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Dietary fatty acids modulate associations between genetic variants and circulating fatty acids in plasma and erythrocyte membranes: meta-analysis of 9 studies in the CHARGE consortium

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Abstract

Scope—Tissue concentrations of omega-3 fatty acids may reduce cardiovascular disease risk, and genetic variants are associated with circulating fatty acids concentrations. Whether dietary fatty acids interact with genetic variants to modify circulating omega-3 fatty acids is unclear.

Objective—We evaluated interactions between genetic variants and fatty acid intakes for circulating alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA).

Methods and Results—We conducted meta-analyses (N to 11,668) evaluating interactions between dietary fatty acids and genetic variants (rs174538 and rs174548 in *FADS1* (fatty acid desaturase 1), rs7435 in *AGPAT3* (1-acyl-sn-glycerol-3-phosphate), rs4985167 in *PDXDC1* (pyridoxal-dependent decarboxylase domain-containing 1), rs780094 in *GCKR* (glucokinase regulatory protein) and rs3734398 in *ELOVL2* (fatty acid elongase 2)). Stratification by measurement compartment (plasma vs. erthyrocyte) revealed compartment-specific interactions between *FADS1* rs174538 and rs174548 and dietary ALA and linoleic acid for DHA and DPA.

Conclusion—Our findings reinforce earlier reports that genetically-based differences in circulating fatty acids may be partially due to differences in the conversion of fatty acid precursors. Further, fatty acids measurement compartment may modify gene-diet relationships, and considering compartment may improve the detection of gene-fatty acids interactions for circulating fatty acid outcomes.

Keywords

FADS1; gene-diet interactions; meta-analysis; omega-3 fatty acids

Introduction

Tissue concentrations of omega-3 fatty acids may reduce cardiovascular disease (CVD) risk [1–5]. Therefore, furthering our understanding of the determinants of circulating omega-3 fatty acids concentrations is essential. Variants in genes encoding fatty acid biosynthetic enzymes and additional proteins external to the pathway influence circulating omega-3 fatty acid concentrations (6–7). In a previous genome wide association study (GWAS) meta-analysis (N=8866), we reported that *FADS1* (fatty acid desaturase 1) and *FADS2* (fatty acid desaturase 2) variants were associated with higher alpha-linolenic acid (ALA) and lower eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA) concentrations. In addition, *ELOVL2* (fatty acid elongase 2) variants were associated with higher EPA and DPA and lower docosahexaenoic acid (DHA) concentrations. These findings support prior evidence that enzymatic genetic variation influences flow through the biosynthetic pathway from ALA to DHA (7). The same study reported that a *FADS1* variant altered the association between circulating ALA and EPA, implying that *FADS1* variation may influence conversion of ALA to EPA. In addition to the genes encoding pathway enzymes, we reported associations between *GCKR* (glucokinase regulatory protein) and *AGPAT3* (1-acyl-sn-glycerol-3-phosphate) variants with circulating DPA and *PDXDC1* (pyridoxal-dependent decarboxylase domain containing 1) variants with circulating ALA. Although all of the named loci encode proteins that participate in lipid metabolism, understanding of how *AGPAT3*, *GCKR*, and *PDXDC1* variants might determine circulating omega-3 fatty acids is limited. Whether habitual diet influences relationships between variants at these six loci for circulating omega-3 fatty acid outcomes is also unexplored, and investigation of gene-diet interactions could increase understanding of the molecular determinants of circulating ALA, EPA, DPA and DHA.

Biologically, several dietary fatty acids (alpha-linolenic acid (ALA), linoleic acid (LA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) could plausibly modify genetic associations for circulating omega-3 fatty acid (ALA, EPA, DPA, DHA) concentrations. First, ALA is a substrate for longer chain omega-3 fatty acids (EPA, DPA, DHA), and genetic factors that influence its conversion could affect long-chain omega-3 concentrations. ALA conversion to EPA/DPA/DHA is limited in humans and demonstrates inter-individual variability that may be related to genetics [8, 9, 10]. A second plausible candidate is the omega-6 fatty acid LA, which may limit ALA conversion to EPA through competitive inhibition of the desaturase enzymes that are shared by the omega-3 and omega-6 fatty acids biosynthetic pathways [11]. Finally, dietary EPA and DHA may also influence omega-3 fatty acid biosynthesis, as shown by differential conversion of ALA to long chain omega-3 fatty acids in fish consumers and non-consumers [12]. Collectively, these studies suggest that habitual intakes of ALA, LA, EPA and DHA may conceivably modulate the genetic contributions to circulating omega-3 fatty acids concentrations.

In addition to being influenced by dietary fatty acids and genetic factors, levels of circulating omega-3 fatty acids vary with the site of fatty acid measurement. Circulating omega-3 fatty acids in human populations are typically measured in total plasma, plasma fractions, or erythrocyte membranes. Differences in fatty acids incorporation, distribution and metabolism may vary based on the measurement compartment [13–16], but

understanding of how genetically-based variability in response to diet may be further modified by measurement compartment is limited [17,18].

The primary objective of the current study was to evaluate interactions between habitual dietary fatty acids (ALA, LA, EPA+DHA) intake and selected single nucleotide polymorphisms (SNPs) for the outcome of circulating omega-3 fatty acids (ALA, EPA, DPA and DHA). We hypothesized that the relationship between SNPs and circulating omega-3 fatty acids would be modified by dietary fatty acids. In a secondary analysis we explored whether these gene-diet interactions differed by the fatty acids measurement compartment (plasma and plasma phospholipids vs. erythrocyte membrane). We performed interaction analyses in 9 independent U.S. and European cohorts, with a total number of samples up to 11,668. The fatty acids were measured in plasma phospholipids in 4 cohorts, in total plasma in one cohort, and in erythrocyte membranes in 4 cohorts.

Materials and Methods

Study Populations

The 9 cohorts included for meta-analysis were the Atherosclerosis Risk in Communities (ARIC) Study, Coronary Artery Risk Development in Young Adults (CARDIA), Cardiovascular Health Study (CHS), Genetics of Lipid Lowering Drugs and Diet Network (GOLDN), Health Professionals Follow-up Study (HPFS), Invecchiare in Chianti (InCHIANTI), Multi-Ethnic Study of Atherosclerosis (MESA), Nurses' Health Study (NHS) and Women's Genome Health Study (WGHS) are described in Supplemental Table 1. All studies were approved by local Institutional Review Boards and all participants provided informed consent. These cohorts participate in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, which was created in 2008 for the purpose of evaluating genome-wide associations and gene-nutrient interactions for cardiovascular disease and risk factors. Jointly developed plans guide the analysis conducted at each cohort and summary statistics are meta-analyzed centrally.

SNP Selection and Genotyping

Six SNPs from five loci were selected from those highly significantly associated at genome-wide level with plasma phospholipid omega-3 fatty acids in a meta-analysis of GWAS of European origin individuals [7]. The SNPs evaluated were rs174538 and rs174548 in *FADS1*, rs7435 in *AGPAT3*, rs4985167 in *PDXDC1*, rs780094 in *GCKR* and rs3734398 in *ELOVL2*. *AGPAT3* and *PDXDC1* variants were previously identified as determinants of circulating glycerophospholipids and sphingolipids (19), and the AGPAT3 protein participates in the incorporation of DHA into phospholipids. (20). GCKR (protein name glucokinase regulatory protein) is a regulator of glucose phosphorylation that acts through competitive inhibition of glucokinase (21). The *GCKR* rs780094 variant has been repeatedly associated with metabolic traits including triglycerides and glucose (22) and was suggested to interact with dietary factors (23). Methods for genotyping are described in Supplemental Table 2.

Circulating fatty acids measurement and dietary fatty acids estimates in each study

In ARIC, MESA, CARDIA, and CHS, plasma phospholipids were first isolated by thin layer chromatography and then separated by gas chromatography. In InCHIANTI, total plasma fatty acids were measured using a similar gas chromatography technique. The cohorts ARIC, MESA, CARDIA, CHS and InCHIANTI previously contributed to a meta-analysis of genome-wide associations for circulating omega-3 fatty acids (7). In GOLDN, HPFS, NHS and WGHS fatty acids were measured in erythrocyte membranes. Details of circulating fatty acid measurements for all cohorts are provided in Supplemental Table 3. Dietary fatty acids were estimated from food frequency questionnaires that are described in Supplemental Table 4.

Statistical analyses by each cohort

Each cohort performed linear regression analysis to generate regression coefficients (β) and standard errors for the associations between intake of ALA, LA, EPA+DHA, PUFA and circulating omega-3 fatty acids (ALA, EPA, DPA, DHA) and interactions between genotypes of 6 SNPs and dietary fatty acids for the outcome of circulating fatty acids

Associations between dietary fatty acids and circulating fatty acids were evaluated continuously using a model adjusting for age, gender, total energy intake and population substructure variables as needed. The regression coefficient represents the difference in the circulating fatty acids outcomes (ALA, EPA, DPA, DHA) in association with each 1 gram greater intake of dietary fatty acid.

Fatty acids-SNP interactions were evaluated by cross-product terms using the likelihood ratio test with an additive genetic model. Thus, the interaction regression coefficient represents the difference in the magnitude of association between dietary fatty acids and circulating fatty acids (ALA, EPA, DPA, DHA) per copy of the effect allele. The interaction model was adjusted for age, gender, total energy intake and population substructure variables (as needed).

Meta-analysis and meta-regression

Meta-analysis was performed using an inverse variance-weighted, fixed effects approach. For meta-analysis of dietary fatty acids associations with circulating fatty acids, R software was used. For SNP x dietary fatty acids interaction meta-analysis, METAL software was used (http://umich.edu/csg/abecasis/Metal/). Although the two *FADS1* SNPs rs174538 and rs174548 are in moderately strong linkage disequilibrium (r^2=0.69 in Europeans) Bonferroni correction was conservatively based on all six SNPs and the four dietary fatty acids evaluated for interaction to establish a significance level with correction for multiple testing (α=0.05/24 tests=0.002). To formally examine a potential source of heterogeneity, we conducted meta-regression analysis with “fatty acids measurement compartment” (plasma phospholipids/plasma vs. erythrocyte membranes) as an independent variable. Meta-regression was performed using Stata software.

Results

Population characteristics, dietary fatty acids and circulating fatty acids in plasma or erythrocytes (expressed as % of total fatty acids) are shown for each cohort (Table 1; Supplemental Table 1). Circulating fatty acids (% total fatty acids) are comparable across the nine cohort studies. Meta-analysis of associations between the selected SNPs and plasma omega-3 fatty acids in five of the nine cohorts were previously described in a meta-analysis of GWAS using plasma phospholipids or total plasma [7]. Similar associations were observed in the current study, in which 4 cohorts that measured erythrocyte fatty acids were included (data not shown).

Associations between dietary fatty acids and circulating omega-3 fatty acids

Meta-analysis of associations between dietary intake of omega-3 fatty acids (in grams/day) and circulating (plasma or erythrocyte membrane) omega-3 fatty acids are shown in Table 2. Each one gram greater intake of ALA was associated with a higher circulating ALA of 0.006 (95% CI [0.004,0.008]; $P<0.001$). Each one gram greater intake of LA was associated with a lower circulating EPA of 0.007(95% CI [−0.009,−0.006]), DPA of 0.004(95% CI [−0.005,−0.003]), and DHA of 0.007 (95% CI [−0.011,−0.003]; all $P<0.001$). Each one gram greater intake of combined EPA+DHA was associated with higher circulating EPA of 0.333 (95% CI [0.298, 0.369] and DHA of 1.49 (95% CI [1.395,1.586]; both P<0.001). The direction of associations between dietary fatty acids and circulating omega-3 fatty acids were generally consistent across individual cohorts.

Interactions between SNPs and dietary fatty acid intake for circulating fatty acids

Of the 6 SNPs tested for interaction with dietary fatty acids for the outcomes of circulating omega-3 fatty acids, none reached Bonferroni adjusted statistical significance (data not shown). However, we observed evidence of heterogeneity by the fatty acid measurement compartment for the interactions of *FADS1* with dietary ALA and LA for the outcomes of circulating DPA (Figure 1A) and DHA (Figure 1B), respectively. Specifically, for plasma measurements in panel A (ARIC, CARDIA, InCHIANTI, MESA) interaction coefficients are negative and for erythrocyte measurements (GOLDN, HPFS, NHS and WGHS) interaction coefficients are positive.

Meta-regression

Using meta-regression methods, we tested whether fatty acid measurement compartment explained between-study heterogeneity and determined that compartment was associated (P<0.05) with the magnitude of the regression coefficient for the interaction terms of two *FADS1* SNPs (rs174548 and rs174538) and both dietary ALA and LA.

Interaction analyses between two FADS1 SNPs and dietary fatty acids for circulating fatty acids, stratified by fatty acids measurement compartment

Because measurement compartment was associated with differences in meta-analysis of interactions, we stratified the meta-analysis by compartment (Table 3). Several patterns emerged. For diet x SNP interactions involving *FADS1* SNPs rs174538 and rs174548, beta

coefficient of meta-analysis of interaction consistently differed in direction by compartment (negative in plasma and positive in erythrocytes).

Specifically, *FADS1* rs174548 (minor allele G) interacted with dietary ALA for the outcome of plasma DPA with negative betas in all cohorts using plasma (beta= −0.010; *P*=0.006) and positive betas in all cohorts using erythrocytes (beta= 0.034; *P*=0.048). Similar cohort-level consistency of beta coefficient direction was also observed for rs174548 interaction with dietary ALA for DHA (beta=0.13; *P*=0.005) and rs174548 interaction with dietary LA for DHA (beta=0.011; *P*=0.009) in erythrocytes. For the second *FADS1* variant, rs174538 (minor allele A), in interactions with dietary ALA and LA, similar but weaker patterns were observed (Table 3). In particular, dietary ALA interacted with rs174538 for DPA (beta= −0.010; *P*=0.007) in plasma phospholipids. Interactions between *FADS1* variants and dietary ALA for circulating EPA did not reach significance; however, the difference by rs174548 genotype for circulating EPA in erythrocytes was significant at an uncorrected threshold (*P*=0.048, Table 3), and the regression coefficient was in the same direction as for DPA and DHA. The association of both SNPs with circulating DPA and DHA (main effects) did not differ by compartment (data not shown).

Discussion

In this large study of up to 11,668 individuals, we observed interactions between dietary fatty acids and selected genetic variants for the outcomes of circulating long chain omega-3 fatty acids only when the data were stratified by measurement compartment. Specifically, dietary intake of the precursor fatty acids LA and ALA modulated associations of *FADS1* variants for the outcomes of the long chain fatty acids DPA and DHA, in a compartment-specific manner. Our study further showed that these relationships may differ by the site of fatty acid measurement.

FADS1/2 is a well-established genetic determinant of circulating omega -3 fatty acids (ALA, EPA, DPA), but studies that evaluate dietary modulation of these genetic associations are relatively few (6,7). In one previous study, investigation of *FADS1* variant rs174561 (r^2= 0.86 with *FADS1* rs174538 and r^2= 0.84 with *FADS1* rs174548 in the current study) demonstrated interaction with dietary fatty acids to modulate DPA and EPA in the plasma compartment [10]. In that study (n=36), homozygous minor allele carriers consuming a flaxseed diet (rich in ALA) had lower DPA and EPA compared to major allele carriers, implying that minor allele carriers may exhibit reduced conversion of ALA to longer chain omega-3 fatty acids. Results from the current meta-analysis, suggest that habitual dietary ALA and LA interacted with *FADS1* SNPs to modulate circulating DPA and DHA.

Whether fatty acid measurement compartment represents an additional modulator of potential *FADS1* gene-diet interactions is unclear. Most large-scale population studies rely on measurements from either the plasma compartment or the erythrocyte compartment, and the current study benefited from the availability of data from both compartments. In general, plasma fatty acids reflect short term fatty acids intakes whereas erythrocyte membranes reflect longer term intakes, so that compartment may be of particular relevance to genetic studies that incorporate dietary data. Further, the consequences of compartment on gene-diet

analyses may vary depending on the fatty acid of interest. For example, EPA and DPA are incorporated into the outer erythrocyte leaflet, which readily equilibrates with plasma, whereas DHA is incorporated into the inner erythrocyte leaflet at the time of erythrocyte formation in the bone marrow (16,24). Of potential relevance, data from two feeding trials, both using EPA+DHA, reported differential finding in the two compartments. In one of these trials (n=12 for 12 weeks duration), erythrocyte (but not serum) EPA differed by *FADS1/2* genotype [18]. In the second trial (n=310 for 6 months duration), *FADS1* genotype appeared to modify delta5 desaturase activity, with some differences between the two compartments [17]. Neither of these studies statistically evaluated the role of compartment. However, a series of previous, non-genetic studies suggest that compartment-based differences in the distribution, metabolism and incorporation of omega-3 fatty acids may be particularly relevant to dietary studies [13–16, 24–25]. In the current study, we statistically evaluated the role of measurement compartment as a source of heterogeneity in *FADS1* x diet interaction analyses, and the different patterns in stratified analyses suggest that compartment could be relevant to interaction analyses.

Several limitations must be considered. First, measurement errors in the assessment of dietary intake might have reduced our ability to detect interactions in the overall sample. Food frequency questionnaires that are used to estimate dietary intakes may have limited ability to capture specific fatty acids such as ALA and LA that are used in food preparation. In the current study, since ALA is a substrate for conversion to EPA whereas LA is not converted to EPA, our finding that ALA and LA appear to interact similarly with *FADS1* genotypes is unexpected and might represent a statistical artifact. In other words, the high correlations between the dietary estimates of ALA and LA, rather than biology, may account for statistically similar findings for these two fatty acids in the stratified analyses. In addition, we detected significant ALA x SNP interactions for DPA and DHA outcomes (Table 3), but interactions did not reach significance for EPA, the first long-chain PUFA product of the biosynthetic pathway of ALA to EPA/DPA/DHA. The directions of regression coefficients were less consistent across cohorts for EPA compared to DPA and DHA, which could be related to dietary or other unmeasured confounders across the nine cohorts. Finally, we cannot establish functionality for the *FADS1* SNPs rs174548 and rs174538, but examination in HapReg v2 software (Broad Institute) showed altered regulatory motifs, promoter or enhancer histone marks, DNAase 1 hypersensitivity, and/or protein binding that support evidence of functionality [26].

Results from the current study improve understanding of the multiple determinants of circulating fatty acids, and may have potential clinical implications. First, they support existing evidence that genetically-based differences in circulating longer chain fatty acids may be due, in part, to differences in the conversion of dietary fatty acids precursors [10]. Accumulating evidence suggests that carriers of *FADS1* variants have reduced capacity to synthesize longer chain omega-3 fatty acids, which may be relevant to dietary recommendations. Replication of genetic findings is essential to establishing scientific credibility, and the level of evidence is improved through verification in our large, multi-cohort sample, and under conditions of habitual intake. Second, our findings suggest that fatty acids measurement compartment may modify gene-diet interaction and therefore add

heterogeneity to meta-analyses that focus on the simultaneous investigations of gene and diet. Awareness of the extent and circumstances under which this heterogeneity is relevant to analyses may improve the detection of gene-diet interactions for circulating fatty acid outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

AGPAT3	1-acyl-sn-glycerol-3-phosphate
ALA	alpha-linolenic acid
ARIC	Atherosclerosis Risk in Communities
CARDIA	Coronary Artery Risk Development in Young Adults
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
CHS	Cardiovascular Health Study
DPA	docosapentaenoic acid
DHA	docosahexaenoic acid
ELOVL2	fatty acid elongase 2
EPA	eicosapentaenoic acid
FADS1	fatty acid desaturase 1
FADS2	fatty acid desaturase 2
GCKR	glucokinase regulatory protein
GOLDN	Genetics of Lipid Lowering Drugs and Diet Network
GWAS	genome wide association study
HPFS	Health Professionals Follow-up Study
InCHIANTI	Invecchiare in Chianti
LA	linoleic acid
MESA	Multi-Ethnic Study of Atherosclerosis
NHS	Nurses Health Study
PDXDC1	pyridoxal-dependent decarboxylase domain
SNP	single nucleotide polymorphism
WGHS	Women’s Genome Health Study

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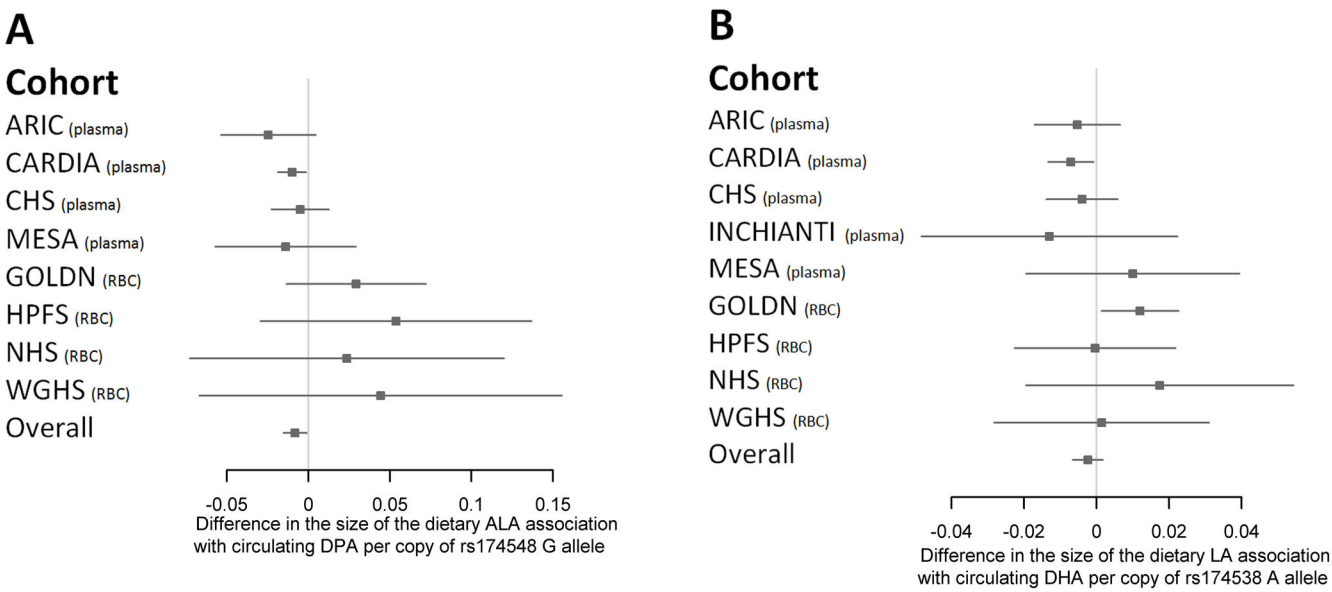

Figure 1.

Interactions between *FADS1* rs174548 and rs174538 and dietary fatty acids for circulating omega-3 fatty acids, in each cohort. In ARIC, CARDIA, CHS, InCHIANTI and MESA, fatty acids were measured in plasma/plasma phospholipids; in GOLDN, HPFS, NHS and WGHS, fatty acids were measured in erythrocyte membranes. Panel A illustrates the association of each one gram/day greater intake of dietary alpha linoleic acid (ALA) with circulating docosapentaenoic acid (DPA) per copy of the rs174548 G allele. Panel B illustrates the association of each one gram/day greater intake dietary linoleic acid (LA) with circulating docosahexaenoic (DHA) per copy of the rs174538 A allele. Circulating DPA was not measured in the InCHIANTI study.

Table 1

Dietary and circulating fatty acids by cohort

					Dietary fatty acids (grams/day)					Circulating fatty acids, % total fatty acids			
	N	**Age (y)**	**% Women**	**Fatty acids compartment**	**ALA**	**LA**	**EPA+ DHA**	**PUFA**	**ALA:LA correlation coefficient**	**ALA**	**EPA**	**DPA**	**DHA**
Atherosclerosis Risk in Communities (ARIC) Study	3266	54±6	51	Plasma phospholipid	0.7±0.3	8.2±4.0	0.2±0.2	9.4±4.3	0.71	0.14±0.05	0.56±0.3	0.9±0.17	2.82±0.88
Coronary Artery Risk Development in Young Adults (CARDIA)	1097	46±3	55	Plasma phospholipid	2.1±2.3	17.7±16.9	0.2±0.3	20.2±19.1	0.92	0.19±0.09	0.85±0.62	0.94±0.21	3.09±1.12
Cardiovascular Health Study (CHS)	2305	75±5	61	Plasma phospholipid	1.5±0.6	12.6±5.2	0.4±0.3	14.9±6	0.94	0.15±0.05	0.59±0.37	0.83±0.17	2.98±0.96
Multi-Ethnic Study of Atherosclerosis (MESA)	646	62±10	53	Plasma phospholipid	1.1±0.5	9.7±5.4	0.1±0.1	11.1±5.8	0.82	0.18±0.06	0.89±0.59	0.96±0.22	3.7±1.41
Invecchiare in Chianti (InCHIANTI)	1059	68±15	55	Total Plasma	1±0.3	5.9±2	NA	7.4±2.4	0.83	0.44±0.25	0.61±0.22	NA	2.29±0.77
Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)	1038	48±16	52	Erythrocyte membranes	1.5±0.8	15.6±7.9	0.1±0.1	17.3±8.7	0.92	0.14±0.04	0.53±0.28	2.11±0.30	3.03±0.89
Health Professionals Follow-up Study (HPFS)	1294	64±9	0	Erythrocyte membranes	1.1±0.4	11.2±4.3	0.3±0.3	12.9±4.7	0.82	0.21±0.22	0.51±0.28	1.97±0.39	3.67±1.2
Nurses Health Study (NHS)	597	60±6	100	Erythrocyte membranes	1.1±0.4	10.8±3.9	0.2±0.2	12.5±4.3	0.86	0.15±0.06	0.68±0.67	1.67±0.31	3.31±1.03
Women's Genome Health Study (WGHS)	635	54±7	100	Erythrocyte membranes	1.1±0.4	9.7±4.0	0.2±0.2	11.4±4.6	0.86	0.16±0.05	0.49±0.19	1.84±0.39	3.27±0.98

ALA, alpha linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid, LA, linoleic acid; NA, not available; PUFA, polyunsaturated fatty acids

Table 2

Meta-analysis of associations between dietary fatty acids and circulating omega-3 fatty acids

	Regression* coefficients (β [95%CI] for dietary ALA (g/d)	***P***	**N**	**Regression* coefficients (β [95% CI] for dietary LA (g/d)**	***P***	**N**	**Regression* coefficients (β [95% CI] for dietary EPA+DHA (g/d)**	***P***	**N**
Circulating fatty acids (%total fatty acids)									
ALA	0.006 (0.004,0.008)	< 0.001	11291	−0.0002(−0.0004,0.0001)	0.141	10232	0.005(0.0003,0.010)	0.038	10656
EPA	0.011(−0.004,0.026)	0.143	11108	−0.007(−0.009, −0.006)	< 0.001	10049	0.333(0.298,0.369)	< 0.001	10473
DPA	−0.004(−0.010,0.002)	0.209	10232	−0.004(−0.005, −0.003)	< 0.001	10232	0.0004(−0.016,0.017)	0.964	9597
DHA	0.027(−0.005,0.058)	0.103	11291	−0.007(−0.011, −0.003)	< 0.001	10232	1.491(1.395,1.586)	< 0.001	10656

*β represents expected change in circulating fatty acids per one gram greater fatty acid intake

ALA, alpha linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid, LA, linoleic acid

Table 3

Meta-analysis of interactions between *FADS1* SNPs (rs174548 and rs174538) and dietary fatty acids in association with circulating omega-3 fatty acids, stratified by fatty acids measurement compartment

Interactions between dietary ALA X rs174548 for plasma omega-3 fatty acids					**Interactions between dietary ALA X rs174548 for erythrocyte omega-3 fatty acids**				
	β	**SEM**	***P***	**β direction**	**β**	**SEM**	***P***	**β direction**	***P****
EPA	−0.0118	0.010	0.223	−−+−+	0.018	0.012	0.120	+−++	0.048
DPA	−0.010	0.004	0.006	−−−−	0.034	0.017	0.048	++++	0.012
DHA	−0.036	0.021	0.085	−−−−+	0.13	0.05	0.005	++++	0.001
Interactions between dietary **LA X rs174548** for **plasma** omega-3 fatty acids					Interactions between dietary **LA X rs174548** for **erythrocyte** omega-3 fatty acids				
EPA	−0.0008	0.001	0.408	+−+−+	0.002	0.001	0.151	+−++	0.103
DPA	−0.001	0.001	0.057	+−−−	0.004	0.002	0.014	++++	0.004
DHA	−0.004	0.002	0.106	+−−−+	0.011	0.004	0.009	++++	0.002
Interactions between dietary **ALA X rs174538** for **plasma** omega-3 fatty acids					Interactions between dietary **ALA X rs174538** for **erythrocyte** omega-3 fatty acids				
	β	**SEM**	***P***	**β direction**	**β**	**SEM**	***P***	**β direction**	***P****
EPA	−0.0135	0.010	0.183	−−+−+	0.010	0.011	0.400	+−++	0.189
DPA	−0.010	0.004	0.007	−−−−	0.024	0.017	0.146	++−+	0.043
DHA	−0.046	0.022	0.033	−−−−+	0.096	0.05	0.041	+−++	0.006
Interactions between dietary **LA X rs174538** for **plasma** omega-3 fatty acids					Interactions between dietary **LA X rs174538** for **erythrocyte** omega-3 fatty acids				
EPA	−0.0009	0.001	0.360	−−+−+	0.001	0.001	0.432	+−−+	0.235
DPA	−0.001	0.001	0.059	+−−−	0.003	0.002	0.074	++−+	0.025
DHA	−0.006	0.002	0.017	−−−−+	0.009	0.005	0.037	+−++	0.003

β represents the difference in the magnitude of the dietary fatty acids association with circulating fatty acids (expressed as difference in circulating fatty acid per 1 gram/day greater intake of fatty acid) per copy of the effect allele

P =*P* value for meta-analysis of interactions between SNP X dietary fatty acids for the outcome of circulating fatty acids

*P** =*P* value for association between fatty acids compartment for the interaction of dietary fatty acid X SNP on circulating fatty acid.

For EPA and DHA in the plasma compartment the cohort order =ARIC, CARDIA, CHS, InCHIANTI, MESA

For DPA the plasma compartment the cohort order =ARIC, CARDIA, CHS, MESA

For EPA, DPA and DHA in the erythrocyte compartment the cohort order =GOLDN, HPFS, NHS, WGHS

ALA, alpha linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid, LA, linoleic acid