**𝛼-linolenic acid interconversion is sufficient as a source of longer chain ω-3 polyunsaturated fatty acids in humans: An opinion**

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**Abstract**

α-linolenic acid (αLNA) conversion into the functionally important ω-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been regarded as inadequate for meeting nutritional requirements for these PUFA. This view is based on findings of small αLNA supplementation trials and stable isotope tracer studies that have been interpreted as indicating human capacity for EPA and, in particular, DHA synthesis is limited. The purpose of this review is to re-evaluate this interpretation. Markedly differing study designs, inconsistent findings and lack of trial replication preclude robust consensus regarding the nutritional adequacy of αLNA as a source of EPC and DHA. The conclusion that αLNA conversion in humans is constrained is inaccurate because it presupposes the existence of an unspecified, higher level of metabolic activity. Since capacity for EPA and DHA synthesis is the product of evolution it may be argued that the levels of EPA and DHA it maintains are nutritionally appropriate. Dietary and supra-dietary EPA plus DHA intakes confer health benefits. Paradoxically, such health benefits are also found amongst vegetarians who do not consume EPA and DHA, and for whom αLNA conversion is the primary source of ω-3 PUFA. Since there are no reported adverse effects on health or cognitive development of diets that exclude EPA and DHA, their synthesis from αLNA appears to be nutritionally adequate. This is consistent with the dietary essentiality of αLNA and has implications for developing sustainable nutritional recommendations for ω-3 PUFA.

KEYWORDS

𝛼-linolenic acid, omega-3, vegetarian, polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid

 Abbreviations: αLNA, 𝛼-linolenic acid, DHA, docosahexaenoic acid, DPAω-3, docosapentaenoic acid ω-3, EFA, essential fatty acids, EPA, eicosapentaenoic acid, *ELOVl*, elongase, *FADS*, fatty acid desaturase, LA, linoleic acid, PUFA, polyunsaturated fatty acids, RR, relative risk, SDA, stearidonic acid, SNPs, single nucleotide polymorphisms, TPN, total parenteral nutrition,

**INTRODUCTION**

Omega-3 (ω-3) polyunsaturated fatty acids (PUFA) are a group of fatty acids that share the presence of a double bond three carbon atoms from the methyl terminus, but differ in the length and unsaturation of the hydrocarbon chain, typically between 18 and 22 carbon atoms in length with between 3 and 6 methylene interrupted double bonds all in the *cis* orientation (Burdge and Calder, 2015). The membrane phospholipids of human tissues are characterised by the presence of differing amounts of the four main ω-3 PUFA; namely, α-linolenic acid (αLNA, 18:3ω-3), eicosapentaenoic acid (EPA, 20:5ω-3), docosapentaenoic acid (DPAω-3, 22:5ω-3) and docosahexaenoic acid (DHA, 22:6ω-3) (Arterburn *et al.*, 2006). Where present, DHA is the predominant ω-3 PUFA in human tissues with smaller amounts of DPAω-3 > EPA > αLNA (Arterburn *et al.*, 2006). DHA is particularly enriched, but EPA is almost undetectable, in tissues that exhibit a high degree of membrane fluidity such neurones and synapses where it facilitates conduction of the electrical current and secretion of neurotransmitters, respectively (Bazan and Scott, 1990). DHA accounts approximately 70% of total fatty acids in retinal membranes which include domains that contain didocosahexaenoyl phospholipid molecular species that are required for optimal rhodopsin activation (Bazan and Scott, 1987). In contrast, αLNA and EPA are almost undetectable in these tissues and each typically account for less than 1% of total fatty acids in most cell types. ω-3 PUFA are minor components of adipose tissue triacylglycerol (TAG) where they account for less than 0.2% of total fatty acids (Walker *et al.*, 2014; Arterburn *et al.*, 2006).

**Membrane and non-membrane functions of ω-3 polyunsaturated fatty acids**

The proportions of individual PUFA in membrane phospholipids can influence cell function by maintaining the homeoviscosity of the phospholipid bilayer (Ernst *et al.*, 2016; Pamplona et al., 2002) which enables conformational changes and protein-protein interactions of integral proteins (Calder *et al.*, 1994b; Bennett and Mitchell, 2008; Mitchell *et al.*, 2012).

 The relative proportions of individual PUFA can also modulate cell function by influencing the pattern of lipid second messengers produced in response to stimulation including oxylipins such as eicosanoids and leukotrienes (Wada *et al.*, 2007), and phospholipid-derived mediators, for example diacylglycerol (Kamiya *et al.*, 2016) and phosphatidic acid (Heung and Postle, 1995a, 1995b). EPA and DHA are substrates for synthesis of specialised pro-resolving mediators that are important for immune homeostasis (Calder, 2017; Ferreira *et al.*, 2022). Moreover, ω-3 PUFA can influence transcription by acting as ligands for transcription factors, for example the peroxisome proliferator-activated receptor (PPAR) family (Forman *et al.*, 1997), and by modifying epigenetic processes (Burdge and Lillycrop, 2014; Perez-Mojica *et al.*, 2020). One possible explanation for differences between cell types in the ω-3 PUFA content of cell membranes is to maintain an optimal environment for integral proteins and an appropriate substrate pool for the synthesis of lipid second messengers. Therefore, cells require a timely and adequate supply of specific PUFA for incorporation into membranes in order to maintain optimal function.

**Dietary and supra-dietary intakes of EPA and DHA are associated with specific health benefits**

There is compelling evidence that consumption of EPA and DHA can ameliorate risk of some non-communicable diseases (Calder, 2017). However, the intakes of EPA plus DHA that are required to achieve such benefits typically exceed the habitual intakes of most high income countries (Givens and Gibbs, 2008). The causal role of EPA and DHA in such health benefits is demonstrated by the efficacy of purified pharmaceutical preparations of ω-3 PUFA (Kar, 2014). Although intakes of EPA and DHA in quantities needed to produce health benefits are unlikely to be achieved through the diet in most populations, with the exception of specific ethic groups such as the North Greenland Innuit (Bang *et al.*, 1980) and the Japanese (Kuriki *et al.*, 2003). Cardiovascular disease risk has also been shown to be related inversely to habitual intakes of EPA plus DHA in high income countries (Hu and Willett, 2002). For example, a pooled analysis of 17 prospective cohort studies involving 42,466 individuals found a significant inverse relationship between the levels of EPA plus DHA, but not αLNA, in blood and risk of all cause and cardiovascular mortality (Harris *et al.*, 2021).

 In the context of such findings, the Governments of the UK and other countries, and a number of authoritative organisations have published recommendations that adults should consume at least 250 mg/d of EPA plus DHA (Scientific Advisory Committee on Nutrition, 2004; Kris-Etherton *et al.*, 2002), while the US Institute of Medicine, Food and Nutrition Board recommended that those who are at increased risk of cardiovascular disease consuming 1.6g/d total ω-3 PUFA (Institute of Medicine, 2005). However, such recommendations are largely ineffective in improving EPA plus DHA intakes (Givens and Gibbs, 2008). For example, less than one third of UK adults who eat fish consume oily fish (Givens and Gibbs, 2008). Consequently, it has been estimated that most UK adults consume less than 50% of the recommended daily amount of EPA plus DHA, and consumption of these ω-3 PUFA by children may be only 1/10th of that reported for adults (Givens and Gibbs, 2008; Givens, 2006). The main barriers to meeting recommended intakes of EPA and DHA have been identified to include the financial cost and perceived unpalatability of oily fish, concerns about contamination with environmental contaminants, and dietary choices that exclude animal-derived foods (Givens, 2006; Givens and Gibbs, 2008). Therefore, there is a need for alternative, widely accepted, sustainable and scalable sources of ω-3 PUFA.

**The dietary essentiality of α-linolenic acid**

αLNA and linoleic acid (LA, 18:2ω-6) are the only PUFA that are essential in the human diet and exclusion of these fatty acids can result in a specific deficiency disease (Holman *et al.*, 1979). The dietary essentiality of LA and αLNA was first demonstrated in rats fed a fat-free diet (Burr and Burr, 1929) which developed a range of symptoms including dermatitis and increased skin permeability, loss of muscle tone, necrosis of the tail, kidney and lung degeneration, raised metabolic rate and electrocardiographic changes (Wheeler *et al.*, 1975). These findings have been replicated in several subsequent rodent studies (Holman, 1971). Similar findings have been reported in studies of non-human primates fed diets lacking αLNA Fiennes *et al.* 1973; Anderson *et al.* 2005). However, the study designs do not exclude the possibility that at least some symptoms could have been caused by a deficiency of fat soluble vitamins. The dermatitis induced by αLNA deficiency may, at least in part, be caused by impaired αLNA accumulation in skin (Fu and Sinclair, 2000; Salem *et al.* 2015; Wheeler *et al.*, 1975).

**EFA deficiency in adult humans receiving total parenteral nutrition**

The evidence for the essentiality of αLNA and LA in the human diet is less robust than for laboratory animals because humans are rarely exposed to the extreme nutritional deprivation used to generate essential fatty acid (EFA) deficiency symptoms in small animal models (Burr and Burr 1929) and non-human primates (Anderson *et al.*, 2005). There is currently no evidence of symptomatic EFA deficiency in the general adult human population, at least in high income countries (Rivers and Frankel, 1981). The direct evidence for the essentiality of αLNA in adult humans is based primarily on the findings of case studies of individuals receiving poor quality total parenteral nutrition TPN) (Hamilton *et al.*, 2006; Mogensen, 2017) which were open to confounding by coincidental low intakes of other nutrients, in particular fat soluble vitamins (Vinton *et al.*, 1990). Collins *et al*. (1971) described EFA deficiency symptoms that included dermatitis accompanied by raised (10 %) 20:3ω-9 concentration in a man who had undergone intestinal resection and was subsequently maintained using fat-free parenteral nutrition for 100 days (Collins *et al.*, 1971). The addition of soybean oil to the parenteral feed, which provided 23g/day LA and an undisclosed amount of αLNA, increased the proportion of arachidonic acid (20:4ω-6) in total plasma lipids, reduced the total circulating triacylglycerol (TAG) concentration in blood to within the normal range and improved skin lesions around the stoma.

Experimental evidence to support the essentiality of LA and αLNA in humans is limited to one report that described induction of EFA deficiency, characterised by dermatitis and a raised serum triene : tetraene (primarily 20:3ω-9 : 20:4ω-6) ratio, by administration of fat-free parenteral nutrition to 28 surgical patients who were aged from infancy to 66 years (O'Neill *et al.*, 1977). The findings showed that the older individuals took longer to develop deficiency symptoms than in the younger patients, which suggests children have a greater EFA requirement than adults, possibly to support growth and development (Holman, 1971). Administration of Intralipid containing both αLNA and LA, reversed the biochemical changes and dermatological symptoms (O'Neill *et al.*, 1977). However, there are no studies that distinguish between αLNA and LA deficiency in adult humans, due, at least in part, to the presence of both EFA in most dietary sources, albeit in differing ratios.

**EFA deficiency in human infants**

EFA deficiency disease has been reported in human infants fed formula milk containing different types of fat. Those fed milk with the lowest LA content developed dermatitis accompanied by a raised triene : tetraene ratio in blood, which were reversed by LA supplementation (Hansen, 1963). These biochemical changes were reversed by standard milk formula that contained both LA and αLNA (Paulsrud, 1972) which supports the view that αNLA is sufficients as a sources of ω-3 PUFA for infants, which is not refuted by the suggestion that DHA may be conditionally essential for very low birthweight preterm infants (Makrides M, Uauy, 2014). Rather it may be antcipated that extremely immature liver would be less able to meet whole body demands for DHA than the more developed organ. Infants maintained by fat-free TPN also developed biochemical changes considered to be indicative of EFA deficiency characterised by dermatitis and a serum phospholipid 20:3 : 20:4 ratio of 18 (Paulsrud, 1972; Holman *et al.*, 1979), while EFA replete infants had a 20:3 : 20:4 ratio < 0.2 (Holman *et al.*, 1979). Holman *et al*. described a 6 year old female maintained with TPN containing a LA : αLNA ratio of 115 : 1 who developed neurological symptoms including numbness, paraesthesia, weakness, inability to walk and leg pain, and blurred vision that were reversed by reducing the LA : αLNA ratio to 11 : 1 (Holman *et al.*, 1982) which is similar to the relative LA and αLNA intakes in some European countries (Burdge and Calder, 2005). Others have also reported neurological symptoms in a patient receiving TPN, although the diagnosis of αLNA deficiency may have been confounded by the presence of other nutrient deficiencies (Meng, 1983).

**Conversion of α-linolenic acid into EPA and DHA in humans**

 The precise metabolic basis of αLNA essentiality has not yet been explained, but suggests a significant physiological function, that is analogous to a vitamin (Taylor, 1972). However, this is unlikely to the dietary essentiality of αLNA is due entirely to any influence on the hoemeoviscosity of cell membranes because of the relatively low proportion of αLNA in the lipid bilayer compared to other ω-3 PUFA, or to its conversion to immunomodulatory hydroxyoctadecatrienoic acids in some leukocytes (Kumar *et al.*, 2016). Therefore, the dietary essentiality of αLNA probably lies in its conversion to longer chain ω-3 PUFA with critical biological functions, namely EPA, DPAω-3 and DHA, by a pathway involving a series of mostly alternating desaturation and carbon chain elongation reactions that were first described in rat liver (Voss and Sprecher, 1988; Voss *et al.*, 1991). Briefly, in the canonical PUFA synthesis pathway (Figure 1) the first reaction, which is considered rate limiting (Sprecher, 2000), is catalysed by Δ6 desaturase (encoded by the *FADS2* gene) which inserts a double bond at the Δ6 position of αLNA to yield stearidonic acid (SDA, 18:4ω-3). This is followed by addition of 2 carbon atoms by elongase-5 (encoded by *ELOVL5*) to form 20:4ω-3 and desaturation by Δ5 desaturase (encoded by *FADS1*) to form EPA. Two further chain elongation cycles are catalysed by elongase-5 and/ or elongase-2 (encoded by the *ELOVL2* gene) which produce DPAω-3 and 24:5ω-3, respectively. Δ6 desaturase also catalyses the conversion of 24:5ω-3 to 24:6ω-3, which is translocated from the endoplasmic reticulum where the preceding reactions take place, to peroxisomes where DHA is formed by removal of 2 carbon atoms by a single cycle of fatty acid 𝛽-oxidation. The reactions downstream of the second Δ6 desaturation have been suggested to regulate DHA synthesis independent of the preceding reactions (Sprecher, 2000). However, the final Δ6 desaturation and 𝛽-oxidation reactions remain a matter for debate since Δ6 desaturase can also catalyse Δ4 desaturation of DPAω-3 to DHA, thus circumventing the synthesis of 24:5ω-3 and 24:6ω-3, translocation of 24:6ω-3 from the endoplasmic reticulum to peroxisomes and the peroxisomal 𝛽-oxidation step, at least in some human cell types (Park *et al.*, 2015). However, the importance of the translocation from the endoplasmic reticulum to peroxisomes and peroxisome 𝛽-oxidation is supported by the finding that patients with peroxisomal disorders including Zellweger’s disease, X-linked adrenoleukodystrophy and adrenomyeloneuropathy have substantially lower levels of DHA in their blood and tissues than healthy omnivore controls (Martinez *et al.*, 1994; Martinez, 2001). Moreover, peroxisomal straight-chain acyl-coA oxidase and D-bifunctional protein are required for DHA synthesis (Su *et al.*, 2001).

**Capacity for synthesis of longer chain ω-3 PUFA from α-linolenic acid in humans**

The liver is the primary organ responsible for PUFA synthesis (Cho *et al.*, 1999a), which represents a technical challenge for the measurement of human PUFA synthesis *in vivo*. The capacity for conversion of αLNA to longer chain ω-3 PUFA has been estimated by dietary supplementation or intervention trials that measured changes in the levels of longer chain ω-3 PUFA in blood and/or cell lipids (Table 1) and tracer studies which measured enrichment stable isotopes in ω-3 PUFA in plasma after consumption of a bolus of [13C]-labelled or deuterated αLNA (Table 2).

**α-linolenic acid dietary supplementation trials**

A review of findings of 38 dietary supplementation trials in which men and / or postmenopausal women consumed between 0.5 g / day and 20 g / day αLNA provided in seed oils or seeds for differing periods of time showed the amounts of EPA and DPAω-3 in individual plasma lipid classes or erythrocyte phospholipids increased in proportion to αLNA intake (Baker *et al.*, 2016). However, 50% of these studies reported a decrease in the proportion of DHA in blood or cellular lipids at the end of the supplementation period compared to baseline, 18% of studies showed no change in DHA level at the end of the supplementation period, while the remaining trials showed a modest increase in DHA content. One study showed that dietary supplementation with either αLNA, stearidonic acid (SDA, 18:4ω-3) or EPA increased the proportions of EPA and DPAω-3 in plasma phospholipids, but were associated with a lower DHA level (James *et al.*, 2003), while another trial reported a small increase in blood DHA level following SDA supplementation (Miles *et al.*, 2004). Rodent feeding trials suggest that because Δ6 desaturase catalyses both the desaturation of αLNA to SDA and 24:5ω-3 to 24:6ω-3, increased αLNA intake may outcompete 24:5ω-3 for Δ6 desaturase activity at the third desaturation reaction and so reduce the formation of 24:6ω-3 and consequently DHA (Gibson *et al.*, 2013) (Figure 1). Whether this occurs in humans is not known. Optimal DHA synthesis in rodents occurred over a narrow range of LA : αLNA and total PUFA intakes which is consistent with competition between LA and αLNA for Δ6 desaturase activity (Gibson *et al.*, 2013).

Further assessment of these trials plus additional studies published between 1999 and 2016 that reported baseline and end of supplementation EPA, DPAω-3 and DHA levels show that 16/39 articles (41%) reported an increase in the level of DHA, 2 studies reported no change and 21/39 studies (53%) showed a decrease in DHA (Table 1). Of the studies that reported a change in the level of DHA, only 1/19 reported the change as statistically significant (Ristic-Medic *et al.*, 2014) (Table 1). It is also notable that the study designs differed such that no two trials were directly comparable to each other and, to date, none of these studies have been replicated in a second cohort. The main differences between trials in study design include the amount of the αLNA supplement consumed and its physical form, the duration of the intervention, the sex and age of the trials participants, and the background diet (omnivorous or vegetarian) (Table 1). Almost one third of these studies (29%) involved fewer than ten participants in the active arm of the trial (Table 1) and, therefore, may have been underpowered. Some studies reported the level of DHA in whole plasma or serum, while others analysed specific plasma lipid classes, typically phospholipids (Table 1). Therefore, the findings of dietary supplementation trials are not sufficiently robust to support a consensus view regarding capacity of humans to synthesise DHA from αLNA.

***Stable isotope tracer studies***

The findings of the nine stable isotope tracer studies reported to date in which human volunteers consumed a bolus of [13C] or deuterated αLNA followed by measurement of labelled EPA, DPAω-3 and DHA in blood as a gross proxy measure of hepatic PUFA biosynthesis broadly support those of the dietary supplementation studies (Table 2) in that, irrespective of the background diet, they all showed stable isotope enrichment of EPA and DPAω-3, and 8/9 studies reported DHA synthesis (Table 2). However, the estimated fractional conversion differed markedly between studies. For example, conversion of αLNA to EPA in men has been estimated to be 8.0% (Burdge *et al.*, 2002; Emken *et al.*, 1994) based on relative area under the concentration – time curve or 0.2% calculated by kinetic modelling (Pawlosky *et al.*, 2001). One study in young men consuming their habitual diet reported stable isotope enrichment of DHA as below the limit of quantification (Burdge *et al.*, 2002). Conversion of αLNA to DHA in men has been estimated to be between below the limit of detection (Burdge *et al.*, 2002; Hussein *et al.*, 2005), 0.05% (Pawlosky *et al.*, 2001) or 4% (Emken *et al.*, 1994) of amount of labelled αLNA consumed (Table 2). The background diet was controlled or adjusted in 4/9 studies (Table 2) such that higher LA or EPA+DHA intakes reduced stable isotope enrichment of longer chain ω-3 PUFA in blood, while consuming 9.5 αLNA/ d compared to 4.5 αLNA/ d did not increase stable isotope enrichment of longer chain ω-3 PUFA in middle aged men (Burdge *et al.*, 2003) and there was no significant effect of increasing αLNA intake the on the proportion of labelled αLNA that was recovered on breath over the first 24 h (approximately 34%) (Burdge *et al.*, 2003). These findings suggest that the positive relationship between αLNA intake and EPA and DPAω-3 levels in blood was not due to increased long-chain PUFA synthesis or lower αLNA partitioning towards 𝛽-oxidation, but could be explained by reduced flux through the reactions upstream of the second Δ6 desaturation exceeding the capacity of the remaining steps, possibly due to competition between αLNA and 24:5ω-3 for Δ6 desaturase (Figure 1) in agreement with the suggested explanation for the inverse relationship between αLNA intake and blood DHA concentration in some studies (Gibson *et al.*, 2013).

 Extrapolating measurements of labelled PUFA in blood to estimate fractional conversion by the liver is, at best, imprecise and the values cannot be relied upon as accurate quantitative measures of the activity of the hepatic PUFA synthesis pathway (Burdge, 2004). Such imprecision is compounded by marked differences in study design, such as the age and sex distribution of the participants, whether or not the background diet was controlled, the lipid pools that were sampled, the duration of sampling, and the method used to calculate conversion. However, when studied using the same experimental and analytical protocols, the proportion of labelled αLNA converted to EPA and DHA was greater in women than men (Burdge *et al.*, 2002; Burdge and Wootton, 2002b). Furthermore, infusion of premenopausal women with unesterified [d5]-αLNA to achieve a steady state concentration in blood to avoid any confounding effects of a test meal, but of less relevance to nutrition than the meal-based models reported use in other studies (Table 2), found DHA synthesis rates (Lin *et al.*, 2018) that were similar to those reported in rats (Rapoport *et al.*, 2010), and may be sufficient to meet the demands of the adult human brain for DHA, which have been estimated to be approximately 2.4 – 3.8 mg/day (Umhau *et al.*, 2009; Domenichiello *et al.*, 2014, 2015).

Therefore, both the findings of dietary supplementation trials and stable isotope tracer studies reported to date do not support the conclusion that humans have limited capacity to convert αLNA to EPA and DPAω-3, and little ability to synthesise DHA (Plourde and Cunnane, 2007; Burdge, 2004), and that consumption of preformed EPA and DHA is required in order to meet demands (Baker *et al.*, 2016; Brenna *et al.*, 2009). Synthesis of EPA and DHA at a level that contributes significantly to meeting demands for these PUFA is consistent with the dietary essentiality of αLNA.

**Polymorphisms in genes associated with PUFA synthesis alter levels of longer chain PUFA in blood and tissue lipids**

A number of polymorphisms have been identified in the *FADS1*/*FADS2* gene cluster that are associated with the levels of specific longer chain PUFA in blood or tissues (Minihane, 2016; Lattka *et al.*, 2010b). For example, one study found that the minor alleles of eleven single nucleotide polymorphisms (SNPs) in the *FADS1*/*FADS2* were associated with higher proportions of αLNA and lower proportions of EPA and DPAω-3, but not DHA, in serum phospholipids from 727 adults (Schaeffer *et al.*, 2006). Two of the eleven SNPs, rs3834458 and rs968567, are located in the *FADS2* promotor and have been shown directly to alter gene transcription (Lattka *et al.*, 2010a) Malerba *et al.* also found in a smaller cohort that SNPs in the *FADS1*/*FADS2* cluster were associated with a higher proportion of αLNA in blood, but were not related to EPA or DHA levels (Malerba *et al.*, 2008) while others have shown that polymorphisms in the *FADS1 /* *FADS2* cluster are associated with the levels of EPA and DHA in blood cells (Lattka *et al.*, 2010b). Furthermore, polymorphisms in *ELOVL2* have been associated with higher levels of EPA and DPAω-3 and a lower proportion of DHA in serum (Lemaitre *et al.*, 2011). Overall, these findings support the suggestion that hepatic αLNA conversion is an important source of blood and cellular EPA and DHA. None of the αLNA supplementation trials or tracer studies reported to date determined the genotype of the participants.

**αLNA conversion in adult humans; restricted or what is required?**

The findings of dietary supplementation trials and experiments using stable isotope tracers have been interpreted as indicating that humans are ‘poor’ converters of αLNA (Plourde and Cunnane, 2007; Burdge, 2004), in particular with respect to DHA synthesis. The use of the terms ‘poor’, constrained or ‘limited’ (Plourde and Cunnane, 2007; Burdge, 2004), severely ‘restricted’(Gerster, 1998) to describe PUFA synthesis in humans presupposes that the level of conversion should be greater, but what this higher level should be as not been defined and is potentially misleading. It cannot be argued that synthesis of longer chain ω-3 PUFA in rodents, which appears to be more efficient than in humans (Voss *et al.*, 1991), is indicative of optimal capacity for conversion because of differences between species in life course history (Hulbert,2008; Hulbert *et al.* 2007) and associated nutritional demands. Rather, capacity for hepatic αLNA conversion in humans is better considered as a product of an evolutionary history and, therefore, nutritionally adequate. This conclusion is supported by the findings of studies of the impact on health of diets that exclude foods that contain EPA and DHA.

**Ω-3 polyunsaturated fatty acids and vegetarian diets**

EPA, DPAω-3, DHA are obtained predominantly from foods of animal origin (Baker *et al.*, 2016) and, therefore, individuals who practice dietary choices that exclude animal-derived foods do not consume these ω-3 PUFA (Welch *et al.*, 2010; Chamorro *et al.*, 2020a). Diets that are broadly classified as vegetarian differ in the extent to which animal-derived foods are consumed, while vegan diets exclude all animal-derived foods (Tonstad *et al.*, 2009). The term vegetarian is used here to capture all dietary choices that completely exclude animal-derived foods. A systematic review of 141 studies found that αLNA intakes were similar in omnivores, vegetarians who occasionally consumed meat or fish, and vegans (Neufingerl and Eilander, 2021). EPA and DHA intakes were essentially undetectable in vegans (Neufingerl and Eilander, 2021) which is consistent with the findings of previous detailed dietary analyses (Welch *et al.*, 2010; Chamorro *et al.*, 2020a). Therefore, vegetarian diets may serve as a ‘natural experiment’ to test whether consuming αLNA as the predominant ω-3 PUFA (most studies do not report SDA or 16:3ω-3 intakes or tissue levels), can maintain blood and tissue EPA and DHA levels that are sufficient for health.

Vegetarian diets are associated consistently with lower levels of EPA and DHA in blood lipids from men and women (Chamorro *et al.*, 2020a; Welch *et al.*, 2010; Burdge *et al.*, 2017; Sarter *et al.*, 2015; Kornsteiner *et al.*, 2008; Neufingerl and Eilander, 2021; Chamorro *et al.*, 2020b) (Table 3), and a lower ω-3 index score (Sanders, 2009; Kornsteiner *et al.*, 2008; Harris and Von Schacky, 2004) compared with omnivores. However, EPA and DHA concentrations in blood and cells from vegetarians are consistently greater than zero (Table 3), despite these fatty acids being absent from the diet (Sanders and Reddy, 1992; Welch *et al.*, 2010; Neufingerl and Eilander, 2021).

Increased blood and tissue docosapentaenoic acid (ω-6) (22:5ω-6, DPAω-6) levels have been found in animal models of severe nutritional deprivation (Reisbick *et al.* 1990, 1994; Bourre *et al.* 1989; Connor *et al.* 190) and in human infants fed milk formulae lacking preformed DHA (Farquharson *et al.* 1995), and has been suggested to be a marker of inadequate body levels or intakes of ω-3 PUFA. This increase in the level DPAω-6, probably reflects reduced competition between ω-3 and omega-6 PUFA for the enzymes of the PUFA synthesis pathway. Although reported rarely, the level of DPAω-6 in blood phospholipids from adult vegetarians has been found not to differ significantly from omnivores (Li *et al.* 1999; Lee *et al.* 200; Huang *et al.* 2013). Moreover, the level of DPAω-6 in umbilical cord artery plasma phospholipids was found to be almost significantly greater (46%) greater in omnivore and vegan pregnancies. Moreover, the DPAω-6 level in erythrocytes from infants breast-fed by vegan mothers was similar to those fed breast milk from omnivorous mothers, and those fed milk formulae Sanders and Reddy, 1992). These observations are in agreement with the suggestion that αLNA conversion contributes significantly to maintaining adeqaute tissue and blood longer chain ω-3 PUFA levels.

This is also consistent with the findings of studies that show polymorphisms in genes involved in the PUFA synthesis pathway can be related to the ω-3 PUFA concentrations in blood (Lattka *et al.*, 2010a; Minihane, 2016). Furthermore, an insertion/deletion mutation (rs66698963) in the *FADS2/FADS1* clusterthat is associated with higher Δ5 desaturase activity, has been found to occur with greater frequency in some populations that have consumed a vegetarian diet over many generations compared with populations that are habitually omnivorous (Kothapalli *et al.*, 2016). However, the findings of two out of the three trials that investigated αLNA supplementation of vegetarians (Fokkema *et al.*, 2000; Li *et al.*, 1999) do not indicate greater capacity for EPA and DHA synthesis than in omnivores, despite lower levels of EPA and DHA that may reduce αLNA conversion by feedback inhibition or up-regulation of the PUFA synthesis pathway to compensate for lack of preformed dietary EPA and DHA.

**αLNA-based diets and cardiovascular outcomes**

Since blood and/or cell EPA and DHA levels can be associated with health benefits, it may be anticipated that consuming plant-based diets that exclude these ω-3 PUFA would be detrimental to health. However, the findings of epidemiological studies show that diets which exclude animal-derived foods are associated with specific health benefits, including reduced risk of cardiovascular disease (Albert *et al.*, 2002; Craig, 2009; Key *et al.*, 2006) and stroke (Chiu *et al.*, 2020) similar to those linked to higher EPA plus DHA levels or intakes; Coronary heart disease has been found to be reduced by 24% in life-long vegetarians compared to matched meat-eaters (Thorogood *et al.*, 1987), and fatal and noω-fatal ischemic heart disease to be reduced by between 24% to 32% compared to omnivores (Crowe *et al.*, 2013; Key *et al.*, 1999). A systematic review of 13 prospective studies of the effects of vegan diets on health outcomes amongst Adventists communities in North America also found that consuming a plant-based diet was associated a modest overall reduction in cancer risk, and 25% lower risk of type 2 diabetes mellitus and 55% lower risk of hypertension compared to omnivores (Le and Sabate, 2014). Moreover, LDL-cholesterol concentration was found to be lower in 10 year old vegan children than in omnivore children (Desmond *et al.*, 2021). In contrast, the effectiveness of αLNA supplementation trials in reducing risk of cardiovascular disease are uncertain. A systematic review of 76 randomised controlled αLNA supplementation trials involving 112,059 participants found evidence of a modest reductions in cardiovascular events (relative risk (RR) 0.95), coronary heart disease mortality ((RR 0.95) and arrhythmia (RR 0.79) with no effect on cardiovascular mortality or coronary heart disease events (Abdelhamid *et al.*, 2018). One randomised controlled trial showed that consuming 30g of milled flaxseed, αLNA intake was not reported, for 6 months increased plasma αLNA, but not DHA, concentrations and reduced blood pressure reduced systolic blood pressure in patients with moderate hypertension by approximately 15mmHg, while systolic blood pressure increased in the placebo group, (Rodriguez-Leyva *et al.*, 2013) by an αLNA-mediated mechanism involving altered plasma oxylipin concentrations (Caligiuri *et al.*, 2014). These findings are supported by a meta-analysis of 15 randomised flaxseed supplementation trials involving 1,303 participants that showed a significant reduction in systolic and diastolic blood pressure in patients with hypertension (Ursoniu *et al.*, 2016).

Compared with the findings of epidemiological studies, the effect of αLNA supplementation on cardiovascular disease outcomes show relatively modest benefits (Sala-Vila *et al.*, 2022). Typical habitual intakes of αLNA, at least in high income countries, are approximately 0.5 to 2.3 g/ day (Baker *et al.*, 2016) which is similar to the suggested optimal αLNA intake to ameliorate risk of cardiovascular disease of 2 g / day (de Lorgeril and Salen, 2004). If, so there may be little capacity for further reduction in cardiovascular disease risk by increasing αLNA intake.

**αLNA-based diets during pregnancy and childhood cognitive development**

Adequate accumulation of DHA by the fetal central nervous system is important for optimal development and function (Innis, 1991). Fetal and infant demands for DHA are considered to be met primarily by the supply of preformed DHA from the mother via the placenta or in breast milk, respectively (Herrera *et al.*, 2006). Interruption of placental supply by premature birth or feeding milk formula lacking DHA can induce deficits in DHA accumulation in fetal brain and retina that impair function, albeit transiently (Molloy *et al.*, 2012; Farquharson *et al.*, 1995). Persistent deficits in neurological function have also been induced in the offspring of non-human primates that were exposed to extreme deprivation of ω-3 PUFA by feeding diets lacking αLNA as well as EPA and DHA during pregnancy (Anderson *et al.*, 2005; Connor *et al.*, 1990; Reisbick *et al.*, 1990, 1994).

Vegetarianism during pregnancy has been associated with approximately 50% lower levels, compared to omnivores, of DHA in maternal blood (Crozier *et al.*, 2018) and breast milk, and in erythrocytes from 3 month old infants (Sanders and Reddy, 1992). Nevertheless, neither consuming a vegetarian diet during pregnancy nor blood DHA concentration during pregnancy in vegetarian women are associated with reduced cognitive function in mid-childhood (Crozier *et al.*, 2018; Crozier *et al.*, 2019) This is consistent with studies that reported that there was no significant relationship between maternal DHA intake or blood levels in omnivorous women during pregnancy and measures of cognitive function and patterns of behaviour in children. Moreover, the findings of a systematic review of 44 studies involving 106,237 mother-offspring pairs found no strong evidence for a beneficial effect of higher seafood consumption during pregnancy on neurocognitive outcomes in the children (Hibbeln *et al.*, 2019). The apparent discrepancy between apparently normal cognitive function in the children of mothers who were vegetarian during pregnancy and the requirement of DHA to support neurological development may be explained, at least in part, by maternal physiological adaptations to lipid metabolism (Postle *et al.*, 1995;Herrera, 2000) which preceed the peroid of rapid DHA accumulation into fetal brain (Kupiers *et al*. 2012) higher DHA levels in blood and greater capacity for DHA synthesis in women than men (Bakewell *et al.*, 2006; Burdge and Wootton, 2002a, 2003; Giltay *et al.*, 2004), increased activity the of the PUFA synthesis pathway in pregnancy under the control of female sex hormones (Childs *et al.*, 2012; Sibbons *et al.*, 2014; Meyer *et al.*, 2016; Oscarsson *et al.*, 1988; Oscarsson and Eden, 1988), placental ‘biomagnification’ of DHA (Yamada *et al.*, 2019; Hanebutt *et al.*, 2008), brain-sparing adaptations to fetal blood flow (Ebbing *et al.*, 2009) and by specific polymorphisms in genes that encode enzymes involved in PUFA synthesis in some populations (Joshi *et al.*, 2019) that potentially protect DHA supply to the developing nervous system irrespective of maternal intake of preformed DHA.

 One possible additional source of DHA for the developing brain is synthesis from αLNA by the fetus. The liver of human infants who are born preterm, which is a proxy for fetal metabolism *in utero*, can convert αLNA to DHA (Mayes *et al.*, 2006; Lin *et al.*, 2010), although this ability declines with increasing gestational age at birth (Mayes *et al.*, 2006; Uauy *et al.*, 2000). Whether fetal hepatic αLNA conversion contributes significantly to meeting the demands of fetal tissues for DHA *in utero* is not known. The finding that EFA deficiency symptoms in these infants can be reversed by providing a source of αLNA (Paulsrud, 1972) suggests that fetal capacity for EFA conversion could be a quantitatively important source of longer chain ω-3 PUFA during development. However, any capacity for EPA and DHA synthesis in preterm infants may reflect a response to the challenge of early transition to *ex-utero* life and cessation of placental PUFA supply rather than the normal physiological function of the fetus *in utero*. However, DHA concentration in the non-esterified fatty acids and cholesteryl esters from umbilical venous blood is higher than in umbilical arterial blood (Lewis *et al.*, 2011) which suggests any contribution of fetal hepatic DHA synthesis to meeting fetal demands is less than placental supply, at least during late gestation.

Overall, these findings support the view that humans can develop and remain healthy in the absence of maternal intakes of pre-formed EPA and DHA during pregnancy.

**Non-hepatic PUFA biosynthesis**

PUFA biosynthesis or the mRNA expression of genes that encode key enzymes involved in this pathway has been reported in several non-hepatic tissues (Burdge, 2019). This suggests an alternative or additional mechanism to hepatic ω-3 PUFA synthesis for meeting cell-type-specific demands for PUFA. For example, *FADS1* and *FADS2* are expressed in human heart, brain, lung, liver. *FADS2*, but not *FADS1*, is expressed in skeletal muscle, kidney, pancreas and placenta (Cho *et al.*, 1999a; Cho *et al.*, 1999b). PUFA biosynthesis has been reported in human femoral artery (Kelsall *et al.*, 2012) and vascular smooth muscle cells (Irvine *et al.*, 2015), T lymphocytes(von Gerichten *et al.*, 2021), testis (Albert and Coniglio, 1977), vascular endothelial cells (Garcia *et al.*, 1990), astrocytes (Pawlosky *et al.*, 1994) and several neoplastic and non-cancerous mammary epithelial cell lines (Grammatikos *et al.*, 1994a, 1994b; Grammatikos *et al.*, 1995), and can be modulated by sex hormones in some breast cancer cell lines (Park *et al.*, 2021), but not other cell types such as peripheral blood mononuclear cells (Sibbons *et al.*, 2018).

The precise function of αLNA conversion has not been demonstrated in most of the non-hepatic cell types in which this pathway has been reported. However, PUFA biosynthesis has been shown to be involved in phenylephrine-induced vasoconstriction of rat aorta and human femoral artery by a mechanism involving the regulation of intracellular calcium release (Irvine *et al.*, 2015; Kelsall *et al.*, 2012). Non-hepatic PUFA synthesis has probably been studied the most in the immune system. The capacity for αLNA and LA conversion differs between white blood cell types and, in some cases, the activation state of the cells. In some leukocytes the PUFA synthesis pathway is truncated compared to hepatocytes, which suggests longer chain PFA synthesis is limited to specific fatty acids that are required for the function of individual cell types (Chapkin *et al.*, 1988; Anel *et al.*, 1990a; Shires *et al.*, 1989; Calder *et al.*, 1994a; Lonnberg *et al.*, 2013; Ferber *et al.*, 1975; Rode *et al.*, 1982; Szamel *et al.*, 1986; Anel *et al.*, 1990b). Furthermore, in CD3+ T lymphocytes the first reaction in the PUFA synthesis pathway is the addition of 2 carbon atoms by elongase 5 activity instead of Δ6 desaturation (Robichaud *et al.*, 2018; von Gerichten *et al.*, 2021) followed by synthesis of ω-3 PUFA limited to PUFA of 20 carbon atoms in length by the absence of *ELOVL2* expression (Robichaud *et al.*, 2018; von Gerichten *et al.*, 2021) leading to newly assimilated αLNA being utilised preferentially for synthesis of 9- and 13 – hydroxyoctadecatrienoic acids (von Gerichten *et al.*, 2021), probably by lipoxygenase-15 activity (Kumar *et al.*, 2016), compared with longer chain PUFA biosynthesis, (von Gerichten *et al.*, 2021). One possible interpretation is that PUFA biosynthesis, at least in the immune system, can be tailored to fulfil ‘on demand’ cell type-specific functions, which may explain why leukocytes have retained capacity for αLNA conversion despite readily accessible pools of longer chain ω-3 PUFA in blood. It also suggests a mechanism by which cells can ensure their demands for specific PUFA are met independent of dietary supply or hepatic synthesis of longer chain PUFA.

**Implications for dietary recommendations**

Adults in higher income countries, including vegetarians, habitually consume between 0.5 to 2.3 g αLNA / day, accompanied by approximately 10-fold greater LA intake (Baker *et al.*, 2016; Neufingerl and Eilander, 2021) (Table 3). Relatively higher intakes of LA compared to αLNA can reduce the flux of αLNA through the PUFA synthesis pathway by competing for Δ6 desaturase activity (Hussein *et al.*, 2005; Holman *et al.*, 1979). However, in the absence of evidence of specific αLNA-induced deficiency disease in the general adult population, it is plausible that αLNA and LA intakes within these ranges permit sufficient longer chain ω-3 PUFA synthesis to meet the requirements at least of most adults.

**Conclusions**

αLNA has generally been dismissed as a quantitatively significant source of longer chain ω-3 PUFA in humans (Sanderson *et al.*, 2002; Plourde and Cunnane, 2007). This view is based, at least in part, on the findings of relatively small, highly heterogeneous αLNA dietary supplementation or tracer studies, and the observation that EPA and DHA levels in individuals who do not consume these PUFA pre-formed are lower than in omnivores Together these findings have been interpreted as indicating that the capacity of humans for αLNA conversion insufficient for meeting EPA and DHA requirements. Therefore, these PUFA need to be consumed preformed for health and development (Burdge, 2004; Plourde and Cunnane, 2007; Gerster, 1998). To the contrary, plant-based diets that exclude EPA+DHA are not detrimental to health and cognitive development, but instead can confer health benefits similar to those induced by consumption of supra-physiological amounts of EPA+DHA. In contrast, diets that lack αLNA can induce specific deficiency symptoms in a manner analogous to a vitamin (Taylor, 1972). Re-evaluation of the studies published to date suggests an alternative interpretation; that EPA and DHA synthesis as a product of human evolutionary history; in this context, hepatic capacity for αLNA conversion, accompanied by PUFA synthesis in peripheral tissues and metabolic adaptations in response to physiological increases in demands, is can be regarded as appropriate for meeting human EPA and DHA requirements. This interpretation does not negate the utility of preformed EPA and DHA as a means of ameliorating some chronic diseases (Calder, 2017; Innes and Calder, 2020), but has important implications for dietary recommendations regarding habitual consumption of ω-3 PUFA, particularly for population subgroups that avoid animal-derived foods including oily fish (Givens and Gibbs, 2008), and for the preservation of marine ecosystems (Salem and Eggersdorfer, 2015).

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**CONFLICT OF INTEREST**

The author declares no conflict of interest.

**CREDIT AUTHORSHIP CONTRIBUTION STATEMENT**

Graham Burdge alone conceived and wrote the manuscript.

**ETHICS STATEMENT**

No humans or other animals were used in this work.

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**FIGURE** 1 The polyunsaturated fatty acid biosynthesis pathway as described initially in rat liver (Voss *et al.*, 1991). Enzymes are named with their genes in parenthesis. Fatty acids are identified by the positions of *cis* double bonds using the delta system (i.e. from the carboxylic acid group) and structural formulae. The PUFA which are the primary focus of this article are also identified by abbreviated trivial names; αLNA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. The first six reactions take place in the endoplasmic reticulum, followed by translocation to peroxisomes. The dotted arrow indicates the point of putative competition between αLNA and 24:5ω-3 for Δ6 desaturase that may explain the reduction in the amount of DHA in blood lipids in some supplementation trials.

**TABLE 1** α-linolenic acid dietary supplementation trials

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | Participants | Age(years) | n | αLNA intake (g / d) | Supplement | Duration(weeks) | Lipid poolanalysed | Difference from baseline (%) |
|  |  |  |  |  |  | EPA | DPAn-3 | DHA |
|  |  |  |  |  |
|  |  |
|  | Studies in which αLNA supplementation induced an increase in DHA |
|  |
|  |  |  |  |  |  |  |  |  |  |  |
| (Sanders and Younger, 1981) | M + F vegans | 26 - 37 | 4 | 5.5 | Linseed oil | 2 | Plasma PC | 233‡ | NA | 15‡ |
| (Kelley *et al.*, 1993) | M | 21 - 37 | 16 | 20 | Flaxseed oil | 8 | Total serum | 0 | -8 | 3 |
| (Mantzioris *et al.*, 1994) | M | 25 - 44 | 15 | 13.7 | Flaxseed oil + spreadLA : αLNA 0.6 : 1 | 8 | Plasma PL | 140‡ | NA | 14 |
| 15 | 1.1 | Placebo LA : αLNA 18 : 1 | 8 | Plasma PL | -14 | NA | 5.8 |
| (Ezaki *et al.*, 1999) | M+F | 67 - 91 | 28 | 4.2 | Perilla oil | 40 | Total serum | 46‡ | ND | 20 |
| (Bemelmans *et al.*, 2002) | MF | 30 – 70 | 51 | NA | Spread LA : αLNA 187 :1 | 52 | Serum CE | 14 | NA | 57 |
| 51 | 6.3 | Spread LA : αLNA 3:1 | 4 | 34 | NA | 41 |
| 6 | 11 | Flaxseed oil capsules | 4 | Plasma PL | 60‡ | NA | 2 |
| (Wallace *et al.*, 2003) | M | 23 ± 2 | 8 | 0.14 | Placebo: 80:20 palm oil–soyabean oil mix | 12 | Plasma PL | -27 | NA | 8 |
| M+F | 25 – 72 | 29 | 9 | Flaxseed oil spread | 24 | 133‡ | 33‡ | 6 |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| (Harper *et al.*, 2006) | M + F | 49 ± 11 | 27 | 3 | Flaxseed oil | 26 | Total plasma | 60‡ | 20‡ | 8 |
| 53 ± 10 | 22 | 0 | 5.2 g Olive oil | 26 |  | -3 | -12 | -15‡ |
| (Patenaude *et al.*, 2009) | M+F | 57 ± 7 | 92 | 3.8 | Baked goods incorporating wheatgerm | 48 | Total plasma | 78‡ | 22‡ | 23 |
| 18 – 29 | 8 | 6 | Mufﬁns incorporating Ground ﬂaxseeds | 4 | Total plasma | 22 | NA | 10 |
| (West *et al.*, 2010) | M+F | 49 ± 2 | 20 | 15.3 | Walnuts, walnut oil and ﬂaxseed oil | 6 | Total plasma | 50‡ | 17‡ | 6 |
| (Taylor *et al.*, 2010) | M+F T2DM | 52 ± 2 | 9 | 0 | Control: Baked goods without flaxseed or oil | 12 | Total plasma | 0 | 7 | 4 |
| (Chiang *et al.*, 2012) | M+F Hyperlipidaemic | 23 – 65 | 25 | 4.7 | Walnut enriched diet that contained EPA +DHA | 4 | Plasma PL | 10 | 6 | 2 |
| (Pintus *et al.*, 2013) | M + F with Hypercholeserolaemia  | 30 – 60 | 42 | 0.5 | Cheese enriched with αLNA | 3 | Total plasma | 36‡ | NA | 11 |
| (Rodriguez-Leyva *et al.*, 2013) | M+F Peripheral artery disease | 67 ± 8 | 58 | 7 | Baked goods incorporating ﬂaxseeds | 24 | Total plasma | 43‡ | NA | 7 |
| 65 ± 9 | 52 | 0 | Placebo: no flaxseed | 24 | Total plasma | 15 | NA | 3 |
| (Ristic-Medic *et al.*, 2014) | M + F with renal failure | 42 – 64 | 30 | 3 | Sesame/pumpkin/ﬂaxseed mix | 12 | Serum PL | 22‡ | 11‡ | 9‡ |
| (Hennebelle *et al.*, 2016) | M + F | 60 ± 3 | 10 | 2 | Flaxseed oil | 4 | plasma | 40‡ | NA | 6 |
|  |  |  |  |  |  |  |
| Studies in which αLNA supplementation induced a reduction in DHA level |
|  |  |  |  |  |  |  |  |  |  |  |
| (Sanders and Younger, 1981) | M + F omnivores | 23 - 47 | 5 | 5.5 | Linseed oil | 2 | Plasma PC | 108‡ | NA | − 14 |
| (Li *et al.*, 1999) | M vegetarians | 34 ± 8 | 10 | 0.9 | Canola oil + spread | 4 | Plasma PL | 0 | 27 | -9 |
| 7 | 3.7 | Linseed oil + spread | 4 | Plasma PL | 150‡ | 47‡ | -10 |
| (Barre *et al.*, 2016) | M + F Type 2 DM | 60 ± 2 | 20 | 5.4 | Flaxseed oil | 12 | Serum | -31 | NA | -24 |
| (Francois *et al.*, 2003) | Lactating F | 28 – 39 | 8 | 11 | Flaxseed oil capsules | 2 | Total plasma | 129‡ | 60‡ | − 8 |
| (Finnegan *et al.*, 2003) | M+F | 26 ± 3 | 30 | 4.5 | Flaxseed oil spread | 24 | Plasma PL | 90‡ | 5‡ | − 3 |
| (James *et al.*, 2003) | M PMF | 18 – 65 | 6 | 0.75 | αLNA ethyl ester capsules | 3 | Plasma PL | 15 | 0 | − 3 |
| 6 | 1. 5 | αLNA ethyl ester capsules | 3 | Plasma PL | 23 | 5 | − 7 |
| (de Groot *et al.*, 2004) | Pregnant F | 30 ± 3 | 29 | 2.8 | Spread (incl. 9g LA) | 26 | Plasma PL | − 26 | NA | − 22 |
| (Goyens *et al.*, 2006) | M + F | M 54 ±12 F 46 ± 4 | 10 | αLNA 1.1% energy; LA 7%e | αLNA enriched spread | 6 | Plasma PL | 53‡ | 3 | -5 |
| 10 | αLNA 1.1%e, LA 3%e | αLNA enriched spread | 6 | Plasma PL | 30‡ | -5 | -4 |
| 9 | Control αLNA 0.4%e, LA 7%e | αLNA enriched spread | 6 | Plasma PL | 3 | 4 | -9 |
| (De Spirt *et al.*, 2009) | F | 18 – 65 | 15 | 1.2 | Flaxseed oil | 12 | Total plasma | 14.1 | -12.5 | -8.8 |
| 15 | 0.01 | Borage oil | 12 | 1.4 | -5.4 | -3 |
| 15 | 0 | Placebo SCFA | 12 | 1.5 | -5.3 | -13.8 |
| (Zhao *et al.*, 2007) | M + PMF | M 36 – 69 PMF 55 – 65 | 23 | Reference: LA 7%e;αLNA 0.4%e | Modified diet: containing walnuts, walnut oil and ﬂaxseed oil | 6 | Total serum | 160 | 33 | − 6 |
| LA 3%e; αLNA 1.1%e | Modified diet: containing walnuts, walnut oil and ﬂaxseed oil | 6 | Total serum | 63‡ | 33‡ | -6 |
| (Bloedon *et al.*, 2008) | M+PMF | 44 - 75 | 32 | 0.4 | Baked goods incorporating wheat | 10 | Total plasma | 11 | 18 | -9 |
| 30 | 1.022 | Baked goods incorporating flaxseed oil | 10 | 7.1 | NA | -1.2 |
| (Kaul *et al.*, 2008) | M+F | 34 ± 2 | 86 | 0.37 | Hempseed oil | 12 | Total plasma | 7.8 | NA | -3 |
| (Austria *et al.*, 2008) | M+F | 18 - 49 | 7 | 6.5 | Mufﬁns incorporating Whole ﬂaxseeds | 36 | Total plasma | -12 | NA | -45 |
| 8 | 6 | Mufﬁns incorporating flaxseed oil | 36 | 90 | NA | -14 |
| 18 | 5.4 | Flaxseed oil | 4 | 46‡ | 20‡ | − 6 |
| 10 | 5.74 | Mufﬁns incorporating Ground ﬂaxseeds | 36 | 14 | NA | 4 |
| (Barden *et al.*, 2009) | M | 20 - 65 | 18 | 5.4 | Olive oil | 4 | Total plasma | 4 | -1.7 | -3.2 |
| (Patenaude *et al.*, 2009) | M+F | 18 - 29 | 10 | 6 | Flaxseed oil | 4 | Total plasma | 64‡ | NA | − 3 |
| (Egert *et al.*, 2009) | M+F | 19–43 | 24 | 4.4 | Spread | 6 | LDL | 24‡ | NA | − 6.8 |
| 15 | 1.2 | Flaxseed oil | 12 | Total plasma | 14 | −5 | − 9 |
| (Taylor *et al.*, 2010) | M+F T2DM | 52.4 ± 1.5 | 13 | 7.9 | Baked goods incorporating milled ﬂaxseeds | 12 | Total plasma | 33‡ | 11 | − 9 |
| 12 | 7.9 | Baked goods incorporating Flaxseed oil | 12 | Total plasma | 44‡ | 20‡ | − 3 |
| (Hutchins *et al.*, 2013) | M+PMF; Obese/over weight | 58.6 ± 6.3 | 25 | 5.8 | Flaxseeds | 12 | Total serum | 20 | NA | − 9 |
| (Dittrich *et al.*, 2015) | M+F Hypertriglyceridaemic | 56 ± 12 | 59 | 4.8 | Flaxseed oil | 10 | Total plasma | 31 | 14‡ | − 7.5 |
| (Lefort *et al.*, 2016) | M+F | 30 ± 2 | 20 | 4.2 αLNA + 1.8 SDA | Buglossoides arvensis oil | 4 | Total plasma | 191‡ | 40‡ | -1 |
| 20 | 5.4 αLNA + 0.0 SDA | Flax seed oil | 4 | 77‡ | 19‡ | -2 |
| (Hennebelle *et al.*, 2016) | M+F | 25 ± 0.9 | 10 | 2 | Flaxseed oil | 4 | Total | 15‡ | NA | -13 |
|  |  |  |  |  |  |  |  |  |  |  |
| Studies in which αLNA supplementation did not alter DHA level |
|  |  |  |  |  |  |  |  |  |  |  |
| (Barre *et al.*, 2016) | M+F Type 2 DM | 59.5 ± 1.7 | 20 | < 0.01 | Placebo (safflower oil) | 12 | NEFA | 8 | NA | 0 |
| (Geleijnse *et al.*, 2012) | M+F MI patients | 60 - 80 | 2911 | 2 | Spread | 160 | Total plasma | 17 | NA | 0 |

‡Means that were statistically significantly different (P < 0.05) between baseline and end of the supplementation period according to the author’s analysis. F, female; PMF, M, male; MI, myocardial infarction; NEFA, non-esterified fatty acids; PC, phosphatidylcholine; post-menopausal female; SCFA, short chain fatty acid, SDA, stearidonic acid; DM, diabetes mellitus. Flaxseed oil and linseed oil are alternative names for the oil extracted from the seeds of *Linum sp.*

**TABLE 2** Estimated conversion of αLNA into longer chain n-3 polyunsaturated fatty acids in stable isotope tracer studies.

|  |  |  |
| --- | --- | --- |
| Reference | Study and participant details | Estimated conversion (%)a |
|  | Sex and age (yrs), sample size | Background diet | Stable isotope tracer | Lipid pools sampled | Duration of sampling | EPA | DPAn-3 | DHA |
| (Emken *et al.*, 1999) | M (28 - 39), | Low DHA < 0.1g/d (90 d) | 2.3g [d4]18:3n-3 | Total plasma | Up to 72h | 33.8 | 16.4 | 19.4 |
| High DHA 6.5 g/d (90 d) | 2.3g [d4]18:3n-3 | Total plasma | Up to 72h | 24.5 | 5.4 | 7.1 |
| (Emken *et al.*, 1994) | M, 23 – 26y, n = 7 | αLNA 1.9g / d + LA 15.1g/ d + SFA 48g/ d; 12 d | Deuterated αLNA Amount administered and number of deuterium atoms | Total plasma | 48h | 8.0 | 4.2 | 4.0 |
| αLNA 1.0 g/ d + 29.8 g/ d + 36.3 g/ d; 12 d | 3.4 | 2.6 | 3.6 |
| (Salem *et al.*, 1999) | Adults (age, sex, and sample size not disclosed) | Habitual | 1g [d5]-18:3n-3  | Total plasma | 168h | 57 ng/mb | nd | < 2 ng/mlb |
| (Pawlosky *et al.*, 2001) | M+ F 26 (22–37)y, n = 5/sex | Habitual diet 21d | 1g [d5]-18:3n-3 | Total plasma | 168h | The fish based diet reduced the rate constant coefficient for the transfer of deuterium fromDPAn-3 and to DHAand decreasedthe amount of DPAn-3 used for DHA synthesis of by 68%. compared to the beef-based diet |
| Beef based diet 21d |
| Fish based diet 21d |
| (Burdge *et al.*, 2002) | M, 36 (27–40)y, n = 6 | Habitual | 0.7g [U-13C]18:3n-3 | Sum of individual plasma lipid classes | 21 d | 8 | 8 | < LoD |
| (Burdge and Wootton, 2002a) | F, 28 ± 4y, n = 6 | Habitual | 0.7g [U-13C]18:3n-3 | Sum of individual plasma lipid classes | 21 d | 21 | 6 | 9 |
| (Burdge *et al.*, 2003) | M, 52 ± 12y, n = 14 | Habitual (8 wks), n = 5 | 0.7g [U-13C]18:3n-3 | Sum of individual plasma lipid classes | 48 h | 2.0 | 1.4 | 0.03 |
| (Vermunt *et al.*, 2000) | M+F, 21 - 66 y, n = 15 | αLNA 8.3 g/d (6 wks), n = 7 | 0.045 g [13C]-18:3n-3 | Total plasma | 168h | 0.04 | 0.01 | 0.04 |
| 18:1n-9 enriched dietc, (6 wks), n = 5 | 0.12 | 0.05 | 0.01 |
| (Hussein *et al.*, 2005) | M, 35 – 60y,n = 11 | Flaxseed oil; αLNA 18.6 g/d (12 wks), n = 6 | 0.40 g [13C]-18:3n-3 | Total plasma | 14 d | 0.29 | 0.05 | < 0.01 |
| Sunflower oil; αLNA 0.9g /d, (12 wks), n = 5 | 0.19 | 0.02 | < 0.01 |

 aValues are area under the time x concentration curve, AUC) as a proportion of the sum of labelled AUCs unless indicated otherwise. bPeak concentration. cBackground diet composition was not disclosed; < LoD, below limit of detection.

**TABLE 3** n-3 Polyunsaturated fatty acids in blood or erythrocyte lipids from vegetarians and omnivores

|  |  |  |  |
| --- | --- | --- | --- |
|  | Proportion of total fatty acid (%) |  |  |
| Reference | αLNA | EPA | DPAn-3 | DHA | Sub group | n | Sex ratio (M:F) | Analyte |
|  |  |  |  |  |  |  |  |  |
| Vegetarian |
|  |  |  |  |  |  |  |  |  |
| (Elorinne *et al.*, 2016) | 1.28 ± 0.58 | 0.63 ± 0.28 | 0.54 ± -0.14 | 0.85 ± 0.3 | Vegan | 21 | 1: 2.7 | TSL |
| (Huang *et al.*, 2013) | 0.42 ± 0.28 | 1.11 ± 1.77 | 1.08 ± -0.43 | 2.1 ± 1.04 | PV | 103 | All M | PPL |
| (Kornsteiner *et al.*, 2008) | 0.17 ± 0.05 | 0.16 ± 0.09 | 0.21 ± -0.07 | 0.35 ± 0.09 | Vegetarian | 25 | 1 : 3 | RBC PC |
| 0.15 ± 0.06 | 0.1 ± 0.0 | 0.17 ± 0.06 | 0.29 ± 0.13 | Vegan | 37 | 1 : 1 | RBC PC |
| (Manjari *et al.*, 2001) | 0.18 ± 0.13 | 0.32 ± 0.01 | 0.18 ± 0.13 | 0.84 ± 0.3 | OLV | 20 | All M | TPL |
| 0.31 ± 0.18 | 0.24 ± 0.04 | 0.31 ± - 0.18 | 1.15 ± 0.23 | OLV | 10 | All F | TPL |
| (Mann *et al.*, 2006) | 0.3 ± 0.1 | 0.7 ± 0.3 | 1.1 ± 0.2 | 2.2 ± 0.7 | OLV | 43 | All M | PPL |
| 0.3 ± 0.1 | 0.6 ± 0.3 | 1.0 ± 0.3 | 2.0 ± 0.4 | Vegan | 18 | All M | PPL |
| (Rosell *et al.*, 2005) | 1.4 (1.3, 1.5)a | 0.5 (0.5, 0.6)a | 0.8 (0.7, 0.8)a | 1.2 (1.1, 1.2)a | OLV | 231 | All M | TPL |
| 1.4 (1.3, 1.5)a | 0.3 (0.3, 0.4)a | 0.7 (0.7, 0.8)a | 0.7 (0.6, 0.8)a | Vegan | 232 | All M | TPL |
| (Lee *et al.*, 2000) | 1.7 ± 2.0 | 0.2 ± 0.5 | nd | 1.7 ± 2.5 | OVL | 60 | 1 : 3 | TSL |
| (Welch *et al.*, 2010)‡ | 13.6 ± 10.1 | 55.9 ± 45.3 | 77.5 ± 38.8 | 222.2 ± 138.4 | Vegetarian | 25 | All M | TPL |
| 12.3 ± 4.8 | 55.1 ± 52.5 | 75.0 ± 32.2 | 223.5 ±137.8 | Vegetarian | 51 | All F | TPL |
| 15.8 ± 9,7 | 65.1 ± 45.5 | 67.2 ± 26.8 | 195.0 ±5 8.8 | Vegan | 5 | All M | TPL |
| 13.71 ± 8.1 | 50.0 ± 29.4 | 90.6 ± 54.0 | 286.4 ± 211.7 | Vegan | 5 | All F | TPL |
|  |
|  | Omnivorous |  |  |  |  |
|  |
| (Elorinne *et al.*, 2016) | 0.73 | 2.33 ± 1.6 | 0.62 ± 0.18 | 2.25 ± 0.8 | Omnivores | 19 | 8 :11 | TSL |
| (Huang *et al.*, 2013) | 0.65 ± 3.21 | 2.98 ± 2.5 | 1.26 ± 0.35 | 5.61 ± 1.36 | Omnivores | 128 | All M | PPL |
| (Kornsteiner *et al.*, 2008) | 0.21 ± 0.13 | 0.21 ± 0.1 | 0.23 ± 0.07 | 0.66 ± 0.22 | Omnivores | 23 | 1 :2 | RBC PC |
| (Manjari *et al.*, 2001) | 0.26 ± 0.17 | 0.28 ± 0.11 | 0.26 ± 0.17 | 1.71 ± 0.44 | Omnivores | 30 | All M | TPL |
| 0.63 ± 0.4 | 0.54 ± 0.3 | 0.63 ± 0.4 | 1.56 ± 0.5 | Omnivores | 14 | All F | TPL |
| (Mann *et al.*, 2006) | 0.2 ± 0.1 | 1.1 ± 0.5 | 1.3 ± 0.2 | 3.4 ± 1.0 | HM | 18 | All M | PPL |
| 0.2 ± 1.0 | 1.0 ± 0.3 | 1.2 ± 0.2 | 3.3 ± 0.8 | MM | 60 | All M | PPL |
| (Rosell *et al.*, 2005) | 1.3 (1.2,1.4)a | 0.7 (0.7, 0.8)a | 0.8 (0.8, 0.9)a | 1.7 (1.6, 1.8)a | MFish | 196 | All M | TPL |
| (Lee *et al.*, 2000) | 0.8 ± 0.6 | 1.3 ± 1.3 | nd | 3.4 ± 2.2 | Omnivores | 194 | 1 : 3 | TPL |
| (Welch *et al.*, 2010)‡ | 10.9 ± 5.7 | 57.5 ± 43.2 | 67.3 ± 29.4 | 239.7 ± 106.2 | Fish eaters | 2257 | All M | TPL |
| 11.8 ± 7.0 | 47.4 ± 30.3 | 70.0 ± 33.4 | 215.6 ± 96.4 | Meat, no fish | 359 | All M | TPL |
| 12.4 ± 6.3 | 64.7 ± 43.4 | 71.8 ±29.6 | 271.2 ± 109.6 | Fish eaters | 1891 | All F | TPL |
| 13.1 ± 7.3 | 57.1 ± 38.4 | 74.7 ± 34.7 | 241.3 ± 109.6 | Meat, no fish | 309 | All F | TPL |

Values are mean ± standard deviation or ± standard error of the mean (except a25th,75th percentiles) proportions of fatty acid expressed as percent total fatty acids in the indicated lipid pools. HM, high meat; MFish, meat plus fish eaters; MM, moderate meat; nd, not disclosed; OLV, ovolacto-vegetarian; PPL, plasma phospholipids; PV, pesco-vegetarian, TPL, total plasma lipids; RBC PC, red blood cell phosphatidylcholine; TSL, total serum lipids. ‡ values are 𝜇mol/L.