The Impact of Common Gene Variants on the Response of Biomarkers of Cardiovascular Disease (CVD) Risk to Increased Fish Oil Fatty Acids Intakes

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Abstract

The cardioprotective actions of the fish oil (FO)-derived long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been demonstrated, and dose-response relationships have been defined. However, there is a substantial and well-recognized within-population heterogeneity in response to FO, the etiology of which is poorly understood. Genetic variation may influence responsiveness. Here we review the available literature relating to gene variants shown to influence tissue LC n-3 PUFA status and response to FO intervention. From this review we conclude that the available evidence is relatively limited. A number of individual genotype × LC-n3 PUFA × phenotype associations have been described, but few have been investigated in subsequent cohorts or confirmed in independent studies. In the context of a more stratified approach to the provision of dietary advice, there is a need for further research to refine current dietary EPA and DHA recommendations.

Contents

INTRODUCTION

Although powerful cardioprotective actions of the long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been demonstrated in a number of secondary prevention trials (12, 32, 127), a positive impact on cardiovascular disease risk is not reported consistently (85, 94). In studies with positive outcomes, benefits on cardiovascular mortality at levels of intake of EPA and DHA of 0.5–1.0 g/d, have been attributed to their antiarrhythmic action (56) or to an effect on plaque morphology and stability (111). Additional cardioprotective benefits such as antithrombotic, anti-inflammatory, and antihypertensive actions and positive effects on vascular reactivity, plasma lipid concentrations, and lipoprotein subclass distribution have been reported in a large number of human intervention trials (38, 94).

However, consistent effects on these intermediate biomarkers of cardiovascular risk are usually observed only at intake levels above 2 g/d, and even at these higher dose levels, significant interindividual variability in response is observed. The ALP study, which recruited individuals with an atherogenic lipoprotein phenotype (ALP, i.e., mildly hyperlipidemic), reported a mean increase in low-density lipoprotein cholesterol (LDL-C) and a decrease in triacylglycerol (TAG) concentrations of 7% and 35%, respectively, and an associated 26% reduction in the percentage of total LDL as LDL3 (74). These mean responses, derived from a study population of 55, represented ranges of −49% to +87% for LDL-C, −114% to +61% for TAG, and −73% to +97% for % LDL3, which highlights the heterogeneity of the response (73). Interindividual differences in the size of the outcome response to dietary intervention is not uncommon in trials with free-living participants; it is attributed to poor compliance and the challenges of achieving desired target intakes when large changes in fat composition are required. In theory such difficulties should be reduced in studies involving the addition of LC n-3 PUFAs, since target intakes can be achieved through the use of capsule supplements or single-food substitutions, and there are reliable biomarkers of subject compliance (45). However, interindividual variations in plasma TAG concentrations were found to be similar before and after fish oil

Table 1 Frequencies of triacylglycerol (TAG) responders and nonresponders to fish oil consumption as observed in the Fish Oil Intervention and Genotype (FINGEN) Study (15)

	Frequency	Percent
Responder	213	69
Nonresponder	97	31
Total	310	100

Nonresponder definition: no reduction in TAG after eight-week consumption of 1.8 g eicosapentaenoic acid + docosahexaenoic acid/day.

supplementation in the Fish Oil Intervention and Genotype (FINGEN) Study, for which a 95% compliance was recorded, with CV % of 51% and 47% for baseline and after 1.8 g EPA+DHA/day, respectively (15). More importantly, however, is the observation that after fish oil treatment in the FINGEN Study, 31% of all volunteers showed no reduction in TAG after 1.8 g EPA+DHA per day for eight weeks (**Figure 1**) (**Table 1**). Although the concept of low responsiveness is widely used in relation to immunity, hypertension, and vitamin A metabolism (10, 44, 97, 119), it has so far not been described in relation to the effectiveness of fish oil supplementation. The only study reporting low responders for a hypotriglyceridemic effect tested the effectiveness of metformin in hypertriglyceridemic patients (105). Innate characteristics such as gender, age, and genetic factors may contribute to the variability in benefit reported from secondary prevention trials and from intervention trials using LC n-3 PUFAs. Supplementary studies have identified that variation in the apolipoprotein (apo) E gene (which codes for a protein involved in lipid transport and antioxidant function) influences the plasma lipid and lipoprotein responses to LC n-3 PUFAs (73, 78). Production of tumor necrosis factor alpha (TNF-α), an inflammatory cytokine, is also modulated by LC n-3 PUFAs, and the extent of modulation is influenced by common polymorphisms in the TNF-α gene (34)

Despite these useful early findings with respect to the influence of genetic variation in apoE and TNF-α, it is clear that a large number of proteins in different tissues have the potential to determine the extent of absorption, uptake, and incorporation of LC n-3 PUFAs into cellular lipids and their subsequent metabolism into bioactive substances implicated in the pathophysiology of cardiovascular disease (**Figure 2**). Given the diverse pathways involved in responses to LC n-3 PUFAs, it is unsurprising that certain biological effects are observed at low dose levels (e.g., antiarrhythmic action), whereas moderately high levels are required for other effects to be seen (e.g., plasma TAG reduction). Metabolic diversity also implies that a range of gene variants will determine variability in LC n-3 PUFA metabolism and/or in pathophysiological pathways that contribute to cardiovascular disease (CVD) risk and that are influenced by altered EPA and DHA status.

Unraveling the genetic determinants of interindividual variation in response to LC n-3 PUFAs presents a major scientific challenge, but it is one that offers significant opportunity for public health benefit. At the present time, dietary advice for prevention of CVD includes the recommendation that healthy populations should achieve minimal intakes of 450–500 mg/d LC n-3 PUFAs, and for individuals with CVD, levels of intake of 1 g/d are advised (18, 52, 99). Given the considerable interindividual variability in phenotypic responses to LC n-3 PUFA supplementation, it is clear that some individuals require higher doses to achieve demonstrable benefit, whereas others are highly sensitive to relatively low doses of LC n-3 PUFAs. There is also some evidence to suggest that individuals with certain genotypes may experience adverse responses with respect to specific risk biomarkers, at least at

higher doses of LC n-3 PUFAs (73). Understanding the genetic determinants of variable responsiveness to LC n-3 PUFAs would provide a more rational basis for advising individuals, or stratified groups of individuals, on intake levels likely to achieve optimal reduction in risk of CVD risk.

The present review aims to assess the current state of knowledge with respect to genotype × LC n-3 PUFA × phenotype associations relevant to risk of CVD. Analysis of the available literature relating to gene variants that have been shown to influence phenotypic response to fish oils, EPA, DHA, total n-3 PUFAs, or alpha linolenic acid (ALNA) was undertaken. A total of 52 original articles were included (**Figure 3**). We conclude that the available evidence is relatively limited. A number of individual genotype × LC n-3 PUFA × phenotype associations have been described but few have been investigated in subsequent cohorts or have been confirmed in independent studies. In the context of a more stratified approach to the provision of dietary advice, there is a need for further research to refine dietary EPA and DHA recommendations in a more focused manner. Particular areas for future focus are highlighted in the Closing Remarks section of this review.

SCOPE AND STRUCTURE OF THE REVIEW

The aim of this review was to investigate LC n-3 PUFA × genotype × phenotype interactions that might underlie interindividual variability in responsiveness of CVD risk markers to supplementation with LC n-3 PUFAs (**Figure 2**). Three major search term groups were used in the literature search: (*a*) fish oil and its constituent fatty acids or fatty acid precursors, (*b*) genetic variation, and (*c*) CVD risk factors (**Table 2**). Within these three groups, the major search terms to be used were predefined, with a total of 17 search terms for "fish oil and its constituent fatty acids or fatty acid precursors" and 9 for "genetic variation." The largest search term group was "CVD risk factors" where five major subgroups were identified: (*a*) general (7 terms), (*b*) blood lipids (18 terms), (*c*) inflammation (56 terms), (*d*) vascular function (33 terms), and (*e*) insulin sensitivity (22 terms) (see **Table 2**). It should be noted that as well as the LC n-3 PUFAs in fish and fish oils, we have also included studies that have investigated genotype × phenotype interactions for studies involving ALNA because bioconversion of this precursor fatty acid to EPA and DHA, and genotype interactions for potential bioconversion, was also considered to be relevant.

In conducting the search, a combination of the three main search term groups was used, requiring that all relevant papers should include at least one term from each group. The majority of papers were identified from cohort studies, secondary prevention trials, and dietary intervention studies, with CVD risk factors or biomarkers as primary end points. However, where relevant, discussions of findings from in vitro studies have been included to provide a mechanistic context to the findings of human studies. A total of 272 individual papers were identified through the two databases that were searched (**Figure 3**). From the abstracts, 122 references were excluded as not directly relevant, and 150 full papers were sourced and read. Of these, 70 were excluded as not directly relevant, leaving 80 papers. These comprised 52 original papers and 28 reviews, with the 52 original papers used as the basis of the current review.

The body of evidence summarized in this review has been structured into two main sections. We consider potential gene variants that may influence LC n-3 PUFA status by modulating (*a*) synthesis of EPA and DHA from ALNA and (*b*) absorption of EPA and DHA from the gut, uptake into cells, and cellular metabolism. In the second section, we focus on potential diet-gene interactions for the main phenotypic cardiovascular risk factors: (*a*) blood lipids and apolipoproteins, (*b*) inflammatory markers, (*c*) coagulation and hemostasis, (*d*) vascular function, and (*e*) insulin sensitivity.

Although the major part of the present review is limited to research related to cardiovascular risk factors and biomarkers, data from

other aspects of the literature, e.g., LC n-3 PUFA × genotype interactions in relation to cancer, where mechanisms common to both cancer and CVD (e.g., inflammation) may be relevant, are also discussed. A summary of the genetic variants, largely single-nucleotide polymorphisms (SNPs), genes, and their protein products for all of the 52 original references included in this review, is given in **Table 3**.

IMPACT OF GENOTYPE ON LC N-3 PUFA SYNTHESIS AND METABOLISM

Genes That Are Involved in Endogenous EPA and DHA Biosynthesis from ALNA

Endogenous production of LC PUFAs from shorter-chain precursors is mediated by delta 5 and delta 6 desaturase enzymes (107). The n-6 PUFA, linoleic acid (LA), and the n-3 PUFA, ALNA, compete as substrates for delta 6 and delta 5 enzymatic desaturation to ultimately form arachidonic acid (AA) or EPA, respectively (107). This shared pathway is crucial to the understanding of the interaction of dietary fatty acids in the regulation of inflammation and the development of CVD. The efficiency of the delta 5 and delta 6 desaturase pathway together with relative substrate availability can alter the AA:EPA ratio and hence may contribute to interindividual variation in response to LC n-3 PUFA supplementation.

In general, the bioconversion rate for n-3 PUFAs is relatively low in humans, with an estimated conversion of ALNA to EPA of 0.2% to 6% and to DHA of 0% to 0.05% (11). It may be predicted that gene variants associated with greater fatty acid desaturase (FADS)1 and FADS2 activity would be associated with greater ALNA to EPA and DHA bioconversion rates and ultimately a higher tissue EPA and DHA status. This may be of particular relevance to individuals with a low consumption of fish who rely on plant sources of n-3 PUFAs (ALNA) to improve tissue EPA and DHA status and may contribute to the variability in effectiveness of LC n-3 PUFA supplementation observed in studies.

Individual desaturase activity can be estimated using the ratio of product to substrate; i.e., EPA:ALNA or AA:LA. In an initial 2006 publication, an analysis of 18 SNPs of the delta 5 and delta 6 desaturase genes, *FADS1* and *FADS2*, respectively, indicated a high degree of SNP and haplotype association with serum phospholipid (PL) n-6 and n-3 PUFA concentrations (96). All haplotypes that included the minor alleles were associated with higher levels of ALNA and LA and lower levels of γ-linolenic acid, AA, EPA, and n-3 docosapentaenoic acid (DPA), with no significant impact evident on DHA or n-6 DPA. A five-locus haplotype explained 27.7%, 5.2%, and 1.4% of the variability in AA, EPA, and DHA levels respectively. Baylin et al. (8) examined the effect of a *FADS* SNP (rs3834458) in a Costa Rican population of 1,694 survivors of myocardial infarction and an equal number of healthy controls. Homozygotes for the deletion allele (−/−) had lower levels of EPA, ALNA, and AA in both adipose tissue and plasma compared to *T* allele carriers, and these fatty acids were highest in *TT* homozygotes. Additional studies have reported a significant impact of *FADS1* and *FADS2* genotype on n-3 PUFA status in the adipose of pregnant women and in one-month postpartum breast milk (124), and in plasma, serum, and erythrocytes (68, 71, 110), with no association evident in the Bavarian Nutrition Survey II (91).

Associations between *FADS1-FADS2* SNPs and haplotypes and blood lipids have been observed in three genome-wide association studies (4, 92, 110). Furthermore, associations between variation in these gene loci and the incidence of diseases with a chronic inflammatory component have been reported (71, 96, 114), although Baylin et al. (8) failed to detect FADS SNP association with incidence of myocardial infarction, despite genotype-dependent variation in tissue PUFA levels.

The endogenous production of LC n-3 PUFAs from dietary precursors also requires the elongase enzyme, which catalyzes the

Table 2 Search terms used for the present literature review

Fish oil and its constituents	Genetic variation	Cardiovascular risk factors				
		General	Blood lipids	Inflammation	Vascular function	Insulin sensitivity
Fish oil*	Polymorphism	Cardiovascular disease	Blood lipids	Inflammat*	Vascular*	Insulin*
Cod liver oil	Restriction fragment length polymorphism	CVD	Cholesterol*	Z Score	Micro-vascular*	Postprandial insulin response
Fish intake	RFLP	Coronary artery disease	HDL	CRP	Microvascular*	Insulin: C-peptide
Fish consumption	RFLPs	Coronary arterial disease	High density lipoprotein	C-reactive protein	Ischemia	Glucose tolerance test
Omacor	Single nucleotide polymorphism	CAD	LDL	C reactive protein	Hypoxia	GTT
n3 PUFA	SNP	Coronary heart disease	Low density lipoprotein	Cytokine*	Vasodilat*	Intravenous glucose tolerance test
n-3 PUFA	SNPs	CHD	VLDL	Interleukin*	Vasoreactivity	IVGTT
n3 fatty acids	Splice variant		Very low density lipoprotein	IL	Endothelial*	RQUICKI
n-3 fatty acids	Haplotype		HDL/LDL ratio	TNF*	FMD	HOMA
Eicosapentaenoic acid			HDL:LDL ratio	Interferon gamma	Flow mediated dilatation	HOMA Index
EPA			TAG	IFN*	DVP	Euglycaemic clamp
Docosahexaenoic acid			Triacylglycerol	Leukotriene*	Digital volume pulse	Euglycemic clamp
DPA			TG	LTB4	LDI	Glycated hemoglobin
Alpha linolenic acid			TRL	LTB3	Laser doppler	Glycemic index
α-linolenic acid			Tag rich lipoprotein	Prostaglandin*	PWA	Hyperglycaemi*
			Plasma fatty acid composition	PGE2	Pulse wave analysis	Hypoglycaemi*
			Blood fatty acid composition	PGE3	PWV	Diabetes*
				Activation markers	Pulse wave velocity	Maturity onset diabetes
				Lymphocyte	Plethysmography	MOD
				Monocyte	Blood flow	
				Neutrophil	Blood pressure	
				Granulocyte		

				CD25 HLA-DR TLR Toll like receptor CD36 Scavenger receptor CD44 CD44v3 CD14 LPS receptor Adhesion molecules ICAM-1 VCAM VCAM-1 E selectin NFκB Nuclear factor kappa B PPAR* Peroxisome proliferator activated receptor gamma MMP Metalloproteinase HA Hyaluron* Nitric oxide NO Nitric oxide synthase NOS eNOS iNOS Lipoxygenase LOX Cyclooxygenase COX	BP Arterial* ABPI Ankle brachial pressure index Hypertension Endothelin ET-1 ADMA Asymmetrical dimethylarginine Endopat Microalbuminuria albuminuria	Juvenile onset diabetes Metabolic syndrome Syndrome X

Table 3 Overview of proteins and gene variations included in the review

Protein	Tissue predominantly produced by	Gene	Chromosome position	Nature of variation	Protein function	References
Delta 5 desaturase	Liver	FADS1	11q12.2	rs174537 G/T near gene 3′ rs174543 A/T near gene 3′ rs174544 C/A 3′UTR rs174545 C/G 3′UTR rs174553 A/G intron rs174556 C/T intron rs174561 T/C intron	Delta 5 and delta 6 desaturases are required for the synthesis of the LC n-3 PUFAs; EPA forms the shorter-chain ALNA. The same enzymatic pathway is used to convert LA to AA. Delta 6 desaturase is also required for the conversion of EPA to DHA	(8, 68, 71, 91, 96, 110, 114, 124)
Delta 6 desaturase	Liver	FADS2	11q12.2	rs174570 T/C intron rs174583 T/C intron rs174589 C/T intron rs174593 C/T intron rs174611 C/T intron rs99780 C/T intron		
Delta 5 and delta 6 desaturase	Liver	FADS1 and FADS2	11q12.2	rs3834458 T/del intragenic rs174627 C/T intragenic rs17831757 C/T intragenic		
	Liver	FADS3	11q12.2	rs1000778 C/T intron		
Elongase	Liver	ELOVL2	6. 4q25	rs953413 C/T near gene	Elongase is involved in the biosynthetic pathway for highly unsaturated n-3 and n-6 fatty acids (the same pathway that involves delta 5 and 6 desaturase)	(110)
Fatty acid binding protein 2	Intestine	FABP2	4q28–31	rs1799883 A/T exon Ala54Thr	Intracellular protein expressed, which is involved in many stages of LC saturated and unsaturated fatty acid, including uptake and targeting of fatty acids toward different metabolic pathways in the enterocyte, protecting cells against the cytotoxic influence of free fatty acids, and modulating enzymes involved in lipid metabolism	(1, 82)

Fatty acid CoA lygase	Liver	FACL4	Xq22.3	rs1324805 C/T intron	Esterifies polyunsaturated fatty acids with coenzyme A FACL4 has preference for EPA and AA; promotes diacylglycerol synthesis and fatty acid storage in TAG)	(128)
Lipoprotein (a)	Liver	LPA	6q26	C/T 93 5′UTR promoter	Lp(a) is composed of apolipoprotein A and LDL-C. It has antifibrinolytic- and thrombus-promoting properties as it is structurally similar to plasminogen	(106)
Cytochrome P450 enzymes	Vascular endothelium Smooth muscle	CYP1A1.1	15q24.1	rs1048943 exon Ile462Val	Detoxification enzyme that metabolizes LC PUFAs, EPA, DHA, and AA. It metabolizes EPA to EPA epoxides, which alter potassium channels in smooth muscle and lead to vasodilation	(98)
	Intestinal tract Liver, pancreas	CYP1A1.4		rs1799814 exon Thr462Asn	Promotes cholesterol catabolism to bile acids	
ApoE	Liver	APOE	19q13.3	3 alleles involve amino acid changes at 2 positions APOE2 Cys112 Cys158 APOE3 Cys112 Arg158 APOE4 Arg112 Arg158	Involved in apolipoprotein metabolism, VLDL secretion, VLDL hydrolysis to LDL, and receptor-mediated uptake of TRL by the liver	(15, 74, 78, 83)
ApoA5	Liver	APOA5	11q23	rs662799 T/C 5′near gene −1131 rs3135506 C/G exon S19W	Affects fasting plasma triglyceride concentrations by impact on VLDL production and lipoprotein lipase–mediated TRL hydrolysis. A component of VLDL, HDL, and chylomicrons	(53)
ApoC-III	Liver	APOC3	11q23.1	rs2854116 T/C near gene −455	A VLDL-associated protein that inhibits lipoprotein lipase and hepatic lipase. Inhibits hepatic uptake of TRL. Induces the development of hypertriglycemia	(79)
Hepatic lipase	Liver	LIPC	15q21	rs2070895 G>A −250	Displays both TAG and phospholipid lipase activity and is involved in hepatic TRL remnant handling. Converts VLDL to LDL and metabolizes HDL	(63)

(*Continued*)

Table 3 (*Continued*)

Protein	Tissue predominantly produced by	Gene	Chromosome position	Nature of variation	Protein function	References
CD36	Macrophages Hepatocytes Myocytes Adipocytes Endothelial cells	CD36	7q11.2	rs1527483 G/A intron rs1049673 G/C 3′ near gene rs1761667 G/A intron rs1984112 G/A intron	Scavenger receptor involved in the uptake of oxidized LDL into macrophages, leading to foam cell formation Aids transport of LC PUFAs into a range of cells	(66)
PPARα	Liver Muscle Heart Adipose Kidney	PPARA	22q13.31	rs1800206 C>G exon Leu162Val rs1800234 T>C exon Val227Ala rs6008259 G>A 3′ UTR rs3892755 C>T 3′UTR	Regulates multiple genes involved in triglyceride, cholesterol, apolipoprotein and lipoprotein synthesis, and fatty acid oxidation	(14, 83, 89, 90, 109, 118, 126)
PPARγ	Most tissues	PPARG	3p25	rs1805192 C>G exon Pro12Ala	Regulates inflammatory gene transcription, adipocyte differentiation, and insulin sensitization	(62, 95)
NF-κB	Most tissues	NFKB1	4q24	rs28720239 ATTG/- 5′ near gene −94	Regulates inflammatory gene transcription	(28)
Cyclo-oxygenase 2	Activated cells at sites of inflammation Platelets Endothelial cells	PTGS2	1q25	rs4648308 G>A 3′ near gene rs4648310 A>G 3′ near gene rs5275 T>C 3′UTR +6365 rs5277 G>C exon neutral Val102Val rs689466 A>G 5′ near gene −1329	Competitively metabolizes AA and EPA to prostaglandins and thromboxanes	(29, 42, 103, 104, 108)
5-Lipoxygenase	Monocytes Macrophages Neutrophils Mast cells	ALOX5	10q11.2	Variable number of tandem Sp1 binding sites (3–8) in gene. Common allele = 5 Sp1 binding sites	Competitively metabolizes AA and EPA to leukotrienes	(23)
PGE4 receptor	Smooth muscle Hypothalamus	PTGER4	5p13.1	rs111866313 G>A exon Val294Ile	Mediates effects of PGE2 in target cells and tissues	(84)

PGE synthase	Endothelium Hypothalamus Some inflammatory cells	PGES	9q34.3	rs7873087 A>T 5′UTR −664	Leads to proinflammatory prostaglandin E2 synthesis. PGE2 induces fever and is a smooth muscle relaxant and vasodilator	(84)
TNF-α	Monocytes Macrophages Lymphocytes	TNF	6p21.3	rs361525 G>A promoter −238 rs1800629 G>A promoter −308 rs1799724 C>T promoter −857	Inflammatory cytokine. Induces fever and C-reactive protein release from liver, impairs insulin signaling, up-regulates endothelial and leukocyte adhesion molecules, and increases phagocytosis	(26, 27, 34, 65, 70, 101)
Lymphotoxin-α	Monocytes Lymphocytes	LTA	6p21.3	rs909253 G>A intron +252	Effects same as those of TNF-α	(34, 64, 70)
IL-6	Monocytes Lymphocytes Adipocytes Smooth muscle	IL6	7p21	rs1800795 G>C near gene −174	IL that has been shown to have both inflammatory and anti-inflammatory actions Induces fever, energy mobilization, and hepatic C-reactive protein synthesis but inhibits TNF production and induces the anti-inflammatory IL-10	(65, 70)
IL-1β	Lymphocytes Monocytes	IL1B	2q14	rs16944 C>T 5′ near gene −511 rs1143643 G>A intron +6054	Inflammatory cytokine	(65, 70, 101)
IL-10	Monocytes Lymphocytes Mast cells	IL10	1q31	rs1800896 A>G 5′ near gene −1082	Anti-inflammatory cytokine. Inhibits the production of proinflammatory cytokines TNF, IFN-γ, IL-2, and GM-CSF and down-regulates monocyte surface marker expression	(65, 70, 101)
CD44v3	Monocytes Lymphocytes Neutrophils	CD44	11p13	Splice variant incorporating exons 3–10 into protein in multiple combinations	Surface receptor involved in leukocyte homing. Ligand for hyaluronate, which is a major constituent of the extracellular matrix. The variant 3 form contains a heparin sulfate-binding site that allows binding of TGFβ and FGF and therefore may be involved in the resolution of inflammation	(67)

(*Continued*)

Table 3 (*Continued*)

Protein	Tissue predominantly produced by	Gene	Chromosome position	Nature of variation	Protein function	References
Fibrinogen alpha chain	Liver	FGA	4q28	exon Thr312Ala	Half of the fibrinogen molecule involved in initiating the clotting cascade leading to thrombus formation	(115)
Factor VII	Liver	F7	13q34	exon Arg353Gln	Involved in coagulation cascade	(64)
Plasminogen activator inhibitor	Endothelium, adipose tissue	SERPINB2	18q21.3	rs1799889 G4/G5 promotor −675	A serine protease inhibitor that inhibits tPA; tPA activates plasminogen to break down blood clots	(24)
Endothelial Nitric oxide synthase eNOS	Endothelium	NOS3	7q36	G>T 894 exon Glu298Asp	Inducible enzyme that regulates the conversion of L-arginine to nitric oxide in the endothelium	(58)
Potassium β channel subunit	Cell membranes of most tissues	KCNE1	KCNE1 21q22.12	rs1805127 G>A exon Gly38Ser	Potassium channels are transmembrane structures that transport potassium. They function to reset a depolarized cell to a resting state following activation. The β subunit modulates their activity	(30)
Adiponectin	Adipose tissue	ADIPOQ	3q27	rs1501299 G>T 3′UTR 276	Regulates glucose and fatty acid metabolism; increases insulin sensitivity; anti-inflammatory	(117)
Leptin receptor	Hypothalamus	LEPR	1p31	rs3790433 G>A intron	Binding of leptin modulates insulin secretion, stimulates glucose uptake and fatty acid oxidation, and reduces appetite	(81)
Complement component 3	Liver and adipose tissue	C3	19p13.3	rs11569562 A>G intron	Involved in clotting cascade Can be converted to acylation-stimulating protein, which aids NEFA transport into adipocytes	(80)

The reference column indicates references in which SNP × LC n-3 PUFA interactions have been observed and have been used in the original reference count (see **Figure 3**). Abbreviations: AA, arachidonic acid; ALNA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; IFN, interferon; IL, interleukin; LA, linoleic acid; LC, long chain; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); NEFA, nonesterified fatty acids; PGE2, prostaglandin E2; PUFA, polyunsaturated fatty acid; TAG, triacylglycerol; TNF, tumor necrosis factor; tPA, tissue plasminogen activator; TRL, triglyceride rich lipoproteins; VLDL, very-low-density lipoprotein.

conversion of AA to 22:4n-6 and ultimately to 22:5n-6 and EPA to DPA and ultimately to DHA. The minor A allele of an SNP in the *EVOVL2* gene (rs953413) has been associated with higher levels of EPA in the InCHIANTI Study and lower levels of DPA in the GOLDN (Genetics of Lipid-Lowering Drugs and Diet Network) study, indicating that the A allele is likely to be associated with lower levels of enzyme activity or concentration (110).

It can be concluded that common SNPs in either desaturase or elongase genes alter endogenous fatty acid metabolism and tissue LC n-3 PUFA status and contribute to the variability in the response to LC n-3 PUFAs; however, the impact of individual SNPs in FADS and elongase genes on CVD risk markers remains to be established.

Genes That Are Involved in EPA and DHA Absorption, Metabolism, and Cellular Uptake

After consumption, the absorption, cellular uptake, metabolism, and transport of LC n-3 PUFAs in the circulation, and intracellularly, are under the control of a host of fatty acid-binding proteins, metabolizing enzymes and membrane transporters. Variants in the genes encoding these proteins have the potential to influence tissue LC n-3 PUFA status.

Genes involved in the absorption of LC n-3 PUFAs. Fatty acid-binding protein 2 (FABP2) is a small (14–15 kDa) intracellular lipid-binding protein that plays a central role in the absorption of LC saturated and unsaturated fatty acids (16). The common *Ala54Thr* variant has been shown to be associated with a greater plasma postprandial TAG (43) and unsaturated fatty acid (3) response following the consumption of a fat-containing meal. This finding is consistent with the reported twofold-increased binding affinities of recombinant FABP-Thr relative to FABP-Ala for LC unsaturated fatty acids (6) and the more efficient transport of LC fatty acids and increased TAG secretion by Caco-2 cells expressing FABP-Thr relative to FABP-Ala (5).

The impact of this polymorphism specifically on LC n-3 PUFA absorption is has been investigated in only two intervention studies. Pishva and coworkers (82) observed a severalfold higher plasma EPA concentration in Thr carriers versus Ala homozygotes following supplementation with 1.8 g EPA per day, with a significant genotype × treatment interaction evident. These data are consistent with the findings mentioned above of greater LC PUFA binding (6) and transport across enterocytes (5) associated with the *T* allele. In a postprandial analysis, Ågren et al. (1) reported that the chylomicron and very-low-density lipoprotein (VLDL) concentrations of the majority of the C14–C18 fatty acids were elevated in Thr homozygotes relative to Ala homozygotes following the consumption of a fish oil–containing test meal. A more modest trend toward greater LC n-3 PUFA absorption in Thr carriers observed in this study may partly be related to small sample sizes (n = 78). The *FABP Ala54Thr* SNP has also been shown to influence the TAG response to fish oil supplementation (see later section). Clearly, polymorphisms that affect LC n-3 PUFA absorption could contribute to the variation of responses observed in supplementation studies.

Genes involved in cellular uptake of LC n-3 PUFAs. CD36 is a scavenger receptor expressed on macrophages and is involved in the uptake of oxidized LDL, which leads to the development of foam cells. CD36 is also involved in the transport of LC PUFAs into hepatocytes, myocytes, adipocytes, and endothelial cells. Haplotypes of SNPs at the CD36 locus are associated with raised fasting plasma nonesterified fatty acid (NEFA) concentrations (66). In a study where 111 men consumed 1.7 g of EPA plus DHA daily for 12 weeks, a haplotype of four SNPs at the CD36 locus (25444GG, 30294GG, −31118GG, and −33137GG) was associated with a greater reduction in fasting plasma TAG concentration (66). This association may have resulted from an effect on CD36

activity or on the availability of its ligand, oxidized LDL (oxLDL).

Genes involved in fatty acid metabolism. In addition to FADS1 and 2, elongase, and FABP, SNPs in a number of other genes encoding fatty acid metabolizing enzymes, including fatty acid coenzyme A ligase 4 (128) and apolipoprotein E (83), have been shown to influence tissue LC n-3 PUFA status (**Table 4**), but these findings have not been confirmed in independent studies. Su et al. (108) have shown that heterozygosity for a polymorphism in the COX-2 gene is associated with lower erythrocyte DHA levels in a Taiwanese population (see **Table 4**).

Given the central role that fatty acid transport and metabolizing enzymes have in determining tissue LC n-3 PUFA status (and therefore ultimately the physiological benefits associated with increased EPA and DHA consumption), further investigation into the above-mentioned associations, along with investigation of variants in genes encoding other important enzymes such as cytochrome P4501A, long-chain acyl co-synthase 3, and lipases, including hepatic lipase, lipoprotein lipase, and phospholipases, is merited (63, 98, 128) (see **Table 4**).

IMPACT OF GENOTYPE ON THE RESPONSE OF ESTABLISHED AND PUTATIVE CARDIOVASCULAR RISK MARKERS TO ALTERED LC N-3 PUFA STATUS AND INTAKE

Genotype × LC n-3 PUFA Interactions as Determinants of Blood Lipid and Apolipoprotein Concentrations

The hypotriglyceridemic benefits of fish oils are well established, with intakes of approximately 3 g EPA+DHA per day shown to reduce fasting TAG levels by 25% to 35% (7, 39). On the basis of this relatively consistent body of available evidence, intakes of 2 to 4 g per day are recommended by the American Heart Association as an effective therapy for hypertriglyceridemia (52) and as an alternative to pharmacological approaches such as use of fibrates. At this level of intake, a potentially deleterious 5% to 10% increase in LDL-C has been reported (7, 39), although it is recognized that the cardiovascular consequence of these raised concentrations is likely to be partly offset by an associated increased in LDL particle size (73).

Although mean population responsiveness of blood lipids to dietary EPA and DHA intakes is well established, the etiology of the recognized heterogeneity in responsiveness remains elusive.

Apolipoprotein E genotype. ApoE plays a central role in fatty acid and general lipoprotein metabolism (41). Two common nonsense mutations lead to three common protein isoforms, namely E2 (Cys112, Cys158), E3 (Cys 112, Arg 158), and E4 (Arg 112, Arg 158). The E4 isoform has been relatively consistently associated with increased risk of CVD (46, 87) (and also with enhanced risk of Alzheimer's disease).

Although the Atherogenic Lipoprotein Phenotype (ALP) trial was not designed to examine the impact of genotype on responsiveness and lacked power to fully examine diet × genotype interactions, retrospective analysis suggested that the individual LDL-C response (group mean increase of 7%) may be modulated by *APOE* genotype with 3%, 1%, and 15% increases evident in *APOE2* carriers, *E3/E3* homozygotes, and *APOE4* carriers, respectively (73). Furthermore, subsequent correlation analysis between changes in platelet fatty acid composition and LDL-C indicated that DHA was largely associated with the LDL-C-raising effect (59). A subsequent "fit-for-purpose" study, with prospective recruitment of healthy volunteers according to *APOE* genotype and supplements of EPA and DHA (3–4 g per day) given separately, confirmed these initial findings, with a 10% increase in LDL-C in *APOE4* carriers following DHA intervention and no significant impact of treatment in any of the other genotype × EPA/DHA subgroups (78). In addition, associated mechanistic studies

Table 4 Gene variants for which interactions with long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs) and cardiovascular risk markers have been reported in only a single study to date

Gene	SNP	Study population	SNP interaction with LC n-3 PUFAs and/or risk factor	Reference
Genes involved in fatty acid absorption, cellular uptake and metabolism				
CD36	25444G>A 30294G>C −31118G>A −33137A>G	114 males	Intervention: 1.7 g EPA+DHA per day for 12 weeks Outcome: TAG lowering only evident in GG homozygotes	(66)
Fatty acid coenzyme A ligase 4	rs132480 C>T	95 males and 116 females 56 individuals with the MetS, 41 with DD, and 113 controls	T allele associated with 17% reduced DHA in the plasma phosphatidylcholine fraction, in MetS but not in controls or DD. No allelic effect was observed for EPA in any group	(128)
Apolipoprotein E (apoE)	E4	28 males, including 8 E4 carriers and 20 non-E4 carriers	Intervention: 1.9 g EPA + 1.1 g DHA for 6 weeks Baseline: 67% higher EPA and 60% higher DHA in plasma TAG Outcome: lower enrichment in plasma (NEFA with EPA and TAG with DHA) in E4 carriers	(83)
Cyclooxygenase 2	rs4648308 G>A	82 male and 50 female patients with chronic hepatitis C, undergoing IFNγ treatment	Erythrocyte DHA content associated with response to IFNγ treatment in AG heterozygotes only	(108)
Genotype × LC n-3 PUFA interactions as determinants of blood lipid and apolipoprotein concentrations				
NF-κB	Ins/Del position −94 in *NFKB1*	Toronto Nutrigenomics and Health Study: 440 males and 256 females, including 593 diabetics and 103 controls	In *Ins/Ins* individuals, a positive association between total dietary n-3 PUFAs and HDL-C was evident, with no association in *Del* carriers	(28)
apoA5	−1131 T>C 56 C>G	Framingham Heart cohort: 1,001 males and 1,147 females	The -1131T>C SNP modulated the association between dietary n-6 PUFAs and plasma TAG Neither SNP modulated the association between total dietary n-3 PUFAs and the plasma lipid profile	(53)
Hepatic lipase	−250 G>A	KANWU Study: 77 males and 74 females	Intervention: SFA- versus MUFA-rich diet +/− 2.4 g EPA+DHA per day for 3 months Outcome: SNP influenced the LDL-C response to SFA- versus MUFA-rich diet. No impact of genotype on either the fasting or postprandial lipid responses to LC n-3 PUFAs	(63)
apoC3	−455T>C	Verona Heart Project: 507 males and 341 females, including 590 with CAD and 258 controls	In T carriers, a negative association between erythrocyte LC n-3 PUFA status and plasma apoC3 was evident, with a positive association in CC individuals. No genotype × LC n-3 PUFA interactions were evident for plasma TAG	(79)

(*Continued*)

Table 4 (*Continued*)

Gene	SNP	Study population	SNP interaction with LC n-3 PUFAs and/or risk factor	Reference
Complement component C3	rs11569562 G>A	Lipgene-SU.VI.Max cohort: 1,014 males and 669 females, with 840 MetS patients and 843 controls	Plasma LC n-3 PUFA × SNP interaction for plasma TAG, with the GG genotype showing an inverse association between plasma LC n-3 PUFA and TAG concentrations. AA or AG genotypes showed a positive association for plasma LC n-3 PUFA and TAG No SNP × LC n-3 PUFA interaction evident for other SNPs	(80)
Lipoprotein (a)	93 C>T	260 males and 387 females	Interaction between SNP and dietary fish intake to alter plasma lipoprotein (a) concentrations	(106)
Genotype × LC n-3 PUFA interactions as determinants of inflammation				
5 Lipoxygenase	Variable Nº of SP1 binding sites in ALOX5 promoter	573 males and females	Dietary intake of n-3 fatty acids reduced the association of SNP with intima media thickness, an indication of atherosclerosis	(22)
PGE2 synthase	−664 A>T	483 CA patients and 582 controls	Decreased risk of CA was associated with increased dietary fish intake only in T allele carriers	(84)
PGE2 receptor EP4	Val294Ile		Increased dietary fish intake was associated with increased risk if CA for variant genotypes but not for Val/Val homozygotes	
TNFα	−857 C/T	39 males and 60 females with Crohn's disease and 116 controls	Interaction of T allele carriers in combination with low dietary n-3 PUFA associated with increased disease activity, indicating increased inflammation	(35)
CD44	Splice variant 3	97 male PVD patients and 108 male controls	CD44v3 was reduced on the surface of monocytes from PVD patients compared to controls. Following 12 weeks supplementation of 1.7 g EPA+DHA per day, CD44v3 was increased toward normal levels in PVD patients, with no effect in controls	(67)
Genotype × LC n-3 PUFA interactions as determinants of coagulation in hemostasis				
Factor VII	Arg353Gln	Diet and Omega-3 Intervention Trial on Atherosclerosis: 204 hypercholesterolemic males	Intervention: Mediterranean diet, 2.4 g EPA+DHA per day (FO), Mediterranean diet + FO Outcome: no significant impact of SNP on Factor VII antigen or its activated form	(64)
Genotype × LC n-3 PUFA interactions as determinants of vascular and cardiac function				
Potassium channel subunit KCNE1	G38S	441 males and females recruited as 80 families, with at least 4 members per family	Erythrocyte n-3 PUFA was inversely associated with QT interval, and the G38S was associated with QT interval No interactive impact of genotype × n-3 PUFA status reported	(30)

(*Continued*)

Table 4 (*Continued*)

Gene	SNP	Study population	SNP interaction with LC n-3 PUFAs and/or risk factor	Reference
Methylene-tetrahydrofolate reductase	C677T	53 males and 73 females 42 of each genotype (M/F) group CC (13/29), CT (19/23), and TT (21/21)	No interaction between cod liver oil use, genotype, and vascular reactivity as assessed by FMD, although the authors state that the findings may be compromised by the small number of subjects taking supplements	(86)
Endothelial nitric oxide synthase (eNOS)	Glu298Asp	117 males and 131 females	Significant association between FMD and plasma and erythrocyte % EPA+DHA in Asp carriers but no association evident in Glu homozygotes	(58)
Genotype × LC n-3 PUFA interactions as determinants of insulin sensitivity				
Complement component C3	rs2250656 G>A	Lipgene-SU.VI.Max cohort: 1,014 males and 669 females, with 840 MetS patients and 843 controls	A allele carriers had an odds ratio of the MetS of 2.59 relative to GG homozygotes. Plasma n-6 PUFA status modified the association, but the association was unaffected by plasma total or LC n-3 PUFA status	(80)
Interleukin 1β	6054 G>A	GOLDN study: 540 males and 580 females, 379 with MetS and 741 controls	6054G>A predicted MetS with odds ratio of 2.22 and 1.79 in GG and GA relative to AA. Impact of genotype only evident in subgroup with an erythrocyte % EPA+DHA <3.4% (group median). No LC n-3 PUFA interactions observed with other SNPs	(101)

Abbreviations: CA, colorectal adenoma; CAD, coronary artery disease; DD, depressive disorder; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FMD, flow-mediated dilation; FO, fish oil; GOLDN, Genetics of Lipid-Lowering Drugs and Diet Network; HDL-C, high-density lipoprotein cholesterol; IFN, interferon; LC, long chain; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; MUFA, monounsaturated fatty acid; NEFA, nonesterified fatty acids; NF, nuclear factor; PVD, peripheral vascular disease; SFA, saturated fatty acid; SNP, single nucleotide polymorphism; TAG, triacylglycerol.

indicated that the LDL-C raising effect of DHA in *APOE4* carriers is likely to be due to decreased hepatic LDL uptake (78) and the production of smaller VLDL particles by the liver (unpublished findings, A.M. Minihane), which serve as LDL precursors. Interestingly, this apparent genotype-specific increase in LDL-C in response to fish oil was not evident at intakes of 0.7 g or 1.8 g EPA+DHA per day in healthy volunteers in the FINGEN trial (15), which recruited 312 healthy adults prospectively according to *APOE* genotype, indicating that there may be a dose threshold below which genotype-specific responses are not apparent.

Furthermore, in the ALP trial there was evidence of an impact of *APOE* genotype on the reduction in % LDL3 following fish oil intervention, with greater reductions in *APOE2* and *APOE4* carriers relative to the wild-type *E3/E3* genotype (73). Two trials conducted in healthy cohorts failed to replicate this finding, indicating that the impact of *APOE* genotype on the LDL3 response may be dependent on baseline lipid levels (15, 78).

Although available data are limited, these results suggest greater TAG lowering in *APOE2* and *APOE4* carriers relative to the *E3/E3* genotype. In the ALP study, a significantly greater blunting of the postprandial incremental TAG response following consumption of fat-containing meals was evident in *APOE2* carriers (73). In the FINGEN trial, although no genotype × diet interaction was evident, a significant genotype × diet × gender interaction

emerged, with a 15% and 23% reduction in fasting TAG in *APOE4* males following consumption of 0.7 g and 1.8 g EPA+DHA per day, relative to equivalent 8% and 11% reductions in the group as a whole (15). Consistent with the indication of greater TAG lowering in *APOE4* males is the observation of a genotype × LC n-3 PUFA interaction for adipose tissue lipoprotein lipase (LPL) gene expression in the ALP study, which included only males, where an almost threefold increase was evident in *APOE4* carriers, with no significant change in the *APOE4* noncarrier group (51).

Transcription factors. EPA and DHA metabolites are recognized as being the most potent dietary derived ligands for the peroxisome proliferator-activated receptor (PPAR) family of transcription factors (17). PPAR-α regulates multiple genes involved in TAG-rich lipoprotein (TRL) and HDL homeostasis such as LPL, apoC3, apoA5, and apoA1 and several enzymes involved in lipogenesis and fatty acid oxidation (50). The PPAR-γ family of transcription factors plays a central role in adipocyte differentiation and insulin sensitivity (19, 102) (see section titled Genotype × LC n-3 PUFA Interactions as Determinants of Insulin Sensitivity). In addition, PPARγ regulates a number of genes involved in lipid storage and metabolism (19, 113).

To date, a number of publications have examined the impact of the *PPAR-α* Leu162Val variant on the association between n-3 PUFA status and a range of outcomes measures related to lipid metabolism. In the first of these analyses, based on the Framingham cohort, the association between *PPAR-α* genotype and an array of plasma and lipoprotein, lipid, and apolipoprotein variables was examined. Overall, carriers of the *Val* allele had lower plasma TAG and apoC3 concentrations relative to noncarriers, when consuming a high-PUFA diet, with n-6 PUFAs and n-3 PUFAs having comparable effects (109). No specific analysis of LC n-3 PUFAs was conducted. Furthermore, no genotype-mediated differences in the association between PUFAs and plasma LDL-C, HDL-C, apoB, or apoA1 was evident. The results are consistent with previous findings, which indicated that ligand binding is associated with higher PPAR transcriptional activations by the 162Val allele relative to the 162Leu allele, but only at high background concentrations of ligand, with the opposite impact of genotype at lower ligand concentrations (25, 93).

A subsequent analysis of the Atherosclerosis Risk in the Community (ARIC) cohort (118) failed to replicate the findings of the Framingham cohort and reported no impact of the *PPAR-α Leu162Val* variant on the association between PUFA intake and lipid levels. Two additional SNPs analyzed showed a complex mode of penetrance, with the impact of the *3′UTR G>A* and the *3′UTR C>T* on plasma cholesterol concentrations dependent on ethnicity. For the latter SNP, in African Americans high LC n-3 PUFA intakes were associated with lower total cholesterol and LDL-C concentrations only in those with the TT genotype, with no interactions evident in white Americans (118).

In individuals prospectively recruited according to *PPAR-α Leu162Val* genotype, Caron-Dorval et al. (14) observed no significant interaction between genotype and the plasma lipid–modulating effects of LC n-3 PUFA intervention (3 g EPA+DHA per day).

Two separate studies have shown n-3 PUFA × PPAR-α interactions (89, 90). An in vivo study showed that 1.9 g EPA + 1.1 g DHA daily for six weeks increased plasma LPL more in Leu162Leu homozygotes compared to 162Val carriers and that LPL activity negatively correlated with plasma TAG levels only in Leu162Leu homozygotes (89). The authors went on to show in transfection studies that Leu162Leu homozygotes were more responsive to LC n-3 PUFAs with regard to LPA transcription (89). A second study reported significantly lower PPAR-α and ApoA1 expression, with a tendency toward lower LPL gene expression in ex vivo macrophages following culture with LC n-3 PUFAs for *PPAR-α 162Val* carriers compared to body mass index (BMI)- and

age-matched *PPAR-α Leu*162leu homozygotes (90). These results indicate that the PPAR-α Leu162Val genotype may in part be responsible for the observed variable response to LC n-3 PUFAs. These two studies should be interpreted with caution, however, as they included only 14 and 6 participants per genotype group.

Therefore, although overall there is evidence that the *PPAR-α* genotype may modulate the lipoprotein response to LC n-3 PUFAs, the findings to date have come from relatively small studies and lack consistency, with the impact of genotype likely to be dependent on background LC n-3 PUFA status. Further research from larger studies in which participants are recruited prospectively on the basis of genotype are needed to provide clarification.

In vitro studies have provided evidence that the Ala12 isoform of PPAR-γ2 is associated with a reduced ability to induce transcription and adipogenesis (20, 72). In the Kuopio, Aarhus, Naples, Wollongong, Uppsala (KANWU) Study, the impact of a saturated fatty acid (SFA)- versus monounsaturated fatty acid (MUFA)-rich diet, supplemented with or without 2.4 g EPA+DHA per day for three months, on a range of lipid and insulin sensitivity–related outcomes was investigated (62). In individuals with a total fat and SFA intake of <37% and 10% of dietary energy, respectively, carriers of the *Ala12* allele had significantly greater reductions in serum TAG levels in response to LC n-3 PUFA supplementation, suggesting that *PPAR-γ Pro12Ala* genotype may contribute to the interindividual variability in the serum TAG response to EPA+DHA intervention.

Given the generic role of a number of transcription factors in modulating the response to EPA and DHA intakes for a wide array of CVD-related outcomes, including lipid metabolism, insulin sensitivity, vascular function, and inflammation, a focus on loci within the PPAR-α and PPARγ genes should represent a priority.

Inflammatory markers. Although cause and effect is difficult to establish, the intimate link between inflammation and dyslipidemia is being increasingly recognized. For example, elevated TNF-α production is associated with increased adipose tissue fatty acid flux, impaired LPL activity, down-regulation of PPAR-α, insulin insensitivity, increased hepatic VLDL-TAG production, and impaired reverse cholesterol transport (31, 55). Three studies by two independent groups have reported on inflammatory-related genotype × PUFA × blood lipid interactions.

In an observational study in 595 young healthy adults, Fontaine-Bisson & El-Sohemy (26) reported that the positive association between total PUFA and HDL-C was evident only in noncarriers of the minor "A" allele for the *TNF-α -238G>A* and *-308G>A* loci. The effect was evident for both n-3 and n-6 PUFAs, but a significant genotype × diet effect was only evident for n-6 PUFAs. The same authors also reported significant PUFA × genotype × HDL interactions in a type 2 diabetic population (27). Markovic et al. (70) investigated the impact of SNPs in a number of inflammatory genes on the response to intervention with 1.8 g EPA+DHA per day for 12 weeks. Although no significant impact of the above-mentioned *TNF-α -308G>A* was evident, a difficult-to-interpret interaction between BMI × *TNF-β+252A>G* × EPA was reported to influence the hypotriglyceridemic response.

Additional genotypes. Associations between individual SNPs and the plasma lipid response to n-3 PUFA tissue status or intake have been reported in single studies, with some reporting no association (53, 63) and others reporting a significant genotype effect (28, 66, 79, 80, 82, 106) (**Table 4**). Two of these studies are worthy of further mention given the large cohort size (80) and that the associations were with the *Ala54Thr* SNP in the FABP2 gene (see section titled Lipid Mediators of Inflammation) (82), whose role in modulating LC n-3 PUFA status and its physiological impact is being increasingly recognized. In the LIPGENE–SU.VI.MAX prospective study, in which 3,000 individuals were followed up for 7.5 years for symptoms of the metabolic

syndrome, numerous complement component C3 polymorphisms were examined (80). Plasma fatty acids were used as a biomarker of dietary fatty acid intakes. One C3 SNP (rs11569562) interacted with plasma LC n-3 PUFAs, with the GG genotype showing an inverse association of plasma LC n-3 PUFAs with circulating TAG concentrations. Conversely, the AA or AG genotypes showed positive associations with plasma LC n-3 PUFAs and TAG. In a cohort of hypertriglyceridemic individuals prospectively recruited according to FABP2 *Ala54Thr* genotype, Thr-carriers were found to be more responsive to supplementation with 1.8 g LC n-3 PUFAs per day, with 52% and 34% decreases in plasma TAG and apoC3 concentrations relative to 19% and 32% reduction in Ala homozygotes (82). This is consistent with the putative increased LC PUFA binding and absorptive capacity associated with the Thr relative to the Ala allele (82).

Genotype × LC n-3 PUFA Interactions as Determinants of Inflammation

Lipid mediators of inflammation. Altered fatty acid composition of plasma membranes, due to genetically determined differences in desaturase activity, may be associated with coronary artery disease risk through modified inflammation. The products of desaturase enzyme activity, AA and EPA, are not in themselves inflammatory lipids but require further metabolism to produce inflammatory leukotrienes and prostaglandins, which are lipid mediators of inflammation. These prostanoids are formed from 20 carbon fatty acids such as AA and EPA, which are metabolized using the cyclooxygenase (COX) or the lipoxygenase (LOX) pathways to form either prostaglandins or leukotrienes, respectively. Although AA produces prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4), which are highly inflammatory molecules (60, 112), the derivatives of EPA are the less inflammatory molecules PGE_3 and LTB_5 (33, 57). As noted previously, EPA and AA are competitors for the same enzyme systems; therefore, the ratio of precursor fatty acids AA/EPA is paramount in determining the individual level of the inflammatory response. Polymorphic differences affecting the activity of either the LOX or COX systems can modify the level of inflammation and so impact the effectiveness of LC n-3 PUFA.

A number of polymorphisms of the COX-2 gene have been shown to interact with dietary fish oil in the context of prostate and colorectal cancer, but no studies have examined COX-2 × fish oil interactions in the context of CVD. From the LOX pathway, a single polymorphism of the 5-LOX gene has been reported to interact with dietary fish oil and AA in altering intima thickness and CHD risk. No studies have directly investigated fish oil interaction with other enzymes of the COX and LOX pathways, but potential candidate genes include ALOX5AP and 15-LOX.

An inverse relationship between prostate cancer risk and dietary fish intake, a source of LC n-3 PUFAs, has been reported (29, 42), and this link is thought to be due to LC n-3 PUFA effects on inflammation (21). Fradet et al. (29) showed that the COX-2 SNP +8897 A/G AA genotype strengthens the inverse relationship between prostate cancer risk and LC n-3 PUFA intake. Carriers of the C allele at COX-2 +6265 SNP had reduced incidence of prostate cancer only in conjunction with frequent oily fish consumption (42). Similarly in colorectal cancer, the COX-2 genotypes *-1329A-G GG*, *V102V GC*, and *2242T-C TT* tend to be protective only in conjunction with high fish intake (103), whereas other COX SNPs failed to show any interaction with fish consumption in reducing colorectal cancer risk (103, 104). It is not known whether these protective alleles are associated with increased or decreased COX-2 enzymatic activity, but decreased COX metabolism of AA and/or increased COX metabolism of EPA would be expected to reduce inflammation. Given these associations between *COX* genotype and cancer, which is likely to relate to an effect on inflammation, examination of the impact of COX-2 gene variants on CVD-related inflammation

and the interaction with LC n-3 PUFAs is merited.

5-LOX is encoded by *ALOX5*, and the ALOX5 promoter has a polymorphic number, 3 to 8, of Sp1 binding sites in tandem. The common genotype has five Sp1 binding sites, with variants of more than five uncommon. Dwyer et al. (23) assessed the degree of atherosclerosis in the posterior wall of the carotid artery in 573 healthy men and women and related this to *ALOX5* polymorphisms and PUFA intake. Individuals with two 5-LOX nonwild-type variants had increased intima media thickness compared with carriers of the wild-type allele. Furthermore, increased dietary AA enhanced the association of the variant allele with intima media thickness, whereas increased n-3 fatty acid intake blunted the association. Plasma C-reactive protein was doubled in individuals carrying two variant alleles, indicating that the association of variant alleles with intima media thickness may be due to increased inflammation (23). Although LC n-3 PUFA interactions with polymorphisms of other genes in the LOX and COX pathways, such as ALOX5AP and 15-LOX, have not been investigated, future investigation is warranted given the potential of this pathway to promote a variable inflammatory response (69, 123).

High dietary fish intake interacted with polymorphisms of PGE_2 synthase and the PGE_2 receptor (84). The PGE_2 receptor *EP4 Val294Ile* genotypes *Ile/Ile* and *Ile/Val* were associated with increased risk of colorectal cancer in groups with high fish intake, whereas reduced risk with increased fish intake was seen in the PGE_2 synthase *664A>T TT* and *AT* genotypes but not the *AA* genotype. This study suggests that high fish consumption interacts with these polymorphisms to affect PGE_2 synthesis and activity; this may be of relevance to the influences of LC n-3 PUFAs on inflammation in other settings such as CVD (84).

Nonlipid mediators of inflammation. Fish oil supplementation has been associated with a reduction in concentrations or production of nonlipid inflammatory mediators such as cytokines (13). PUFAs can modify transcription of a range of inflammatory genes through interaction with transcription factors such as nuclear factor κB and PPARs (13). Thus, polymorphisms in individual inflammatory genes that are the targets of these transcription factors may interact with LC n-3 PUFAs to reduce CVD risk by reducing inflammation.

Most of the literature in this area has centered on *TNF-α* and *TNF-β* SNPs, which have been shown to interact with PUFAs and n-3 PUFAs to alter blood lipids in diabetics and controls, to affect TNF-α release from monocytes in controls, and to improve walking distance in patients with peripheral vascular disease. However, SNPs in other cytokine genes, such as *IL-1β*, *IL-6*, and *IL-10*, have also been shown to interact with dietary fish oil.

TNF-α is a proinflammatory cytokine that has been shown to alter expression of genes involved in lipid metabolism, such as LPL, ApoA-I and A-IV, and PPAR-α and -γ (49, 120, 125). Polymorphisms in the *TNF-α* gene and the adjacent *TNF-β* gene, also known as lymphotoxin alpha, alter the amount of TNF-α produced in response to an inflammatory stimulus (9). An *A* allele at −238 reduces TNF-α production, whereas an *A* allele at −308 increases TNF-α production (34). TNF-α release from stimulated human peripheral blood mononuclear cells (PBMCs) is fairly constant for cells from a given individual, with a given stimulus, but displays vast interindividual variability (34, 48). Similarly, the anti-inflammatory effect of fish oil also has interindividual variability. Grimble et al. (34) studied PBMCs cultured from healthy men who had been supplemented with 1.8 g EPA+DHA daily for 12 weeks. Although TNF-α production was increased by fish oil supplementation in LTα +252 AA homozygotes, fish oil had a negative effect on TNF-α production in the AG heterozygotes. Fish oil supplementation reduced TNF-α in all genotypes at TNFα −308. However, the highest TNF-α producers at baseline were carriers of an A allele at −308, and this group showed the greatest reduction in TNF-α production in response to fish oil supplementation, indicating

that baseline TNF-α levels determine the response to LC n-3 PUFA supplementation (34). In the same study, baseline levels of C-reactive protein positively correlated with TAG only in genotypes *TNF-α −308 GG*, *TNF-β +252 AG*, *IL-1β −511 TT*, and *IL-6 −174 GG*.

The influence of supplementation with 1.7 g EPA+DHA daily for 12 weeks on a group of peripheral vascular disease patients with limited walking distance was to generally increase their walking distance (65). However, this increase in walking distance was dependent on BMI in that a greater effect was obtained in the group with BMI >25 kg/m^2 than in those <25 kg/m^2. The increase in walking distance was also dependent on genotypes at three inflammatory loci. Similar to findings of Markovic et al. (70), there was a three-way interaction between fish oil supplementation, inflammatory genotype, and BMI (65). In the group with BMI >25 kg/m^2, *TNF-α −308 AA* or *AG* reduced the effect of fish oil on walking distance in comparison with *GG*, *IL-1β −511 T* carriers showed a reduction of the fish oil effect on walking distance in comparison with CC, and IL-10-1082 G allele also reduced the effect of fish oil on walking distance in comparison with AA. These three genotypes are associated with increased inflammation.

Interactions between n-3 PUFAs and a different SNP within the IL-1β gene have also been reported (101). The G allele of SNP 6054 was associated with increased prevalence of the metabolic syndrome, but the association was lost in subjects with high erythrocyte membrane n-3 PUFA content. This suggests that a high LC n-3 PUFA status may be protective against genetically predisposed metabolic syndrome via an effect on inflammation. Similarly, Guerreiro et al. (35) have demonstrated that *TNF-α −857 TT* genotype is associated with increased inflammation in Crohn's disease in the context of low dietary n-3 PUFAs (**Table 4**).

CD44 splice variants. Variation at the gene level is not the only genetic mechanism by which phenotypic variation can come about. Posttranscriptional modifications due to mRNA splicing are common. A single report observed LC n-3 PUFA interaction with CD44 splice variants (67) (**Table 4**). CD44 is known to exhibit polymorphic mRNA splicing, for which the mechanism of control is unknown. The cell surface receptor CD44 is expressed on many cells, including monocytes. Its principal ligand is hyaluronic acid, a major constituent of the extracellular matrix. The CD44 gene consists of nine variant exons that can be spliced together in all possible combinations (47). The variant 3 (v3) exon contains a heparin binding site that allows binding of TGF-β and FGF and therefore may be involved in fibrosis and the resolution of inflammation. Madden et al. (67) reported that peripheral blood monocyte expression of CD44v3 was down-regulated in patients with peripheral vascular disease compared with healthy controls. Furthermore, following supplementation with 1.7 g of EPA+DHA daily for 12 weeks, CD44v3 expression was increased on monocytes from patients with peripheral vascular disease, with no effect on monocytes from healthy controls. Therefore, it appears that fish oil may interact with surface markers to effect posttranscriptional variation in function.

Genotype × LC n-3 PUFA Interactions as Determinants of Coagulation and Hemostasis

It is known that fish oil supplementation is associated with antithrombotic actions ascribed to direct effects on the platelet (36) as well as on the proteins of the coagulation cascade (69), the activation of which leads to thrombus formation. These antithrombotic actions are, at least in part, thought to be responsible for the reported effects of fish oil fatty acids in reducing rates of secondary CHD (as reviewed by 95).

Fibrinogen. Fibrinogen plays a central role in thrombus formation, with the fibrinogen molecule consisting of the alpha and beta chains, each produced from different genes.

The *Thr312Ala* polymorphism in the alpha gene has been shown to interact with dietary fish oil in the determination of plasma fibrinogen levels in 25 healthy males (115). The *Ala* allele was associated with higher baseline fibrinogen levels and greater reduction in fibrinogen levels following supplementation with 3 g fish oil daily for four weeks. Fish oil supplementation did not decrease plasma fibrinogen levels in *Thr312* homozygotes. Furthermore, the reduction in fibrinogen correlated with the decrease in thrombin generation following supplementation. In a subsequent study, no fish oil interactions were observed for three SNPs within the *fibrinogen Beta* gene and two SNPs within the *plasma activation factor V* gene (116).

Other genotypes. In a single study, no significant impact of *Factor VII* genotype on factor VII antigen or its activated form was reported (64) (**Table 4**).

Increased plasma plasminogen activator inhibitor 1 (PAI-1) activity is associated with increased risk of thrombosis, and elevated concentrations have been found in young post-MI patients, where they are linked to recurrence of cardiovascular events (37). An insertion polymorphism in the promoter region of the *PAI-1* gene has either four or five guanine bases. The *4G* allele infers increased PAI-1 activity and is more commonly found in young MI patients. PAI-1 transcription is controlled by binding of a VLDL inducible transcription factor adjacent to the polymorphic site. The *5G* allele can bind a suppressor protein in competition with the VLDL inducible transcription factor (24). To date, the interactions between PAI-1 and LC n-3 PUFAs have not been examined. However, given the known effects of LC n-3 PUFAs on circulating VLDL, this could provide the link between thrombosis and altered blood lipids, which is thought to be a potential mechanism by which fish oils protect in heart disease. Therefore, this is an excellent candidate gene in which to investigate genotype–LC n-3 PUFA interactions.

The role of genotype in determining the impact of LC n-3 PUFA status on coagulation and hemostasis is currently under investigated. Given the central role of thrombosis in the occurrence and severity of acute cardiovascular events, further research in this area is merited

Genotype × LC n-3 PUFA Interactions as Determinants of Vascular and Cardiac Function

LC n-3 PUFAs, and in particular DHA, are recognized as having a positive impact on vascular function, reactivity, and tone (76), which is becoming increasingly recognized as a CVD risk factor and highly predictive of future coronary events (54).

Only two studies, each focusing on different genes, have to date looked at SNP × LC n-3 PUFA interactions with respect to vascular reactivity, with Pullin et al. (86) reporting no association with the *methylenetetrahydrofolate reductase C677T* SNP and Leeson et al. (58) reporting a significant impact of the *endothelial nitric oxide synthase* (*eNOS*) *Glu298Asp* SNP (**Table 4**). This latter association is highlighted as a priority for further investigation given that eNOS produces nitric oxide, which is a potent vasodilator, and the *eNOS Glu298Asp* SNP has frequently been reported to influence CVD risk, with an odds ratio of 0.83 reported in a recent meta-analysis of 56 studies (61).

A prolonged QT interval measured by electrocardiogram is a risk factor for ventricular tachyarrhythmias and sudden and nonsudden cardiac death (2), against which fish oil supplementation has been shown to be effective in secondary preventive studies (12, 32, 95, 127). A single study has examined interactions with genotype × n-3 PUFA × QT interval (**Table 4**). Investigators reported no interactive association between genotype and n-3 PUFA status, although erythrocyte n-3 fatty acids showed an inverse association with QT interval, and QT interval was also influenced by the *G38S* SNP in the *potassium beta channel subunit KCNE1* gene (30).

Genotype × LC n-3 PUFA Interactions as Determinants of Insulin Sensitivity

Tissue fatty acid composition has been purported to affect insulin sensitivity by a variety of mechanisms, including an impact on circulating TAG and free fatty acid concentrations, cell membrane fluidity, and cell-signaling processes (100). At a population level, the impact of EPA and DHA status on insulin sensitivity is equivocal. Although a 2008 Cochrane report concluded that increased LC n-3 PUFA status "has no statistically significant effect on glycemic control or fasting insulin" (40), there are numerous reports in the literature to the contrary (for recent review, see 88). Therefore, it is likely that for certain individuals or for population subgroups, increased EPA and DHA intakes may represent a meaningful approach to improving insulin sensitivity status.

PPAR-γ. The impact of the above-mentioned PPAR-γ *Pro12Ala* polymorphism on the association between insulin sensitivity or its biomarkers and n-3 PUFA status has been reported in three independent studies, including two observational studies and one randomized controlled trial. In a study in 140 obese Italian children, although a significant interaction between the PPAR-γ *Pro12Ala* SNP and plasma phospholipid total n-6/total n-3 PUFA ratio and HOMA-IR (biomarker of insulin sensitivity) was reported, no significant independent interaction was evident for the LC n-3 PUFAs (95). In contrast, in the Botnia Dietary study (126), significant associations were reported between a number of the dietary and plasma measures of LC n-3 PUFA status, measures of insulin sensitivity (which included HOMA-IR, fasting and nonfasting insulin glucose, and free fatty acid levels) and *PPAR-γ Pro12Ala* genotype. Interestingly, the negative association between LC n-3 PUFA status and insulin sensitivity status tended to only be in the Pro12Pro group in men and in Ala carriers in women (126). This highlights a much ignored point in nutrigenetic research: that the penetrance of genotype may be gender specific and that considering large cohorts as homogeneous entities with respect to genotype-phenotype associations, which is typical of both candidate-gene and genome-wide association studies approaches, may result in incorrect null findings (122). In the KANWU intervention trial, the *Pro12Ala* genotype was not associated with changes in plasma glucose, serum insulin, or free fatty acids following LC n-3 PUFA intervention (62).

Leptin receptor and complement C3. The leptin receptor (LEPR) is associated with insulin resistance, and this may be related to the actions of leptin in modulating insulin secretion and insulin action as well as direct effects of the adipokine in stimulating uptake of glucose and fatty acid oxidation (75, 77). In the LIPGENE-SU.VI.MAX study, *LEPR GG* homozygotes for the rs3790433 SNP had an increased risk of the metabolic syndrome compared with the minor *A* allele carriers (81). Low plasma LC n-3 PUFA and high n-6 PUFA status increased the risk conferred by GG homozygosity by approximately two fold. In an attempt to replicate the findings, the authors examined SNP × LC n-3 PUFA status interactions in an independent LIPGENE MetS case-only intervention trial where individuals received a low-fat/high-carbohydrate diet +/− 1.24 g EPA+DHA per day for 12 weeks (81). Interestingly, a SNP × LC n-3 PUFA interaction was again observed, with improvement in insulin sensitivity only evident in *GG* homozygotes.

In the LIPGENE-SU.VI.Max cohort, although plasma n-6 PUFA status modified the association between the complement *C3* rs2250656 SNP and risk of metabolic syndrome, the association was unaffected by plasma total or LC n-3 PUFA status (80) (**Table 4**).

Additional genotypes. Plasma PL n-6/n-3 LC PUFA has been shown to modulate the association between adiponectin 276G>T genotype and HOMA-IR (a biomarker of insulin sensitivity) (117), and in the relatively large GOLDN cohort, erythrocyte % EPA+DHA had a highly significant impact on the association between the *interleukin 1β*

6054G>A genotype and risk of metabolic syndrome (101).

In summary, there is accumulating evidence to suggest that insulin sensitivity is more responsive to LC n-3 PUFA status in certain genotype subgroups. With greater clarity provided by further research, genotyping may provide a useful approach to identify those subgroups in which LC n-3 PUFA status may offer an effective tool to improve insulin sensitivity status.

CLOSING REMARKS

Although at a population level the impact of EPA and DHA on CVD clinical endpoints and biomarkers of CVD risk has been relatively quantitatively described, there is a distinct lack of information on factors that determine the individual responsiveness to increased intake. *FADS1* and *FADS2* genotypes have emerged as potentially important modulators of the bioconversion of ALNA to EPA and perhaps to DHA, and in nonfish consumers they may represent a meaningful determinant of tissue LC n-3 PUFA status. Although data are limited, in vitro evidence and results from three intervention studies in humans (which included two acute studies) indicate that *FABP2 Ala54Thr* genotype may be an important regulator of EPA and DHA absorption and their subsequent impact on blood lipid concentrations. Confirmation of these potentially important findings is needed, with a focus on a range of CVD risk factor endpoints. Information is distinctly lacking on the impact of gene variants of other fatty acid transport proteins and proteins involved in the cellular uptake, partitioning, and metabolism of EPA and DHA into bioactives. Given their central role in overall fatty acid metabolism, a focus on such proteins is highlighted as a priority. *PPAR* genotypes have also emerged as being potentially important. However, the data are limited and inconsistent. The LDL-C-raising effects of high-dose LC n-3 PUFA supplementation (>3 g/day, which is in the 2–4 g/day range recommended by the American Heart Association as a hypotriglyceridemic dose) is well recognized. Limited but nevertheless consistent evidence is indicating that apoE genotype affects the LDL-C response to DHA specifically, with the LDL-C-raising effect evident predominantly in those with an *APOE4* genotype. Again, limited but consistent evidence indicates interactions of TNF-α genotypes with LC n-3 PUFAs, with outcomes relating to both inflammation and blood lipid responses. Although data are currently limited to cancer, the literature suggests an interactive impact of *COX* genotype and LC n-3 PUFA with respect to colorectal and prostate cancer; the etiological basis for this interaction is assumed to be the lipid-mediated inflammatory response. The *COX* genotype $\times$ LC n-3 PUFA interaction within the context of CVD risk is unknown and worthy of investigation.

The ongoing FINGEN/FINGEN2 trial, which is investigating the impact of 52 common SNPs on the response of a range of CVD risk indicators to supplementation with either 0.7 g or 1.8 g EPA+DHA per day for eight weeks in 312 British adults (15) [with plans to confirm the most significant association in the independent SoFIA intervention (65)], will significantly contribute to current knowledge on the genetic determinant of the response to LC n-3 PUFAs.

The available literature on physiological (including genetic) modulators of the response to an increase LC n-3 PUFA intake currently takes a simplistic approach, with single factors considered in isolation. There is a need to move to a more meaningful scenario, where the impact of multiple gene variants along with other potential mediators such as gender, BMI, and epigenetic profiles are considered in combination. Limited examples of the usefulness of combinations of SNPs in phenotypic prediction are available in the literature (22, 121), with no such approach currently employed to predict response to LC n-3 PUFAs.

In conclusion, although the available literature highlights the potential of specific genotype in modulating the physiological response to increased n-3 PUFA intakes, its

usefulness is limited because the associations reported often are not investigated in subsequent cohorts, and few have been confirmed in independent studies. Given the recognized biopotency of LC n-3 PUFAs along with evidence of considerable heterogeneity in response, current moves toward a more stratified approach to dietary advice, and diminishing worldwide fish stocks, investigations in this area are of wide public health relevance.

DISCLOSURE STATEMENT

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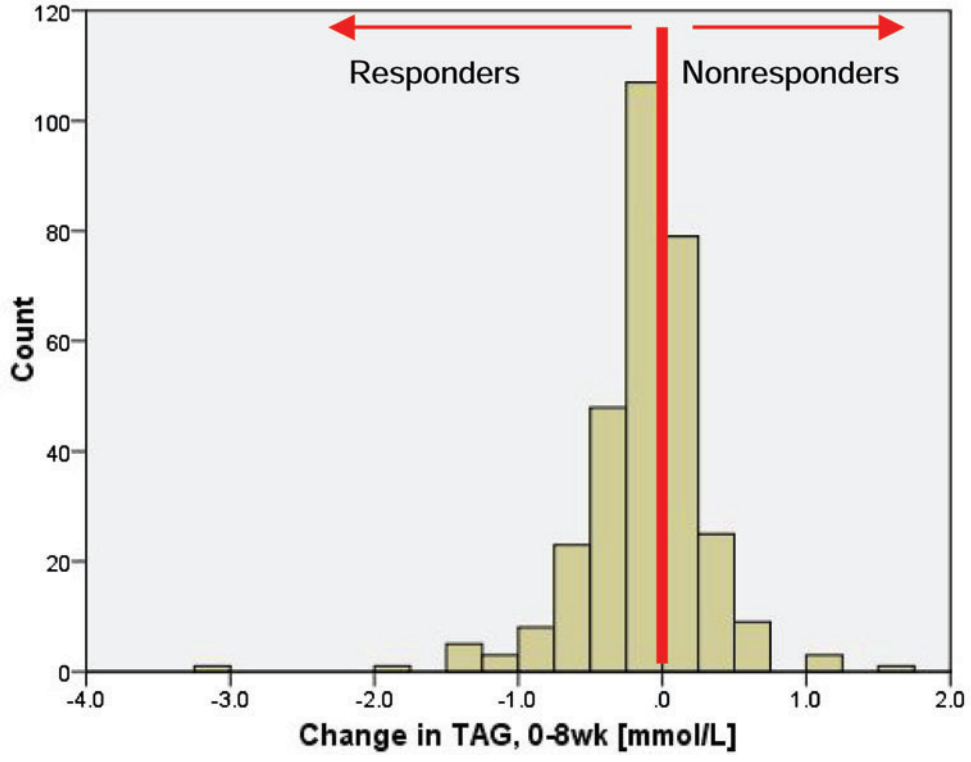

Figure 1

An example of the interindividual triacylglycerol (TAG) response in 312 healthy controls supplemented with 1.8 g of EPA+DHA per day for eight weeks. Data are taken from (12).

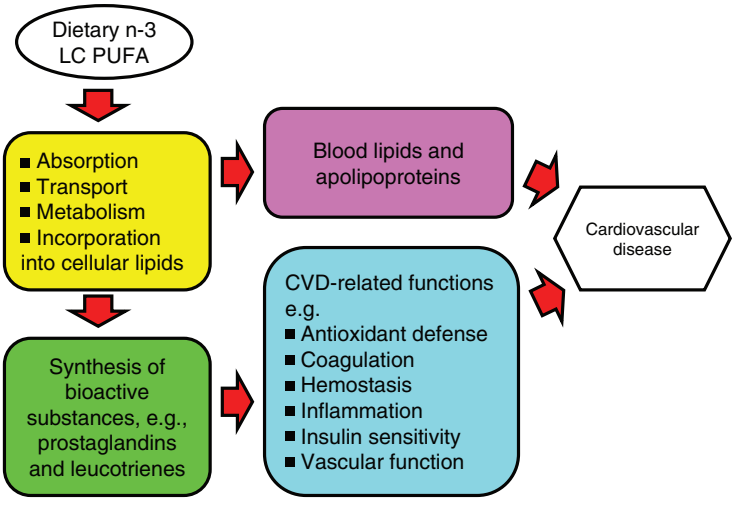

Figure 2

Conceptual diagram indicating aspects of metabolism and related functions and processes involving long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs) that may influence cardiovascular risk. This review assesses the available evidence for gene-nutrient interactions in the areas highlighted in colored boxes in the diagram.

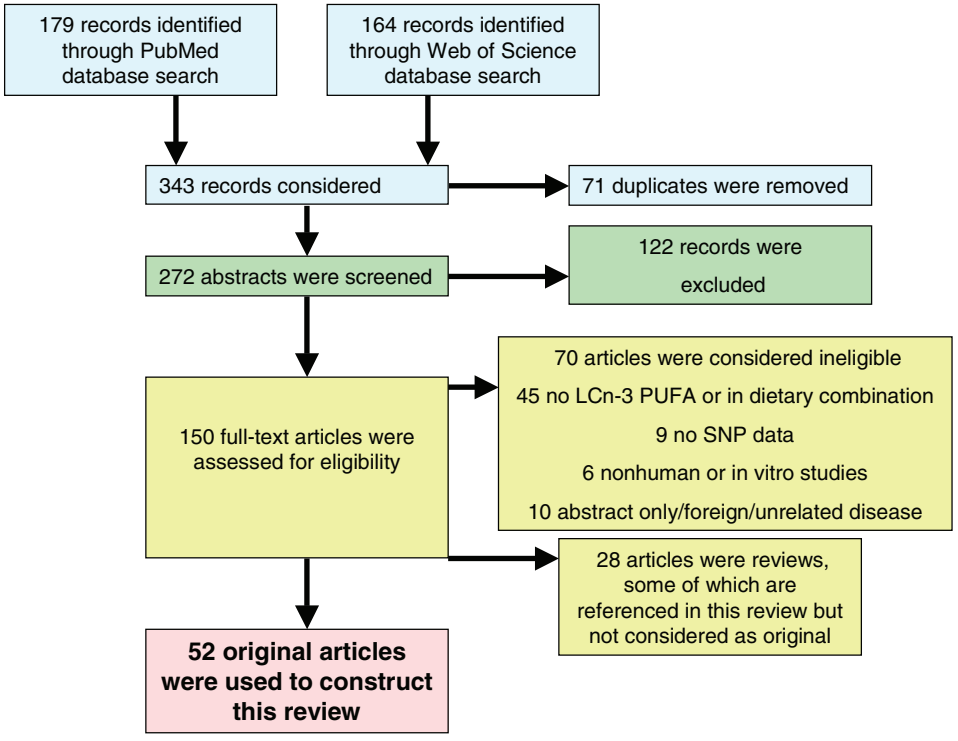

Figure 3

Representation of the four phases of selecting the literature to be reviewed: identification (*blue*), screening (*green*), eligibility (*yellow*), and included (*pink*).

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Errata

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