Alpha-Linolenic and Linoleic Fatty Acids

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Good sources of the long-chain n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) include cold-water fish and seafood; however, vegan diets (VGNs) do not include animal-origin foods.

Keywords: n-3 fatty acid ; n-6 fatty acid ; alpha-linolenic acid ; ALA ; linoleic acid ; LA ; EPA ; DHA ; vegans

1. Introduction

The polyunsaturated n-6 and n-3 fatty acids are essential for a variety of functions in the body, including the synthesis of prostaglandins, leukotrienes, cellular membranes, phospholipids, retinal photoreceptors (vision), cerebral gray matter (brain tissue), testes, and sperm. Linoleic (18:2n-6; LA) and arachidonic acids (20:4n-6; AA) are classified as n-6 fatty acids, and α-linolenic (18:3n-3; ALA), eicosapentaenoic (20:5n-3; EPA) and docosahexaenoic acids (22:6n-3; DHA) are n-3 fatty acids [1]. Of these fatty acids, LA and ALA are considered essential and must be provided by the diet.

The Dietary Reference Intakes (DRIs) are "nutrient reference values" developed by the Institute of Medicine of The National Academies. They are intended to serve as a guide for good nutrition and provide the scientific basis for the development of food guidelines in both the United States and Canada, and these nutrient reference values are specified on the basis of age, gender and lifestage groups" [2]. The United States DRIs are used to make informed judgements during the dietary planning process. New research or discoveries of physiological factors, inborn errors of metabolism, health risks, characteristics of the nutrient sources, and nutrient bioavailability may require adjustments in DRI nutrient values for planning individual and group dietary intakes. The present 2003 version of the DRIs states that the nutrients of concern for vegetarians and vegans (VGNs) are vitamin B12, vitamin D, calcium, iron, zinc, and protein [3]. Essential fatty acids in the VGN and vegetarian diets are not presently a DRI concern.

When the DRI concludes that there is inadequate information to set either LA or ALA Estimated Average Requirements (EAR) or the Recommended Dietary Allowance (RDA) for healthy individuals, the Adequate Intake (AI) is used. The present essential fatty acid AI is based on "the highest median intake of LA and ALA in United States adults, where a deficiency is basically nonexistent in non-institutionalized populations" [4]. The present n-6 AI requirement range is 12–11 g/day for men and 17–14 g/day for adult women (non-pregnant/lactating), and the AI n-3 fatty acid recommendations are 1.1 g/day of ALA for women and 1.6 g/day for men [4]. However, it is unknown if the AIs are beneficial or physiologically adequate because dose-response data studies are lacking, Essential fatty acid status is not usually clinically tested, and absence of deficiency symptoms is not necessarily evidence of adequacy.

The authors utilized the definition of 'vegan' as the following: a diet which is "devoid of all flesh foods. It excludes eggs and dairy products and may exclude honey" [5]. Frequently, the term 'strict vegetarian' or 'total vegetarian' is used instead of 'vegan' to describe their dietary pattern. Thus, the abbreviation 'VGN' is used in this manuscript as a description of the dietary pattern of total vegetarians/strict vegetarians and vegans.

People choose VGN or vegetarian diets for different reasons, which include but are not limited to health reasons, compassion toward animals, a desire to better protect the environment, to lower their risk of chronic diseases, or to therapeutically manage diseases; however, these diets require careful dietary planning. According to the Position Paper of the Academy of Nutrition and Dietetics regarding vegetarian diets, "Well designed vegetarian diets provide adequate nutrient intakes for all stages of the lifecycle and can also be useful in the management of some chronic diseases" [5].

Upon examination of the published articles that relate to 'vegetarian', the researcher's definitions for the terms 'vegan' and 'vegetarian' are inconsistent, and some researchers consider plant-based diets to be 'semi-vegetarian'. However, VGN diets are very different from omnivore diets and even diets that are considered to be 'vegetarian' (ex. 'lacto-ovo', 'pesco-vegetarian', 'plant-based vegetarian', 'pollo-vegetarian', or 'semi-vegetarian'). These 'vegetarian' diets may also include animal-origin foods such as eggs, dairy, fish, or chicken. Thus, dietary patterns and levels of biochemical indicators of essential fatty acid status are very different between VGN and omnivore diets or even other types of vegetarian diets. This narrative review focuses on apparently healthy VGNs and comparisons of VGNs and 'omnivore' or 'meat-eating' diets, rather than the comparisons of VGN to vegetarian diets or other terms that include the word 'vegetarian'.

Diet study results between VGNs and omnivores/meat-eaters are inconsistent. Additionally, interpretation or comparison is difficult when some of the information is not reported, or missing. For example, some studies report dietary total polyunsaturated fatty acids (PUFAs), total n-6, total n-3, or collected some, but not all lipid fractions [6][7][8][9][10][11], which limits interpretation of essential fatty acid biological indicators as compared to dietary intakes.

Additional fatty acids of interest are EPA and DHA. They are not considered to be essential since they can be converted from ALA; however, they may be of concern for VGNs, since VGN diets are typically absent of EPA and DHA unless VGNs consume supplements containing EPA and DHA [9][12][13][14][15][16].

2. Dietary Sources of the Essential Fatty Acids

The most plentiful dietary n-6 polyunsaturated fatty acid is LA. N-6 fatty acid food sources commonly consumed by VGNs include nuts, seeds, certain vegetables, and vegetables oils such as soybean oil, safflower oil, and corn oil. Therefore, any diet that is mostly plant-based leads to a high dietary intake of LA as well as fiber. Since there are few plant sources high in ALA compared to LA, this may present an intake challenge for VGNs to meet the ALA DRI requirements.

The most abundant n-3 PUFA is ALA, which is found in plant-based oils and/or oil food sources like flaxseed (linseed), English walnut, hemp seed, and chia [17]. The major dietary plant-based sources of LA and ALA are shown in **Table 1**.

Table 1. Energy, protein, total lipid, 18:2 n-6, 18:3 n-3, carbohydrate, and fiber contents of oils and foods commonly consumed by vegans and vegetarians for the essential fatty acids.

Nutrient [1]		Energy	Protein	Total Lipid	18:2n-6	18:3n-3	CHO	Total Fiber
	Unit	Kcal	g	g	g	g	g	g
Oils								
Oil, Canola	100 g	884	0	100	18.64	9.137	0	0
Oil, Flaxseed/Linseed (Panos)	100 g	884	0.110	99.98	14.25	53.37	0	0
Oil, Soybean	100 g	763	0	100	50.42	6.789	0	0
Oil, Walnut	100 g	884	0	100	52.90	10.40	0	0
Oil, High Oleic Sunflower	100 g	884	0	100	3.61 *	0.192 **	0	0
Oil, High Oleic Safflower	100 g	884	0	100	12.72	0.096	0	0
Oil, Culinary Algae	100 g	800	0	93.33	n/a	n/a	0	0
Ovega-3 supplement [2]	1 gel	n/a	0	n/a	n/a	0.5	0	0
Deva Vegan supplement [3]	1 cap	5	0	0.5	n/a	0.2	0	0
Nordic Naturals supplement [4]	2 gels	10.0	0	1.00	n/a	0.715	0	0
Food Sources								
Almonds Raw	100 g	579	21.15	49.93	12.30	0.003	21.55	12.50

Nutrient [1]		Energy	Protein	Total Lipid	18:2n-6	18:3n-3	CHO	Total Fiber
	Unit	Kcal	g	g	g	g	g	g
Amaranth	100 g	371	13.65	7.020	2.736	0.042	65.25	6.70
Avocados, Raw, California	100 g	167	1.960	15.41	1.674	0.111	8.640	6.80
Black Walnuts Dried	100 g	619	24.06	59.33	33.80	2.680	9.580	6.80
Brazil Nuts, Dried	100 g	659	14.32	67.10	23.859	0.018	11.74	7.50
Brown Rice Cooked	100 g	123	2.740	0.970	0.355	0.011	25.58	1.60
Bulgur Cooked	100 g	83	3.08	0.240	0.094	0.004	18.58	4.50
Cashews Raw	100 g	553	18.22	43.85	7.782	0.062	30.19	3.30
Chia Seeds Dried	100 g	486	16.54	30.74	5.840	17.80	42.12	34.4
English Walnuts Dried	100 g	654	15.23	65.21	38.09	9.08	13.71	6.70
Flaxseed Raw	100 g	534	18.29	42.16	5.903	22.81	28.88	27.3
Hempseed Hulled	100 g	553	31.56	48.75	1.340	8.864	8.670	4.00
Millet Cooked	100 g	119	3.510	1.000	0.480	0.028	23.67	1.300
Oat Bran Cooked	100 g	40	3.210	0.860	0.324	0.015	11.44	2.60
Pistachio Raw	100 g	560	20.16	45.32	13.10	0.210	27.17	10.60
Poppy Seeds	100 g	525	17.99	41.56	28.30	0.273	28.13	19.50
Quinoa	100 g	368	14.12	6.070	2.977	0.260	64.16	7.00
Rye	100 g	338	10.34	1.630	0.659	0.108	75.86	15.1
Sesame Seeds dried	100 g	573	17.73	49.67	21.375	0.376	23.45	11.8
Soybeans Raw	100 g	446	36.49	19.94	9.925	1.330	30.16	9.30
Soybeans, Boiled	100 g	141	12.35	6.400	2.657	0.354	11.05	4.20
Sunflower Seeds	100 g	584	20.78	51.50	23.05 *	0.06 **	20.00	8.60

[1] Source: US Department of Agriculture Nutrient Data Base, 2019 [17]. * undifferentiated 18:2, ** undifferentiated 18:3. [2] Ovega-3 i-Health, Inc., 2017 [18]. [3] Deva Nutrition LLC, 2017 [19]. [4] Nordic Naturals Inc., 2017 [20].

Good sources of EPA and DHA fatty acids are typically found in animals, eggs from laying chickens fed high sources of ALA or DHA, fish or livestock fed n-3 supplements, cold water fish and seafood, or fish which feed on food sources high in

ALA, EPA and/or DHA. Some cold water marine algae (except spirulina) contain long chain n-3 fatty acids, and negligible amounts of ALA and LA (**Table 1**).

Many of the food sources high in LA also contain ALA (**Table 1**). Thus, it is very difficult to obtain ALA without also increasing the amount of LA in the diet, unless specific foods high in ALA are consumed such as flaxseed, flaxseed/linseed oil, hemp seeds, chia or oils high in high oleate sunflower oil and low in LA (**Table 1**). Decreasing LA intake in VGNs could be an option; however, decreasing LA intake without monitoring and/or increasing ALA intake might also affect EPA and DHA conversion.

Additionally, there are concerns and considerations such as nutrient bioavailability, physiological implications, and possible health risks of high LA and low ALA in the diet, as well as high LA in plasma, serum, erythrocytes, platelets, breastmilk and adipose tissue.

3. Nutrient Bioavailability

It is possible that high fiber diets interfere with fat absorption, including essential fatty acids. Since VGNs typically consume plant products, their diets are typically high in total fiber [6][7][8][14][21]. Soluble fibers such as psyllium, gums and beta-glucan [17], bind fatty acids and prevents them from being absorbed and binds bile, which is necessary for micelle formation. Micelles are required for uptake of long-chain fatty acids into the enterocytes. Insoluble fiber, such as wheat bran, fruit skins, and whole grains [17] increase transit time through the intestine and can also interfere with uptake of fats as well as nutrients in general, because both types of fiber are not digested or absorbed in the small intestine, and humans do not have enzymes to digest fiber. Presently, there are no studies on the effects of high soluble or insoluble fiber on fat digestion in VGNs.

4. Physiological Reasons for Special Consideration-Conversion of ALA to EPA and DHA

The essential PUFAs, LA and ALA, must be consumed from the diet, and since VGNs do not consume EPA and DHA from the diet, VGNs rely on endogenous synthesis to obtain long chain n-3 PUFAs. ALA is endogenously converted to EPA and DHA by the elongation and desaturation enzymes in the animal (or marine algae) and becomes incorporated into the animal's cells and/or stored in adipose tissue. Thus, almost all EPA and DHA dietary sources come from animals and VGNs are limited to algal supplements of EPA and DHA.

Most humans (except those with inborn errors of metabolism) can convert LA to AA and modestly convert ALA to EPA and/or DHA. The human conversion rate of ALA to EPA and DHA is about 5%–8% [22][23][24]. This low conversion rate suggests humans should consume dietary sources of EPA and DHA; however, evidence is not conclusive regarding the amount needed to maintain physiological function.

Both LA and ALA are metabolized by the same biochemical pathway, and excess consumption of LA or ALA results in competition between the elongation and desaturation enzymes for EPA and AA. Excess LA competitively interferes with the ability of ALA to utilize the elongation and desaturase enzymes, thereby suppressing the conversion of ALA to EPA and EPA to DHA [22][23][24][25][26][27] (**Figure 1**).

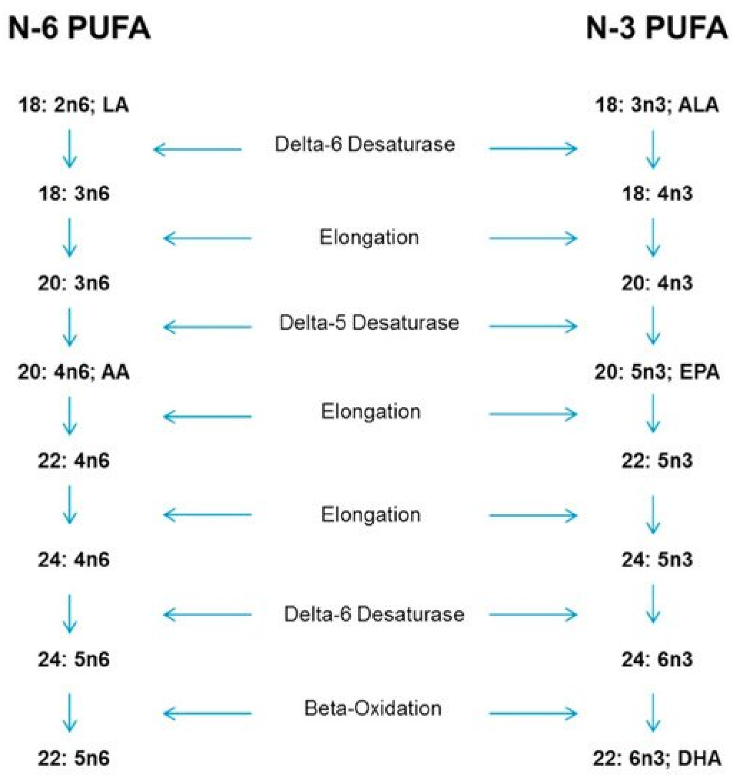

Figure 1. The elongation and desaturation of the essential fatty acids, linoleic acid (LA) and alpha-linolenic acid (ALA). AA: arachidonic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; PUFA: polyunsaturated fatty acids. Permission by authors and Elsevier [28].

Adult and infant studies have demonstrated the conversion of ALA to EPA and DHA through desaturation and elongation, and LA desaturates and elongates to form AA. Through the process of elongation, desaturation and beta oxidation 22:5n-6 forms from AA, using the same enzyme system needed for conversion of EPA to DHA [19][20][21][22][23][24][25][26][27]. In supplemented omnivores and vegetarians, 9.4% of serum phospholipid DHA can be retro-converted to EPA [12].

It may be possible to observe alterations in the synthesis of EPA and DHA from ALA by following a VGN diet over the long-term, as it has been demonstrated that changes in dietary patterns may affect the synthesis of n-3 fatty acids. For example, there is an increased synthesis of DHA from ALA, especially if LA is decreased [29]; ALA is elongated and desaturated in a tissue-dependent manner [30]; and n-3 PUFAs may be depleted during overnutrition [31].

5. Recommended Intakes of n-3 and the n-6:n-3 Ratio

Expert opinions differ when it comes to n-3 and n-6:n-3 ratio recommendations (**Table 2**—most recent studies are listed first) and overall, the recommendations for dietary n-6:n-3 suggested by experts and researchers are lower than 10:1 and between the range of 2–4:1 [32][33][34][35].

Table 2. Recommendations by researchers and reviewers for adult vegans/total vegetarians (VGNs) (most recent studies first).

Author, Year	Recommendation: Males; Females Combined	18:2n-6 LA	18:3 n-3 ALA	20:5 n-3 EPA	22:6 n-3 DHA	n-6:n-3 or Omega-3 Index
Agnoli et al., 2017 [36]	Females	Limit intake of sources of n-6 FA, & TFA. Limit consumption of processed, deep-fried foods, and alcohol.	-	Pregnant/breastfeeding or women with increased requirement for long chain n-3 fatty acids, should be advised to consume an algae-based supplement of known nutrient content.	Pregnant/breastfeeding or women with increased requirement for long chain n-3 fatty acids, should be advised to consume an algae-based supplement of known nutrient content.	-
	Combined-Males and Females	-	Improve n-3 nutritional status by regular consumption of good sources of alpha-linolenic acid.	-	-	-
Burdge et al., 2017 [37]	Females	-	-	-	Need more cognitive studies for children of vegetarian females due to low DHA levels.	-
Pinto et al., 2017 [9]	Combined	-	Further research whether populations with low n-3 status are more at risk of having a pro-inflammatory profile.	-	-	-

Author, Year	Recommendation: Males; Females Combined	18:2n-6 LA	18:3 n-3 ALA	20:5 n-3 EPA	22:6 n-3 DHA	n-6:n-3 or Omega-3 Index
Melina et al., 2016 [5]	Females	-	-	-	Low dose microalgae DHA supplements for pregnancy and lactation.	-
	Combined	High intakes of LA may suppress ALA conversion.	May be prudent to ensure higher intakes of ALA. N-3 needs of healthy individuals can be met with ALA alone; endogenous synthesis of EPA and DHA from ALA is sufficient.	Clinical relevance of reduced EPA and DHA status in VGNs are unknown. Low-dose micro-algae based DHA supplements are available for those with increased needs.	Clinical relevance of reduced EPA and DHA status in VGNs are unknown. Low-dose micro-algae based DHA supplements are available for those with increased needs.	A ratio of LA/ALA not exceeding 4:1 has been suggested fo optimal conversion.
Harris, 2014 [38]	Combined	Consume more ALA and less LA to increase the Omega-3 Index.	Consume more ALA and less LA to increase the Omega-3 Index.	-	-	Omega-3 Index >8%.
Sarter et al., 2014 [16]	Combined	-	-	VGNs respond robustly to a relatively low dose of a vegetarian omega-3 supplement.	VGNs respond robustly to a relatively low dose of a vegetarian omega-3 supplement.	No direct evidence tha omega-3 index confers additional health benefits over and above their already protective VGN diet.

Author, Year	Recommendation: Males; Females Combined	18:2n-6 LA	18:3 n-3 ALA	20:5 n-3 EPA	22:6 n-3 DHA	n-6:n-3 or Omega-3 Index
Saunders et al., 2013 [15]	Combined	-	Double current AI of ALA if no direct sources of EPA and DHA are consumed. Increased needs or reduced conversion may benefit from DHA and EPA supplements derived from microalgae of 200–300 mg/day of DHA and EPA (pregnant and lactating women) and reduced conversion ability.	-	-	-
Craig, 2010; Review [39]	Combined	-	Regular consumption of plant foods naturally rich in n-3 fatty acid ALA, such as ground flaxseed, walnuts, soy products, and hemp seed beverages.	-	Pregnant and lactating women may benefit from DHA-fortified foods and microalgae-derived DHA supplements.	-

Author, Year	Recommendation: Males; Females Combined	18:2n-6 LA	18:3 n-3 ALA	20:5 n-3 EPA	22:6 n-3 DHA	n-6:n-3 or Omega-3 Index
Welch et al., 2010 [40]	Combined	-	Further research for conversion of ALA to long chain n-3 PUFAs for maintenance of adequate status in non-fish and fish-oil consumers is required.	-	-	-
Simopoulos, 2008 [41]	Combined	-	-	-	-	Ratio of 4:1 i associated with 70% decrease in total mortality in secondary prevention o cardiovascula disease.
Kornsteiner et al., 2008 [32]	Combined	-	Erythrocyte phospholipid n-3 status of VGNs is critical. It is important to maintain n-3 fatty acid intake during adult life.	-	-	Ensure physical, mental and neurological health, reduc n-6/n-3 ratio with an additional intake of direct source of EPA and DHA, regardless o age and gender.
Mann et al., 2006 and Li et al., 1999 (Mann used data collected from Li, 1999) [42]	Combined	-	Advised to increase intake of n-3 fatty acids to increase platelet PL n-3 PUFA and reduce platelet aggregability.	-	-	-

Author, Year	Recommendation: Males; Females Combined	18:2n-6 LA	18:3 n-3 ALA	20:5 n-3 EPA	22:6 n-3 DHA	n-6:n-3 or Omega-3 Index
Rosell et al., 2005 [10]	Combined	-	Suggests (with caution) VGNs increase intake of ALA and limit intake of LA to optimize FA status. The importance of long chain fatty acids in the diet needs further investigation.	-	-	-
Davis et al., 2003 [34]	Combined	5.5–8% Kcals from n-6 FA. Reduce high n-6 oils in the diet, decrease processed foods. Primary fat should be MUFA.	<1.5–2% of calories should be obtained from n-3. Decrease EtOH and trans fatty acids to increase conversion of ALA to EPA and DHA. Double intake of ALA; provide >1% of energy from n-3 or about 1.1 g/1000 calories. Increased needs require 2.2 g/1000 calories. Aim for 2–4 g of ALA/day.	Not essential, but it is important to ensure sufficient levels by relying on conversion from parent fatty acids. Two important steps to improve EPA status: 1) Maximize conversion of ALA to EPA and DHA and 2) Provide a direct source of EPA and DHA.	Not technically essential, but ensure sufficient levels by relying on conversion from parent fatty acids. Supplements of DHA should be 100–300 mg/day. DHA and ALA should also be adequate.	To achieve the 4:1 ratio, <1.5–2% of calories should be obtained from n-3 and 5.5–8% of calories from n-6 FA.

Author, Year	Recommendation: Males; Females Combined	18:2n-6 LA	18:3 n-3 ALA	20:5 n-3 EPA	22:6 n-3 DHA	n-6:n-3 or Omega-3 Index
Simopoulos, 2000 [35]	Combined	-	-	-	-	Ratio was 1:1 to 2:1 in ancient diets Present ratio is 10 to 1:20 to 25 to 1- indicates a deficiency in Western Diets of n-3.
Fokkema et al., 2000 [33]	Combined	-	-	-	-	Found a 3:1 ratio increased EPA from 0.3 to about 1.0% in VGN plasma. A 3.7 g/day ALA die for 4 weeks (ratio of 3.8:1 augmented ALA about 1% more. Total n 3 levels increased from 2.3 to 3.4% in plasma. DHA status was nc increased.
Agren et al., 1995 [43]	Combined	Depressed levels of n-3 FA are depressed due to very low diet levels and high LA and oleic acid intake.	-	-	-	-

Author, Year	Recommendation: Males; Females Combined	18:2n-6 LA	18:3 n-3 ALA	20:5 n-3 EPA	22:6 n-3 DHA	n-6:n-3 or Omega-3 Index
Sanders et al., 1978 [44]	Females	-	More research is needed on low delta 4 desaturase in lactating women.	-	-	-
	Combined	-	Further research needed to establish whether differences in the proportion of n-3 derivatives in tissues are of physiological importance.	-	-	-

The ratio of n-6 fatty acids to n-3 fatty acids can influence the conversion of ALA to EPA and DHA [45][46]. Gerster found that a diet high in n-6 reduces the ALA to EPA and DHA conversion by 40–50% [45]. When healthy men increased dietary intake of LA from 15 g/day to 30 g/day (increased n-6:n-3 ratio) this resulted in a 40–54% increase in conversion of LA to AA, as well as a subsequent decrease in conversion of ALA to EPA and DHA [46]. Additionally, high n-6:n-3 ratios in obesity are directly related to non-alcoholic fatty liver disease [31].

Several VGN studies have determined dietary intake and status of the n-6:n-3 ratios. The majority of VGNs have n-6:n-3 plasma ratios that are 'unbalanced' [10][13][21][32][43][34]. Kornsteiner et al. reported that a ratio of 10:1 promoted n-3 tissue declines and reduced desaturation and elongation of n-3 fatty acid-related products, and suggested that VGNs achieve a balanced ratio of n-6:n-3 in their diet to enhance the conversion of ALA into EPA and DHA [32]. A reduction in the n-6:n-3 ratio to 2–4:1 was shown to maintain normal metabolism and increase the amount of long chain PUFAs synthesized in the body [21]. Simopoulos affirms a balanced n-6:n-3 ratio is a determinant of health because n-6 and n-3 fatty acids influence gene expression, and advocates that a balanced ratio of LA to ALA of 2:1. She also stated that the n-6:n-3 ratio of 10:1 in the diet indicated Western diets are deficient in n-3 [35]. Davis and Kris-Etherton suggested optimizing status by consuming double the intake of ALA (≥1% of energy or 1.1 g/1000 Kcals and aim for 2–4 g/ALA/day) and a direct source of DHA in the range of 100–300 mg/day [34]. The authors of the Position Paper of the Academy of Nutrition and Dietetics on Vegetarian Diets suggest that the LA/ALA ratio should not exceed 4:1 and that "it may be prudent to ensure a somewhat higher intake of ALA" [5].

A dietary increase in flaxseed (linseed) oil increases plasma ALA and EPA and lowers the ratio of n-6:n-3 [40][47][48][49]. Li et al. showed dietary ALA from canola and linseed (flaxseed) oil increased the EPA tissue profile 2.5-fold in a high ALA diet compared with a 0.5-fold increase in a moderate ALA diet in male subjects 20 to 50 years old [50]. Indu found that a constant intake of 3.7 g/day of dietary ALA may have biological effects similar to those of 0.3 g/day of dietary long chain n-3 PUFAs from fish oil. Eleven grams of ALA from flaxseed produces 1 g of the long chain n-3 PUFAs, EPA and DHA, and results in a calculated ratio of 14.8 g LA: 3.7 g ALA equivalent to a 4:1 ratio [48]. Supplementation with high amounts of ALA (>5.3 g/day) increased EPA plasma fatty acid and platelet concentrations [49][51]. Bjerve et al. noted that the minimum requirement for ALA in immobile adults was equivalent to 0.2% of total energy intake when n-3 long chain fatty acids were 0.08% of energy [52].

References

1. Spector, A.; Kim, H.Y. Discovery of Essential Fatty Acids. J. Lipid Res. 2014, 56, 11–21.
2. The National Academies of Sciences Engineering Medicine. Dietary Reference Intakes tables and application. Available online: http://nationalacademies.org/hmd/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx (accessed on 18 August 2019).
3. Institute of Medicine (IOM). Introduction to dietary reference intakes. In Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids; National Academics Press: Washington, DC, USA, 2005; pp. 29–37.
4. Institute of Medicine (IOM). Dietary fats: Total fat and fatty acids. In Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids; National Academics Press: Washington, DC, USA, 2005; pp. 470–472, 030908525X (pbk.) 0309085373 (hardcover).
5. Melina, V.; Craig, W.; Levin, S. Position of the Academy of Nutrition and Dietetics: Vegetarian Diets. J. Acad. Nutr. Diet. 2016, 116, 1970–1980.
6. Alles, B.; Baudry, J.; Mejean, C.; Touvier, M.; Peneau, S.; Hercberg, S.; Kesse-Guyot, E. Comparison of Sociodemographic and Nutritional Characteristics between Self-Reported Vegetarians, Vegans, and Meat-Eaters from the NutriNet-Sante Study. Nutrients 2017, 9, 1023.
7. Clarys, P.; Deliens, T.; Huybrechts, I.; Deriemaeker, P.; Vanaelst, B.; De Keyzer, W.; Hebbelinck, M.; Mullie, P. Comparison of nutritional quality of the vegan, vegetarian, semi-vegetarian, pesco-vegetarian and omnivorous diet. Nutrients 2014, 6, 1318–1332.
8. Rizzo, N.S.; Jaceldo-Siegl, K.; Sabate, J.; Fraser, G.E. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. J. Acad. Nutr. Diet. 2013, 113, 1610–1619.
9. Pinto, A.M.; Sanders, T.A.; Kendall, A.C.; Nicolaou, A.; Gray, R.; Al-Khatib, H.; Hall, W.L. A comparison of heart rate variability, n-3 PUFA status and lipid mediator profile in age- and BMI-matched middle-aged vegans and omnivores. Br. J. Nutr. 2017, 117, 669–685.
10. Rosell, M.S.; Lloyd-Wright, Z.; Appleby, P.N.; Sanders, T.A.; Allen, N.E.; Key, T.J. Long-chain n-3 polyunsaturated fatty acids in plasma in British meat-eating, vegetarian, and vegan men. Am. J. Clin. Nutr. 2005, 82, 327–334.
11. Elorinne, A.L.; Alfthan, G.; Erlund, I.; Kivimaki, H.; Paju, A.; Salminen, I.; Turpeinen, U.; Voutilainen, S.; Laakso, J. Food and Nutrient Intake and Nutritional Status of Finnish Vegans and Non-Vegetarians. PLoS ONE 2016, 11, e0148235.
12. Perrin, M.T.; Pawlak, R.; Dean, L.L.; Christis, A.; Friend, L. A cross-sectional study of fatty acids and brain-derived neurotropic factor (BDNF) in human milk from lactating women following vegan vegetarian and omnivore diets. Eur. J. Clin. Nutr. 2019, 58, 2401–2410.
13. Conquer, J.A.; Holub, B.J. Supplementation with an algae source of docosahexaenoic acid increases (n-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. J. Nutr. 1996, 126, 3032–3039.
14. Geppert, J.; Kraft, V.; Demmelmair, H.; Koletzko, B. Docosahexaenoic acid supplementation in vegetarians effectively increases omega-3 index: A randomized trial. Lipids 2005, 40, 807–814.
15. Saunders, A.V.; Davis, B.C.; Garg, M.L. Omega-3 polyunsaturated fatty acids and vegetarian diets. Med. J. Aust. 2013, 199, S22–S26.
16. Sarter, B.; Kelsey, K.S.; Schwartz, T.A.; Harris, W.S. Blood docosahexaenoic acid and eicosapentaenoic acid in vegans: Associations with age and gender and effects of an algal-derived omega-3 fatty acid supplement. Clin. Nutr. 2015, 34, 212–218.
17. U.S. Department of Agriculture (USDA). Nutrient Database. Available online: https://ndb.nal.usda.gov/ndb/nutrients/index (accessed on 11 June 2019).
18. Ovega-3 i-Health Inc. Available online: https://www.ovega.com/ovega-3 (accessed on 25 October 2017).
19. Deva Nutrition LLC. Available online: http://www.devanutrition.com/vegan-omega-3-dha-delayed-release.html (accessed on 25 October 2017).
20. Nordic Naturals Inc. Available online: https://www.nordicnaturals.com/en/Products/Product_Details/514/?ProdID=1654 (accessed on 25 October 2017).
21. Sanders, T.A.; Roshanai, F. Platelet phospholipid fatty acid composition and function in vegans compared with age- and sex-matched omnivore controls. Eur. J. Clin. Nutr. 1992, 46, 823–831.
22. Burdge, G.C.; Wootton, S.A. Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. Br. J. Nutr. 2002, 88, 411–420.

23. Burdge, G.C.; Jones, A.E.; Wootton, S.A. Eicosapentaenoic and docosapentaenoic acids are the principal products of alpha-linolenic acid metabolism in young men*. Br. J. Nutr. 2002, 88, 355–363.
24. Brenna, J.T. Efficiency of conversion of alpha-linolenic acid to long chain n-3 fatty acids in man. Curr. Opin. Clin. Nutr. Metab. Care 2002, 5, 127–132.
25. Sauerwald, T.U.; Hachey, D.L.; Jensen, C.L.; Chen, H.; Anderson, R.E.; Heird, W.C. Effect of dietary alpha-linolenic acid intake on incorporation of docosahexaenoic and arachidonic acids into plasma phospholipids of term infants. Lipids 1996, 31, S131–S135.
26. Salem, N., Jr.; Wegher, B.; Mena, P.; Uauy, R. Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. Proc. Natl. Acad. Sci. USA 1996, 93, 49–54.
27. Emken, E.A.; Adlof, R.O.; Gulley, R.M. Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. Biochim. Biophys. Acta 1994, 1213, 277–288.
28. Akerele, O.A.; Cheema, S.K. A balance of omega-3 and omega-6 polyunsaturated fatty acids is important in pregnancy. J. Nutr. Intermed. Metab. 2016, 5, 23–33.
29. Domenichiello, A.; Kitson, A.; Bazinet, R. Is docosahexaenoic acid synthesis from α-linolenic acid sufficient to supply the adult brain? Prog. Lipid Res. 2015, 59, 54–66.
30. Barceló-Coblijn, G.; Murphy, E. Alpha-linolenic acid and its conversion to longer chain n-3 fatty acids: Benefits for human health and a role in maintaining tissue n-3 fatty acid levels. Prog. Lipid Res. 2009, 48, 355–374.
31. Valenzuela, R.; Videla, L. The importance of the long-chain polyunsaturated fatty acid n-6 / n-3 ratio in development of non-alcoholic fatty liver associated with obesity. Food Funct. 2011, 2, 644–648.
32. Kornsteiner, M.; Singer, I.; Elmadfa, I. Very low n-3 long-chain polyunsaturated fatty acid status in Austrian vegetarians and vegans. Ann. Nutr. Metab. 2008, 52, 37–47.
33. Fokkema, M.R.; Brouwer, D.A.; Hasperhoven, M.B.; Martini, I.A.; Muskiet, F.A. Short-term supplementation of low-dose gamma-linolenic acid (GLA), alpha-linolenic acid (ALA), or GLA plus ALA does not augment LCP omega 3 status of Dutch vegans to an appreciable extent. Prostaglandins Leukot. Essent. Fat. Acids 2000, 63, 287–292.
34. Davis, B.C.; Kris-Etherton, P.M. Achieving optimal essential fatty acid status in vegetarians: Current knowledge and practical implications. Am. J. Clin. Nutr. 2003, 78, 640S–646S.
35. Simopoulos, A.P. Human requirement for N-3 polyunsaturated fatty acids. Poult. Sci. 2000, 79, 961–970.
36. Agnoli, C.; Baroni, L.; Bertini, I.; Ciappellano, S.; Fabbri, A.; Papa, M.; Pellegrini, N.; Sbarbati, R.; Scarino, M.L.; Siani, V.; et al. Position paper on vegetarian diets from the working group of the Italian Society of Human Nutrition. Nutr. Metab. Cardiovasc. Dis. 2017, 27, 1037–1052.
37. Burdge, G.C.; Tan, S.Y.; Henry, C.J. Long-chain n-3 PUFA in vegetarian women: A metabolic perspective. J. Nutr. Sci. 2017, 6, e58.
38. Harris, W.S. Achieving optimal n-3 fatty acid status: The vegetarian’s challenge... or not. Am. J. Clin. Nutr. 2014, 100, 449S–452S.
39. Craig, W.J. Nutrition concerns and health effects of vegetarian diets. Nutr. Clin. Pract. 2010, 25, 613–620.
40. Welch, A.A.; Shakya-Shrestha, S.; Lentjes, M.A.; Wareham, N.J.; Khaw, K.T. Dietary intake and status of n-3 polyunsaturated fatty acids in a population of fish-eating and non-fish-eating meat-eaters, vegetarians, and vegans and the product-precursor ratio [corrected] of alpha-linolenic acid to long-chain n-3 polyunsaturated fatty acids: Results from the EPIC-Norfolk cohort. Am. J. Clin. Nutr. 2010, 92, 1040–1051.
41. Simopoulos, A. The importance of the omega6/omega 3 fatty acid ratio in cardiovascular disease and other diseases. Exp. Biol. Med. (Maywood) 2008, 223, 674–688.
42. Mann, N.; Pirotta, Y.; O’Connell, S.; Li, D.; Kelly, F.; Sinclair, A. Fatty acid composition of habitual omnivore and vegetarian diets. Lipids 2006, 41, 637–646.
43. Agren, J.J.; Tormala, M.L.; Nenonen, M.T.; Hanninen, O.O. Fatty acid composition of erythrocyte, platelet, and serum lipids in strict vegans. Lipids 1995, 30, 365–369.
44. Sanders, T.A.; Ellis, F.R.; Dickerson, J.W. Studies of vegans: The fatty acid composition of plasma choline phosphoglycerides, erythrocytes, adipose tissue, and breast milk, and some indicators of susceptibility to ischemic heart disease in vegans and omnivore controls. Am. J. Clin. Nutr. 1978, 31, 805–813.
45. Gerster, H. Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? Int. J. Vitam. Nutr. Res. 1998, 68, 159–173.
46. Emken, E.A.; Adlof, R.O.; Duval, S.M.; Nelson, G.J. Effect of dietary arachidonic acid on metabolism of deuterated linoleic acid by adult male subjects. Lipids 1998, 33, 471–480.

47. Mantzioris, E.; James, M.J.; Gibson, R.A.; Cleland, L.G. Dietary substitution with an alpha-linolenic acid-rich vegetable oil increases eicosapentaenoic acid concentrations in tissues. Am. J. Clin. Nutr. 1994, 59, 1304–1309.

48. Indu, M. n-3 fatty acids in Indian diets—Comparison of the effects of precursor (alpha-linolenic acid) Vs product (long chain n-3 poly unsaturated fatty acids). Nutr. Res. 1992, 12, 569–582.

49. Mest, H.J.; Beitz, J.; Heinroth, I.; Block, H.U.; Forster, W. The influence of linseed oil diet on fatty acid pattern in phospholipids and thromboxane formation in platelets in man. Klin. Wochenschr. 1983, 61, 187–191.

50. Li, D.; Sinclair, A.; Wilson, A.; Nakkote, S.; Kelly, F.; Abedin, L.; Mann, N.; Turner, A. Effect of dietary alpha-linolenic acid on thrombotic risk factors in vegetarian men. Am. J. Clin. Nutr. 1999, 69, 872–882.

51. Sanders, T.A.; Younger, K.M. The effect of dietary supplements of omega 3 polyunsaturated fatty acids on the fatty acid composition of platelets and plasma choline phosphoglycerides. Br. J. Nutr. 1981, 45, 613–616.

52. Bjerve, K.S.; Mostad, I.L.; Thoresen, L. Alpha-linolenic acid deficiency in patients on long-term gastric-tube feeding: Estimation of linolenic acid and long-chain unsaturated n-3 fatty acid requirement in man. Am. J. Clin. Nutr. 1987, 45, 66–77.