef cattle breed (Charolais cross) when the animals had a protected fish oil product included in their diet for the final 90 d pre-slaughter⁽¹²⁴⁾. As a result, 70 g of beef would provide 78 mg EPA + DHA, which would be a significant contributor to daily intake, especially in non-fish consumers. The problem, however, is the high quantity of dietary DHA which needs to be included in the diet of the animals to provide this level of enrichment.

An alternative approach to consider for milk is fortification of milk by incorporating the DHA (e.g. as algal oil) directly into the milk. Such products are currently available for sale in the USA, providing 32 mg DHA (Horizon Organic DHA Whole Milk) or 50 mg DHA (Family First™, Organic Valley) per serving.

Interestingly, it appears that the incorporation of DHA from dietary sources into meat is greater in ovine than bovine animals. Ponnampalam *et al.*⁽¹²⁵⁾ showed that, whereas lambs fed a control diet had 25 mg EPA + DHA per 100 g meat, lambs fed a diet with DHA-containing algae had 85 mg EPA + DHA per 100 g meat. However, as with pork, consumption of ovine-derived milk and meat products (lamb and mutton) in the UK population is low.

Givens and Gibbs (2008) reported that enriched animal-derived foods could contribute 231 mg per person per day of EPA + DHA to the UK diet⁽⁹⁾. Using more up-to-date adult (19–64 years of age) food intakes from the UK National Diet and Nutrition Survey⁽¹²⁶⁾, a recalculation indicates that they could contribute some 266 mg EPA + DHA per person per day with the increase relating mainly to increased poultry meat consumption⁽¹²⁷⁾. However, since enrichment of milk and dairy foods is very inefficient, it is unlikely that enriched dairy foods will make a future contribution, leaving about 193 mg EPA + DHA per person per day from meat and eggs.

Algal oils

As mentioned above, when feed for animals is enriched in EPA + DHA, usually fish oil or microalgae biomass/oil is used as the source. EPA and DHA from microalgae lead to less taste or odour problems in the resulting meat and eggs than can occur with fish oil⁽¹¹¹⁾. Algal oils can be a good source of EPA and DHA that is acceptable to vegetarians and vegans and therefore are a good candidate, not just for animal feeds, but for direct fortification of foods for human consumption and as supplements. Algal oil is also a more environmentally acceptable raw material than fish oil, although it is not environmentally neutral, requiring a source of carbon (typically sugar from cane) and heat and light for heterotrophic growth and processing. The EPA and DHA contents of the oils of different algae can differ. Heterotrophic microalgal species such as *Schizochytrium*, *Aurantiochytrium* and *Cryptocodinium cohnii* are essential producers of DHA, and in their oils, DHA content ranges from 43% to 55%, 24% to 53%, and 24% to 54% of the total fatty acids, respectively⁽¹²⁸⁾. Photosynthetic microalgae, such as *Phaeodactylum*

tricornutum, *Nannochloropsis oceanica* and *Dunaliella salina* primarily produce EPA, which can reach up to 36%, 42%, and 46% of the total fatty acids, respectively^(128,129). Genetic engineering has been used to increase the EPA and DHA contents of different microalgae species and is discussed in detail elsewhere^(130,131). Even so, many wild type microalgae produce oils that contain much more DHA than is present in fish oil (20–55% of fatty acids) and some also contain EPA. EPA and DHA in algal oils are readily bioavailable and increase EPA and DHA status in blood and blood cells just as fish oil does. Algal oils also have the same impact on cardiovascular risk factors as fish oil. For example, a meta-analysis of eleven randomised controlled trials using algal oil in adults identified a significant 0.2 mM reduction in fasting triacylglycerol concentrations with no evidence of heterogeneity⁽¹³²⁾; an effect size similar to that seen with fish oil⁽¹²⁾. There was also an increase in both low- and high-density lipoprotein cholesterol⁽¹³²⁾; effects also seen with fish oil⁽¹²⁾ and with pure DHA⁽¹³³⁾. These observations support the use of algal oils as an alternative source of EPA and DHA to fish and fish oils.

Biotechnology-derived sources

An exciting innovation happening in this space is the use of plant biotechnology to produce oilseeds as new, sustainable sources of EPA and DHA⁽¹³⁴⁾.

Camelina sativa is an oilseed crop native to Europe and grown widely across a range of pedo-climatic zones. Over recent years, camelina has received significant attention because of its remarkable agronomic versatility and environmental adaptability. For the metabolic engineer, camelina is simple to transform and has a short life cycle, allowing more progress in 3 years than is achievable with any other crop. Therefore, engineering iterations can be rapidly tested until an optimised oil profile is achieved. Researchers at Rothamsted Research have engineered the biosynthetic pathway for EPA and DHA production from marine diatoms and microalgae consumed by fish (as their source of EPA and DHA) into the seeds of camelina. The result is an oil containing commercially relevant amounts of EPA and DHA, with levels of enrichment up to 30 g per 100 g oil⁽¹³⁵⁾ (Figure 3). Using a similar approach, researchers from CSIRO and NuSeed (Australia) have engineered canola to produce DHA⁽¹³⁶⁾; this novel source has been approved for feed and food uses in multiple countries (including for aquaculture in Norway). Camelina prototypes producing seed oil containing significant amounts of EPA or EPA + DHA have been successfully grown in replicated field trials around the world, demonstrating the feasibility of this approach to sustainably supply EPA + DHA⁽¹³⁴⁾.

Several fish feeding trials have been undertaken with oil from the modified camelina, which found that the camelina oil performed as well as fish oil supplements with respect to fish welfare, growth and fatty acid metabolism, as well as the nutritional quality of the fillets^(138,139). More recently, the utility of these novel oils in diets for salmon grown to market weight has been demonstrated⁽¹⁴⁰⁾.

In a mouse feeding study, comparable liver, brain and muscle EPA enrichment, and expression of PUFA metabolising and responsive genes, was evident following EPA-enriched camelina oil v. EPA-rich fish oil feeding⁽¹⁴¹⁾. Furthermore, in a recent adult human subject postprandial trial, 450 mg of EPA + DHA was consumed as either oil from transgenic camelina or a blended fish oil in a test meal⁽¹⁴²⁾. Over 8 h there were no differences between

the oils in EPA and DHA incorporation into lipid fractions, or plasma lipoprotein concentrations and inflammatory biomarkers. In a chronic study, with the same camelina and fish oil products, there was comparable EPA and DHA enrichment⁽¹⁴³⁾. Therefore, the research to date demonstrates the large potential for this enriched camelina oil as a sustainable EPA and DHA source for both aquaculture and direct human consumption. However, as will be discussed in the 'Policy, regulation and effecting change' section, the realisation of the benefit of this oil has been severely hampered by ongoing regulatory issues.

Bioavailability considerations

Bioavailability in pharmacology refers to the fraction (%) of an administered drug that reaches the systemic circulation. In addition to intake, differences in bioavailability from different sources could be an important determinant of EPA + DHA status. As discussed earlier, EPA + DHA as TG or PL found in foods are likely to be more bioavailable than EPA or DHA consumed as the ethyl ester form. Visioli *et al.*⁽¹⁴⁴⁾ and Elvevoll *et al.*⁽¹⁴⁵⁾ both demonstrated that EPA and DHA were more bioavailable to consumers when consumed as part of the food matrix (in this case as fish) compared with as a supplement.

Stanton *et al.*⁽¹⁴⁶⁾ reported a 1.4% increment in OM3I with an additional intake of 100 mg/d of EPA + DHA from omega-3-PUFA enriched chicken meat and eggs, which equals or exceeds previously recorded values for oily fish (0.6–0.8%), and fish oil supplements (0.2–0.6%)^(147,148). This may be due to the fact that in eggs⁽¹⁴⁹⁾ and in chicken meat⁽¹⁵⁰⁾ a significant proportion of EPA and DHA is present in the highly bioavailable PL form. Coates and colleagues⁽¹⁵¹⁾ considered the effects of consuming DHA-enriched pork meat providing 1.3 g EPA + DPA + DHA per week in healthy volunteers. At these relatively modest intakes, a 15% increase in erythrocyte DHA was observed along with a decrease in serum TG levels. In their dietary intervention study using red meat from animals offered a grass diet compared with a concentrate diet, the authors concluded that the increases observed in plasma and platelet EPA + DHA confirmed the bioavailability of EPA + DHA from red meat from grass-fed animals.

As detailed in the 'Algal oils' and 'Biotechnology-derived sources' sections earlier, rodent, fish and human studies have indicated that the bioavailability of plant sources of EPA and DHA from algal oil or metabolically engineered oilseed is equivalent to that of fish-derived EPA and DHA.

In summary, there are several viable foods/food groups that can be bio-enriched to make a meaningful contribution to population EPA and DHA intake and status as a sustainable alternative to oily fish or fish-sourced EPA + DHA supplements. The choice of food/food groups is likely to depend on context, with the factors to consider summarised in Figure 4.

Approaches to increase endogenous EPA + DHA biosynthesis

In addition to diversifying EPA and DHA sources available to consumers, approaches that increase endogenous EPA and DHA biosynthesis (Figure 1) have the potential to increase EPA and DHA status, which to date has received limited research attention. Thus, factors that affect the conversion of ALA to EPA and DHA need to be considered, which include polymorphisms in genes encoding the desaturase enzymes, insulin sensitivity, sex, linoleic acid and ALA intakes, and intakes of select micronutrients and non-nutrient bioactives.

Females have higher DHA status than males⁽¹⁵²⁾. Consistent with this, Walker and colleagues found that premenopausal women had higher EPA and DHA levels in plasma, blood cells and adipose tissue than men⁽¹⁵³⁾. Studies with ¹³C-labeled ALA showed greater conversion to EPA, and especially to DHA, in young adult women than in young adult men⁽¹⁵⁴⁾. This is believed to be due to upregulation of desaturases by oestrogens and/or progestogens^(155–157). This effect is likely lost post-menopause. In this regard, postmenopausal women taking hormone replacement therapy (HRT) were found to have higher erythrocyte DHA compared with those not on HRT⁽¹⁵⁸⁾.

One interesting observation made in the EPIC cohort, was that despite significantly lower EPA + DHA intakes in non-fish eaters relative to fish eaters (mean intake of 310 mg and 250 mg/d in men and women fish eaters *v.* 10–20 mg/d in meat eating, vegetarian or vegan non-fish eating groups), the differences in plasma EPA + DPA + DHA concentrations were marginal, with typically up to a 10% difference between groups⁽⁷⁸⁾. The product to precursor ratio was greater in non-fish-eaters than in fish-eaters, indicating an increased efficiency of converting ALA to EPA + DHA. Increased ALA intake has been shown to increase EPA concentrations in human subjects⁽¹⁰⁷⁾; however, evidence from human trials suggests conversion to DHA appears to be limited. Lowering linoleic acid intake, while keeping ALA intake constant, also increases EPA concentrations⁽¹⁵⁹⁾, although the effects may be modest⁽¹⁶⁰⁾.

In addition to the impact of PUFA intakes on EPA and DHA biosynthesis, some work has been done looking at micronutrients (e.g. iron, zinc and B-vitamins) and non-nutrient bioactives (e.g. polyphenols) on EPA and DHA levels⁽¹⁶¹⁾. There is evidence that vitamin B₆ status may be associated with EPA and DHA status⁽¹⁶²⁾, although causality in human subjects remains to be established. Although Toufektsian *et al.*⁽¹⁶³⁾ reported that anthocyanin supplementation increased plasma EPA + DHA in rats, subsequently, Vauzour *et al.*⁽¹⁶⁴⁾ found no effect of anthocyanins and anthocyanin-rich food intake on EPA or DHA status in a variety of model systems. Wheat⁽¹⁶⁵⁾ and rye⁽¹⁶⁶⁾ polyphenols have been shown to increase EPA, and EPA and DHA, respectively, in rodents.

There is also emerging evidence that statin use may affect PUFA levels, due to upregulation of FADS1 and FADS2, as observed in cell lines^(167,168). In participants with hypercholesterolaemia, simvastatin reduced total fatty acid concentrations by 22%, with an increase in the percentage of arachidonic acid and DHA⁽¹⁶⁹⁾.

Overall, despite the large potential for upregulation of the biosynthetic process to improve EPA and DHA status, there is currently limited evidence and research activity in this area, particularly in human subjects.

Policy, regulation and effecting change

As detailed above, most of the UK population (along with most other global populations) has lower than recommended intakes of EPA and DHA, with associated health consequences. Collective leadership from government health policy and regulatory agencies, the food industry and academia will be required to affect a measurable change in intake. The provision to consumers of the capability, opportunity and motivation⁽¹⁷⁰⁾ to increase EPA and DHA intakes, requires a multi-prong approach including improved consumer awareness, altered national food policy, and a consideration of current innovation and the regulatory landscape affecting the translation of research findings into commercially available EPA and DHA enriched food products.

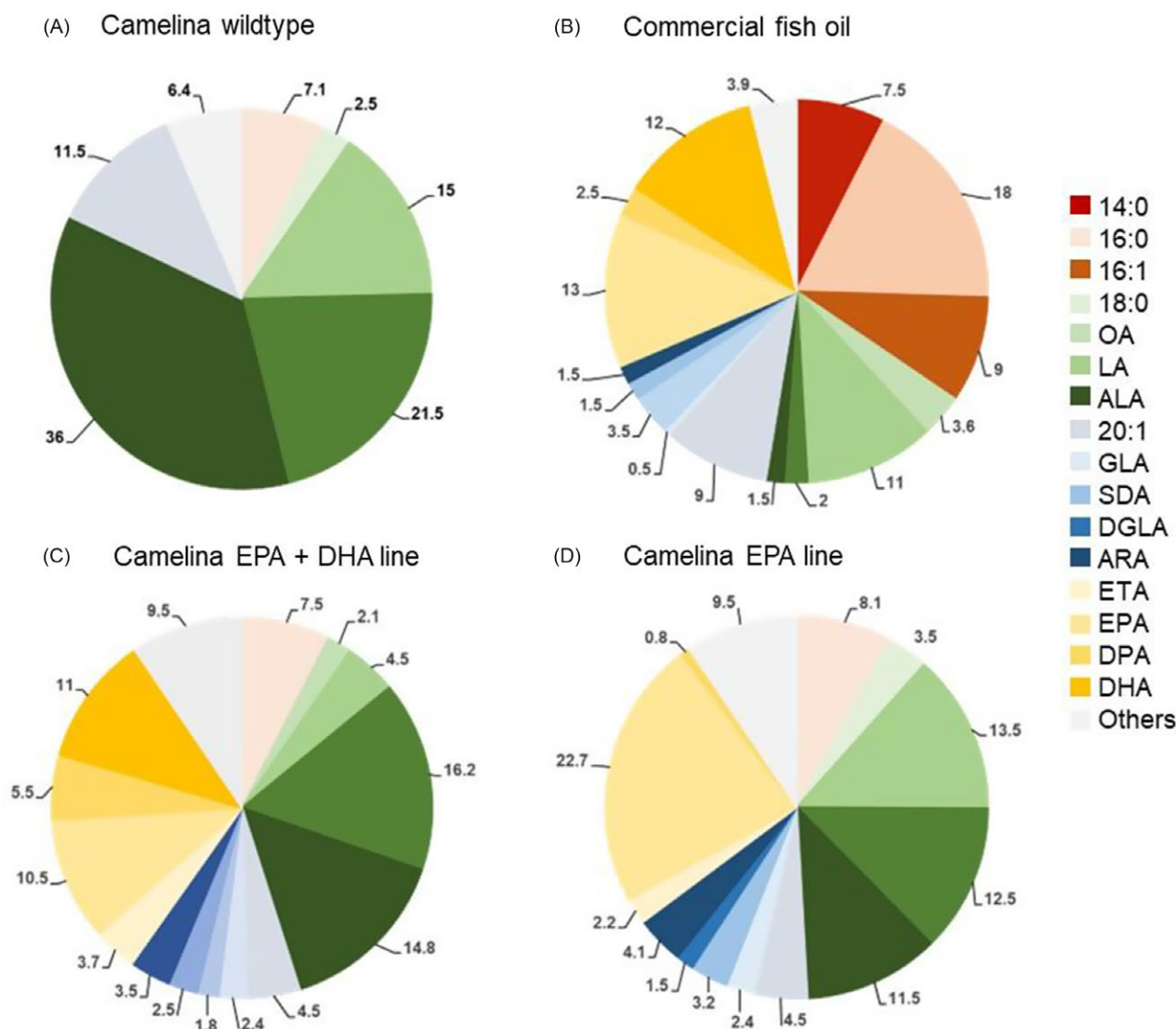


Fig. 3. Engineered oilseeds as a terrestrial source of EPA and DHA. Seed oil fatty acid composition (Mol%; carbons:desaturations; GC-FID analysis of fatty acid methyl esters derivatised from pooled samples) are shown for wildtype camelina (A), commercial fish oil (B), camelina engineered to produce EPA and DHA (C), and camelina engineered to produce EPA (D). Data are reproduced from Han *et al.* (2022)⁽¹³⁴⁾, Sprague *et al.* (2016)⁽⁹⁵⁾ and Ruiz-Lopez *et al.* (2015)⁽¹³⁷⁾

The current UK government advice to: ‘Eat at least two portions of fish per week of which one should be oily... contains approximately 0.45 g of EPA + DPA + DHA’ dates back to 2004⁽⁶⁹⁾, with the two portion (140 g per portion) message a component part of the 2016 Eatwell guide⁽¹⁷¹⁾. However, there is widespread public confusion regarding the health benefits of increased fish and EPA and DHA intakes, the difference between ALA and EPA/DHA, what constitutes an oily fish, whether the canned version of the fish is equivalent to the fresh fillet, toxicological concerns and sustainability issues, and product sustainability, certification and labelling⁽¹⁷²⁾.

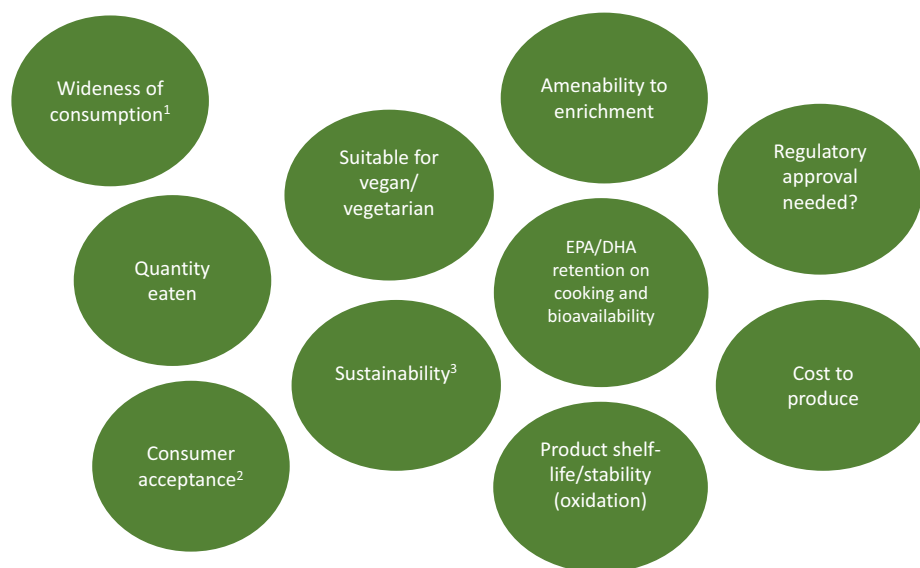
Nutrition public health campaigns over the last decade, such as Healthier Families, have focused on the five-a-day intake of fruit and vegetables, and to a lesser degree, salt, sugar and saturated fat reductions⁽¹⁷³⁾. As highlighted in recent publications: ‘Urgent

public health campaigns are needed to improve UK intakes (of oily fish), which should include a combined approach of dietary and supplemental sources⁽⁷³⁾ and ‘It therefore appears there is work to be done in the UK to encourage wider consumer engagement with government recommendations for fish consumption⁽¹⁷⁴⁾.

In addition to improving consumer awareness, government policies should consistently align with dietary recommendation to support increased intake. Currently in the UK, by sales, five seafood species, namely salmon, cod, tuna, warm-water prawns and haddock, represent 80% of the seafood consumed⁽⁹⁶⁾. Mackerel and herring are the two most landed fish in the UK, with the vast majority exported. There is a real opportunity in the derivation of Post-Brexit Fisheries Management Policy, along with fiscal policy, to create a ‘context’ where there is a greater nationwide availability of affordable seafood products, and in particular, oily fish.

Table 2. Suggested next steps identified by the symposium speakers

Research focus
• Future RCT could be improved and more impactful by: - Considering the impact of the chemical form of EPA and DHA, food matrix and the fat content of the meal on EPA and DHA bioavailability - Considering any oxidation issues of EPA + DHA provision - Ensuring study power/sample size is appropriate for the primary endpoint - Ensuring the length of intervention is appropriate for the primary endpoint - Ensuring the research is inclusive, attractive and accessible to a diverse range of possible participants • Consider the most appropriate life stage and age of participants for the health endpoint of interest • Consider co-supplementing with other food bioactives with additive or synergistic mechanisms of action on the molecular target or health endpoint of interest • Analyse EPA + DHA in plasma, erythrocytes or the target tissue of interest as a measure of status and/or adherence to intervention • Consider EPA and DHA partitioning and uptake into tissues • Understand the determinants of endogenous conversion of ALA to EPA and DHA, such as genetics, age, sex, body fat level, micronutrient status, ethnicity and disease status • Investigate the physiological role and impact of docosapentaenoic acid (DPA) on health outcomes • Compare the bio-efficacy of algal oil and EPA/DHA fortified foods in human trials • Conduct long-term stability and bioavailability (measured by impact on erythrocyte omega-3-index after at least 3 months of consumption) studies for all foods and supplements that have a health claim linked to omega-3-PUFA (DHA and EPA) • Conduct technological and sensory analysis of new alternative sources of omega-3 fatty acids in human subjects • Develop a more integrated and comprehensive understanding of the potential benefits (or not?) of switching to alternative non-oily fish sources of EPA and DHA – for example, the knock-on effects of land, water, fertiliser use for growing plant-based sources v. utilising wild-caught small pelagic fish (e.g. sardines, herring) as an omega-3 source
Next steps in research mobilisation and implementation
• Consider whether there is a rationale for the establishment of official dietary reference intake (DRI) for EPA and DHA • Improve availability of up-to-date omega-3 compositional data (through national analytical surveys) of fish and non-fish EPA and DHA sources. In the UK, omega-3 composition data for oily fish, available within the McCance and Widdowson's Composition of Foods, is more than 10 years old and for some fish more than 20 years old^(176,177) • Initiate public health campaigns to improve consumer awareness around omega-3 sources, health impacts and labelling (omega-3 health claims and ALA v. EPA/DHA) • Have a greater understanding of consumer perceptions of omega-3 fatty acids, including health benefits, required intakes, ability to identify products, and barriers/facilitators affecting willingness to purchase products containing or enriched in omega-3 PUFA • Understand the barriers to commercialisation for enriched foods – technological, economic, supply chain and regulatory • Understand consumer perception of enriched foods • Understand barriers to scaling innovations in this area, e.g. pilot facility access, capital investment needs • Conduct health-economic analysis to establish the cost effectiveness of omega-3 (especially EPA + DHA) provision

**Fig. 4.** Considerations for the identification of food fortification approaches to increase population EPA + DHA intakes: (1) in the general population and population subgroups; (2) perception, willingness to buy, organoleptic properties, cultural practices, dietary habits; and (3) greenhouse gas emissions, water, land use, wild fish stocks and so on.

There is also a pressing need to accelerate the translation pathway for the availability of the non-fish seed-oil EPA and DHA sources, described earlier. However, there are regulatory hurdles associated with both the commercial cultivation and animal feed and human food use of such novel oils, complicated by national variations in the

approval process. Recently, the transgenic camelina oil described above has been approved for commercial cultivation in the USA, opening the way to potentially unlimited production of a terrestrial source of EPA + DHA. Similarly, DHA-canola has received approval for cultivation in North America and has also been approved for feed

and food use⁽¹⁷⁵⁾. Algal oils and these metabolically engineered oilseeds hold tremendous promise to increase population EPA/DHA intake, particularly suited to vegans and vegetarians.

As described earlier, a myriad of animal-derived foods can be bio-enriched by incorporating these novel EPA and DHA sources into the animal diet. These enriched foods (Figure 4) could then be included as recommended/mentioned sources in dietary guidance, policies, consumer awareness campaigns, etc., alongside oily fish. We should encourage and de-risk commercialisation, to span the 'translational valley of death' and ensure a multitude of food sources of EPA + DHA are available for purchase.

Closing remarks

Available research is indicative that an intake of EPA + DHA of 1 g/d or above, is needed to optimise health and reduce the life-long risk of disease. However, intakes for most of the population are only a fraction (perhaps 10% or less) of this, with oily fish consumption not a viable or attractive source for many. There is an urgent need to develop and make available a range of innovative, acceptable, sustainable and affordable EPA + DHA bio-enriched foods and supplements to support improved EPA + DHA status, with the aim of improving the health and wellbeing of the population. The impact of such innovation needs to be supported by fit-for-purpose public health campaigns which increase consumer awareness, regulations which clearly require the differentiation between ALA and EPA/DHA on food labels, along with legislative development around the use of transgenic oils in the food supply.

The symposium speakers identified key research and implementation priorities, which are summarised in Table 2, including under the headings: (1) advance current knowledge around omega-3 intake and status and health and (2) ensure that existing and emerging knowledge is mobilised into population benefit.

Author contributions. E.L., E.McD., A.S., M.H. and A.M.M. organised the symposium, which is the basis of this review article, with E.L., S.S., R.P.H., M.T., A.S., A.S., R.N.M.S., M.H., P.C.C. and A.M.M. presenting at the symposium, and drafting the associated review sections. J.N. and D.I.G. drafted additional review sections. All authors have read and commented on the manuscript and approved the final version.

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Competing interests. A.M.M. has received funding from Abbott Healthcare. J.N. has acted as a consultant for Yield10 Bioscience and BASF and is listed as an inventor on several patent families associated with the production of EPA + DHA in transgenic plants. P.C.C. acts as an *ad hoc* consultant/advisor to BASF, Danone Nutricia Research, dsm-firmenich, Bunge, Fresenius-Kabi, B. Braun Melsungen, Nestle, Baxter Healthcare, Abbott Nutrition, Haleon and Natures Crops, and has received speaking honoraria from Fresenius-Kabi, Abbott Nutrition and Eology. E.L. and E.McD. are employed by Humanativ Ltd. Humanativ is a fully owned subsidiary of Mara Renewables Corporation. S.S. worked as a nutrition scientist at the British Nutrition Foundation at the time of the symposium (information about the Foundation's activities and funding can be found at <https://www.nutrition.org.uk/aboutbnf/>). M.S. was employed by Devenish Nutrition Ltd. at the time of the symposium <https://www.devenishnutrition.com/>.

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