Supplementary Table 2. Detailed characteristics of the studies preliminary selected.

Study design & duration	PUFA assessment & Intervention details	Genetic variants	Health status	Study origin	Population/ Ancestry	Sample size	Sex	Biospecimen	Gene-diet interaction results	Reference
Interventional, prospective (2 months)	High polyunsaturated fatty acid (PUFA) hypocaloric diet.	LEPR (Lys656Asn)	Obesity	Spain	Spanish	132	Both	Serum/plasma	Carriers of ASn656 allele have a different response than wild-type obese, with a lack of decrease in insulin levels, leptin levels, and HOMA-IR. However, obese patients with this mutant allele have a better lipid profile after weight loss	1
Cross-sectional	A 3-day, 24-h dietary recall was employed to measure dietary intake.	PPARGC1A (rs11290186, rs2970847)	Obesity	Iran	Iranian	288	Women	Serum/plasma	AA genotype of PPARGC1A (rs11290186) had a direct association with polyunsaturated fatty acids and linoleic acid intakes	2
Cross-sectional	Using data from the LIPGENE cohort, a randomized dietary intervention study with four isoenergetic diets distinct in fat quantity and quality: high-SFA, high-monounsaturated fatty acids and two low-fat, high-complex carbohydrate (LFHCC) diets, supplemented with long chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs) (1.2 g per day) or placebo, for 12 weeks.	IRS-2 (rs2289046)	Metabolic Syndrome	Spain	Spanish	452	Both	Serum/plasma	Individuals carrying the G allele and with the highest level of ω-3 polyunsaturated fatty acids (above the median) showed lower fasting insulin and HOMA-IR as compared with A/A subjects	3
Cross-sectional	Using data in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study where dietary intake was estimated by use of the DHQ, a food frequency questionnaire developed by staff at the Risk Factor Monitoring and Methods Branch.	IL-6 (rs2961298)	Overweight	USA	European ancestry	848	Both	Serum/plasma	Higher n-3 PUFA is associated with lower methylation at IL6 promoter, which may be modified by IL6 SNPs	4
Cross-sectional	Total intake of polyunsaturated fat from fish and fish oil was estimated using a food frequency questionnaire in a subsample (n = 962) of the Metabolic Syndrome in Men Study.	FADS1 (rs174550)	Middle-aged/older adults (medicated)	Finland	Caucasian	962	Men	Serum/plasma and RBC	FADS1 variants may modulate the relationship between marine fatty acid intake and circulating levels of long-chain ω-3 fatty acids.	5
Secondary retrospective analysis (6 months)	Secondary retrospective analysis of a randomized, double-blind. placebo-controlled trial to examine the effects fish-oil supplementation on cognitive performance in participants over 65. Fish-oil supplementation containing 1800 mg of eicosapentaenoic acid and docosahexaenoic acid per day.	APOE ε4	Healthy	Dutch	N/A or N/S	23	Both	PBMCs	The increased expression of IFN signaling and cholesterol biosynthesis pathways might explain part of the association between APOE4 and CVD. Fish-oil supplementation may particularly benefit APOE4 carriers by decreasing expression of IFN-related genes	6
Randomized controlled intervention (8	Participants, homozygous for FADS1 rs174550 variant (TT and CC), followed a	FADS1 (rs174550)	Middle-aged/older adults	Finland	Caucasian	118	Men	Serum/plasma	The high-LA diet increased the concentration of plasma LA, but not its lipid mediators. The concentration of plasma arachidonic acid decreased in carriers of CC and remained unchanged in the TT	7

weeks)	high alpha-linolenic acid (ALA, 5 percent of energy (E-%)) or a high linoleic acid (LA, 10 E-%) diet during an 8-week randomized controlled intervention.		(medicated)						genotype. The high-ALA diet increased the concentration of plasma ALA and its cytochrome P450-derived epoxides and dihydroxys, and cyclooxygenase-derived monohydroxys. Concentrations of plasma eicosapentaenoic acid and its mono- and dihydroxys increased only in TT genotype carriers.	
Retrospective cohort study	Utilizing the UK Biobank dataset, we evaluated the impacts of FAs on the risk of elderly-onset AD and explored the combined effects of FA levels and genetic susceptibility.	rs1692120, rs174448	Atopic dermatitis	China	UK biobank dataset	68226	Both	Serum/plasma	Individuals with low genetic risk and high ω-3 levels had the lowest AD risk, a 38% reduction compared to the reference category. Additionally, individuals with GA/AA on rs1692120 exhibited a significantly elevated AD risk, whereas those with more A alleles for rs174448 demonstrated a significantly diminished AD risk.	8
Case-control	Disease was diagnosed by liver ultrasound and volunteers were clinically and nutritionally assessed. Food groups were extracted from a 172 food-item FFQ questionnaire.	PNPLA3 (rs738409), TM6SF2 (rs58542926), GCKR (rs780094)	Non-Alcoholic Fatty Liver Disease	Greece	N/A or N/S	351	Both	Serum/plasma	Fish intake exerts an additive effect on NAFLD risk for carriers of the TM6SF2 polymorphism. This novel finding provides further rationale on the need for personalized nutritional advice, based on the genetic background of NAFLD patients	9
Cross-sectional	Usual food intake was measured by SQFFQ.	FADS1 (rs174547), FADS2 (rs2845573)	Metabolic Syndrome	Korean	Korean	8842 (Ansan/Ansung cohort) and 5512 (City-Rural cohort)	Both	Serum/plasma	PUFA intake did not interact with FADS1 and FADS2 genetic variants in the development of MetS	10
Randomized controlled intervention (4 weeks)	Sunflower oil supplemented diet resulting in 17-28 g of LA on top of the usual daily intake.	FADS1 (rs174550)	Healthy	Finland	Caucasian	59	Men	Serum/plasma	In response to the high-LA diet, LA phospholipids and long-chain acylcarnitines increased and lysophospholipids decreased in fasting plasma similarly in both genotypes	11
Cross-sectional	Retrospective, medical records-based analysis.	APOE ε4	Cardiovascular Disease risk	USA	N/A or N/S	136701	Both	Serum/plasma and RBC	No evidence for a deleterious relationship between lipid biomarkers and the ω-3 Index by APOE genotype	12
Cross-sectional	LC PUFA status in mild cognitive impairment (MCI) patients, focusing on omega-3 index (EPA and DHA levels) in erythrocyte membranes and associations with FADS gene polymorphisms. Secondary outcomes: Associations between FADS SNPs and LC PUFA levels with serum lipid levels and depressive symptoms.	FADS1, FADS2, FADS3 (12 SNPs)	Mild Cognitive Impairment	Germany	N/A or N/S	111	Both	Serum/plasma and RBC	Minor allele carriers of specific FADS2 and FADS3 SNPs showed higher triglyceride levels, Minor allele carriers of certain FADS3 SNPs had higher total and LDLc levels	13
Cross-sectional	Dietary intake of basic components and fatty acids was obtained from a 7-day weighed food record.	PPARG (Pro12Ala, C1431T), ADRB3 (Trp64Arg)	Dyslipidemia	Poland	N/A or N/S	271	Women	Serum/plasma	Polymorphism analysis showed significant associations between gene variants and nutrients (fat, SFA, PUFA, and saccharose) and elevated LDLc levels. Women with the protective Ala12/X polymorphism who had higher PUFA intake did not show increased risk of dyslipidemia despite having visceral fat distribution. The Arg64/X polymorphism combined with higher intake of energy, fat, and arachidic acid (C20:0) was associated with dyslipidemic state	14
Randomized, double-blind, placebo-controlled crossover trial (4 weeks)	3 intervention arms: Control oil, EPA-rich oil (ERO, 3.3g EPA/day), DHA-rich oil (DRO, 3.7g DHA/day), separated by 10-week washout periods.	APOE (ε3/ε3, ε3/ε4)	Healthy (normolipidemic)	UK	N/A or N/S	38	Men	Serum/plasma	High-dose DHA supplementation increases total cholesterol in apoE4 carriers, primarily through increased LDLc levels.	15
Cross-sectional	Analysis from the Multi-Ethnic Study of	APOE	Healthy	USA	Multi-ethnic	234	Both	Serum/plasma	APOE genotype significantly contributes to the relationship between EPA and lipid profiles, particularly regarding HDLc and HDL particle	16

	Atherosclerosis (MESA).								concentrations	
Cross-sectional	Analysis of 2013-2017 health examination data from Japanese adults aged ≥40 years in Shika town, Ishikawa Prefecture.	APOC3 (rs2854116)	Non-Alcoholic Fatty Liver Disease	Japan	N/A or N/S	464	Both	Serum/plasma	Significant interactions were observed between NAFLD and APOC3 genotypes and the intake of fat, vegetable fat, MUFAs, PUFAs, cholesterol, n-3 FAs, and n-6 FAs. In other words, participants with NAFLD who have TT genotype (rs2854116) have a higher fat intake than participants without NAFLD. The intake of carbohydrates and SFAs had a trend for interaction between NAFLD and the APOC3 genotypes. Participants with NAFLD who presented with the TT genotype were more likely to have a higher intake of sucrose, cholesterol, and n-3 fatty acids than those without NAFLD	17
Cross-sectional	Comparison between individuals with and without MetS, with focus on gene-fatty acid interactions.	IL1B (rs16944, rs1143623, rs1143627, rs1143634, rs1143643), IL6 (rs1800795, rs1800796, rs1800797), IL10 (rs1554286, rs1800871, rs1800872, rs1800890, rs3024490)	Metabolic Syndrome	Brazil	N/A or N/S	301	Both	Serum/plasma	The IL6 gene SNP rs1800795 G allele is associated with increased odds for MetS. Plasma fatty acid profiles interact with IL1B and IL10 gene variants to modulate the odds for MetS. These interactions between risk factors may account for the unexplained heritability of MetS and could potentially lead to new strategies for genome-customized prevention approaches.	18
Randomized dietary intervention trial (3 months)	Hypocaloric diet with either: Diet P: High polyunsaturated fat (PUFAs) content or Diet M: High monounsaturated fat (MUFAs) content.	CB2R (rs3123554)	Obesity	Spain	Caucasian	362	Both	Serum/plasma	No significant gene-diet interactions were observed for weight loss, BMI, fat mass, waist circumference, blood pressure. No gene-diet interactions for total cholesterol, LDLc, insulin and HOMA-IR. The genetic effect appeared to be diet-independent for most measures, with non-A allele carriers consistently showing better responses regardless of fatty acid composition	19
Cross-sectional	Genome-wide association study (GWAS) with nutrient interaction analysis.	GWAS	CVD risk	Korea	Korean	8842	Both	Serum/plasma	PTPN11_rs11066325, RPH3A_rs886477, OAS3_rs2072134 were associated with serum HDLc levels. Minor-allele carriers of the haplotype showed: 1.534-fold increased odds for decreased HDLc compared to major-allele carriers, 1.645-fold increased odds for elevated LDLc, Lower serum triglyceride levels compared to major-allele carriers, No significant changes in total serum cholesterol levels. Significant interactions between the haplotype and nutrient intake were found for: Protein, Fat, SFA, PUFA. The negative effect of minor alleles on HDLc was more pronounced with high intake of protein, fat, SFA, and PUFA, but not with low intake.. People carrying the minor alleles of the identified haplotype (PTPN11_rs11066325, RPH3A_rs886477, OAS3_rs2072134) should avoid diets high in protein and fat, especially those rich in saturated and polyunsaturated fatty acids, as these dietary patterns may exacerbate the genetic predisposition to lower HDLc levels	20
Prospective cohort study	UK Biobank. Dietary intake was assessed by a food frequency questionnaire.	APOE (rs429358, rs7412)	Dementia	UK	N/A or N/S	215083	Both	Serum/plasma	Fish oil supplement use was significantly associated with lower risk of all-cause dementia: Multivariable-adjusted hazard ratio: 0.87 for fish oil users compared to non-users, Significant dose-response trend. A marginal interaction was found between fish oil supplementation and APOE gene variants on dementia risk (p = 0.057). Fish oil supplementation was not significantly associated with the risk of specific dementia subtypes: Alzheimer's disease, Vascular dementia, Frontotemporal dementia. Intake of fish oil supplements was associated with lower risk of all-cause dementia among adults aged 60-73 years. These findings provide new population-based evidence linking fish oil supplement use with dementia prevention, though the effect may vary by APOE genotype and was not significant for specific dementia subtypes.	21
Prospective cohort study	UK Biobank. Dietary intake was assessed by a food	APOE ε4	Dementia	UK	N/A or N/S	445961	Both	Serum/plasma	Fish oil supplement use was associated with: Lower risk of all-cause dementia: HR 0.90, Lower risk of vascular dementia: HR 0.85, No	22

	frequency questionnaire.								significant association with AD risk. Significant interaction between fish oil use and APOE ε4 dosage was observed: Protective associations for all-cause dementia and vascular dementia were attenuated with increasing APOE ε4 dosage, Notably, fish oil supplement use was associated with an 86% higher risk of vascular dementia in participants with two APOE-ε4 alleles. fish oil supplements is differently associated with risks of all-cause dementia and vascular dementia according to APOE ε4 allele dosage. While generally protective in the overall population, fish oil supplements may increase vascular dementia risk in carriers of two APOE-ε4 alleles, suggesting important gene-nutrient interactions in dementia risk.	
Cross-sectional	Association of n-3 PUFA biomarkers with blood lipids in two large human cohort studies.	CD36 (rs1527483)	Healthy	China	Chinese	4786	Both	Serum/plasma and RBC	CD36 rs1527483-GG carriers showed better response to high n-3 PUFA exposure: Higher HDLc, Lower triglycerides. DHA identified as the key n-3 PUFA driving the interaction with rs1527483. Higher n-3 PUFA levels were associated with improved blood lipids and gut microbial features only among CD36 rs1527483-GG carriers. These findings highlight a potential role of the gut microbiome in linking CD36 genetic variants, n-3 PUFAs, and blood lipids, revealing a new research direction for understanding gene-diet interactions in cardiometabolic health.	23
Case-control study	Examination of PUFA composition and FADS gene variants in relation to T2DM risk.	FADS1-FADS2 (rs174545, rs2072114, rs174602, rs174616)	Type 2 Diabetes Mellitus	China	Han people	752	Both	Serum/plasma and RBC	Desaturase activity markers in T2DM patients compared to controls: Significantly increased AA/LA ratio (reflecting Δ6 desaturase activity): Markedly decreased EPA/ALA ratio (reflecting Δ5 desaturase activity). Genetic findings: the minor allele (T) of rs174616 was associated with decreased risk of T2DM. PUFA composition by genotype: T carriers showed reduced AA/LA ratio in both controls and T2DM patients, T carriers with T2DM showed an increased proportion of LA compared to controls. In northern Han Chinese people, the minor allele (T) of rs174616 in the FADS1-FADS2 gene cluster is associated with a decreased conversion rate of linoleic acid (LA) to arachidonic acid (AA), which may contribute to a reduced risk of developing type 2 diabetes mellitus. This finding confirms that FADS genetic variants influence PUFA metabolism and T2DM risk in this population, similar to observations in European populations.	24
Randomized controlled trial (180 days)	Intervention groups: Omega-3 fatty acid group (n=100): Fish oil subgroup (n=56), Flaxseed oil subgroup (n=44), Control group (n=50).	CD36 (rs1527483), NOS3 (rs1799983), PPARG (rs1801282)	Type 2 Diabetes Mellitus	China	N/A or N/S	150	Both	Serum/plasma and RBC	Significant gene-diet interactions were observed for: CD36 variant on triglycerides, PPARG variant on low-density lipoprotein-cholesterol. Significant interactions between changes in erythrocyte phospholipid omega-3 fatty acid composition and NOS3 genotype on: Triglycerides, Total cholesterol, Ratio of total cholesterol to HDLc. Response patterns by genotype: CD36-G, PPARG-G and NOS3-A allele carriers showed better response to omega-3 fatty acids for improving lipid profiles. The observed gene-diet interactions were primarily attributed to fish oil supplements rather than flaxseed oil supplements. Type 2 diabetes patients with different genotypes at CD36, NOS3, and PPARG respond differently to omega-3 fatty acid supplementation in terms of blood lipid profiles. This finding supports the potential for genotype-based personalized nutritional interventions for managing dyslipidemia in T2D patients	25, 26
Cross-sectional	Characterize the relationship between single nucleotide polymorphisms (SNPs) in key genes and blood concentrations of environmental chemicals and nutrients.	140 SNPs (toxicokinetics /toxicodynamics, cardiovascular health, lipid metabolism)	Healthy	Canada	Inuit people	665	Both	Serum/plasma and RBC	rs4244285 in CYP2C19 significantly associated with DHA after Bonferroni correction. Polymorphisms in environmentally-responsive genes can influence biomarker levels of key toxicants and nutrients in the Inuit population	27
Observational	Identify and characterize genetic variants under positive selection in Native Americans of Mexico and evaluate their associations	FADS2 (rs174616)	Healthy	Mexico	Native Americans	1570 (GEA Mexican Cohort) and 165	Both	Serum/plasma and RBC	In the GEA cohort, the derived allele (T) was associated with: Increased BMI, Lower LDLc levels, Decreased risk of subclinical atherosclerosis in women, Significant gene-diet interactions affecting lipid, apolipoprotein and adiponectin levels. In the Genotype-related Effects of PUFA trial, the derived allele was associated with: Lower	28

	with metabolic traits, with a focus on the FADS2/rs174616 variant. Selection scan followed by association analyses in two independent cohorts.					(GRE-PUFA Trial)			Δ-6 desaturase activity, Lower erythrocyte membrane dihomo-gamma-linolenic acid (DGLA) levels, Increased Δ-5 desaturase activity, Higher eicosapentaenoic acid levels. The relationship between DGLA and other erythrocyte membrane LC-PUFA indices with HOMA-IR (insulin resistance) differed according to rs174616 genotype. identified rs174616 in FADS2 as a novel signal suggesting positive selection in an independent linkage disequilibrium block in Native Americans of Mexico. The variant was associated with cardiometabolic traits and erythrocyte measurements of long-chain polyunsaturated fatty acids in two independent Mexican cohorts and showed significant gene-diet interactions. These findings have implications for the interpretation of fatty acid indices in relation to insulin resistance and highlight the importance of considering genetic background in nutritional studies.	
Retrospective case-control study	Evaluate the relationship between daily intake of saturated, monounsaturated, and polyunsaturated fatty acids in individuals with/without oral cancer or precancerous lesions, and assess possible associations with TP53-R72P and pri-miR 34b/c-rs4938723 genetic polymorphisms. Dietary assessment: Quantitative food frequency questionnaire. Controls (n=27), Potentially malignant oral lesions (PPOL) (n=24), Oral squamous cell carcinoma (OSCC) (n=29).	TP53 (rs1042522), pri-miR 34b/c (rs4938723)	Oral cancer	Argentina	N/A or N/S	80	Both	Serum/plasma	Genetic associations with OSCC: Patients carrying the GC genotype of TP53 rs1042522 had 4 times higher risk of OSCC compared to controls, Patients carrying the GC+CC genotypes (vs. GG) of TP53 rs1042522 had higher OSCC risk. Carriers of the T allele of Pri-miR 34b/c rs4938723 had 3 times higher risk of OSCC compared to C allele carriers. Genetic associations with PPOL: Patients with T allele of Pri-miR 34b/c rs4938723 were 8 times more likely to develop premalignant lesions. Dietary findings: Significantly higher intake of SFA, MUFA and PUFA (linoleic, alpha-linolenic) in cases vs. controls, Higher omega-6/omega-3 ratio in cases compared to controls. High-fat dietary intake and the presence of mutant alleles of TP53 (rs1042522) and pri-miR 34b/c (rs4938723) were associated with an increased risk of oral squamous cell carcinoma and potentially malignant oral lesions. This study highlights the potential interaction between dietary factors and genetic susceptibility in the development of oral cancer.	29
Longitudinal cohort study	Dietary assessment: 144-item food frequency questionnaire.	APOE ε4	Alzheimer's Disease	USA	62% African Americans	336	Both	Not applicable	Among APOE-ε4 carriers: Higher intake of long-chain n-3 polyunsaturated fatty acids (LC-n3 PUFA) was associated with slower cognitive decline. In APOE-ε4 carriers, higher saturated fat intake was associated with faster cognitive decline, while higher LC-n3 PUFA intake was associated with slower cognitive decline. These findings suggest that saturated fat may exacerbate the adverse effects of APOE-ε4 on cognition, whereas LC-n3 PUFA might mitigate these effects. Precision nutrition targeting metabolic pathways altered by APOE4 might provide a tool for preventing the disease	30
One-arm intervention (6 weeks)	Oral supplementation with 3 capsules of FO (GNC Preventive Nutrition® Triple Strength Fish Oil) per day, each containing 647 mg of eicosapentaenoic acid (EPA) and 253 mg of docosahexaenoic (DHA) (daily intake: 2.7 g/day of DHA and EPA in fish oil).	PPARA (L162V), PPARG (P12A)	Healthy	Mexico	N/A or N/S	191	Both	Serum/plasma and buffy coat	Carriers of the minor alleles of PPARα L162V and PPARγ2 P12A showed greater reductions in TG and fasting insulin, respectively. FO supplementation may effectively reduce triglycerides and fasting insulin levels, especially in individuals with specific PPAR genotypes,	31
Cross-sectional	Long-term intake of n-3 PUFA was estimated using the nitrogen stable isotope ratio (δ15N) of red blood cells (RBC).	Whole genome linkage scan	Healthy obese	Alaska	Yupik people	982	Both	Serum/plasma	n-3 PUFA modified the association between obesity related traits and two additional variants (rs2048417 on chromosome 3 for adiponectin and rs730414 on chromosome 11 for percentage body fat). This study presents evidence of novel genomic regions and gene-diet interactions that may contribute to the pathophysiology of obesity-related traits among Yupik people.	32
Prospective population-based cohort	Estimate the associations between plasma levels of EPA and DHA and cognitive	APOE ε4	Cognitive decline	France	N/A or N/S	1228	Both	Serum/plasma	EPA was associated with slower cognitive decline (as measured by the Benton Visual Retention Test, BVRT) in ApoE-ε4 carriers and individuals with high baseline depressive symptoms. DHA was	33

study (7 years)	decline.								associated with slower BVRT decline only in ApoE-ε4 carriers. EPA and DHA may delay decline in visual working memory in ApoE-ε4 carriers.	
Cross-sectional	The Boston Puerto Rican Health Study (BPRHS) used a semi-quantitative food frequency questionnaire (FFQ). The ARIC study used a modified 66-item interviewer-administered FFQ.	LPL (rs320, rs2083637, rs17411031, rs13702, rs2197089)	Healthy	USA	Puerto Rican ancestry, African American and European American	1171 (BPRHS) and 10875 (ARIC)	Both	Serum/plasma	In women, SNP rs320 showed significant interactions with PUFA intake for BMI and waist circumference (WC). Higher PUFA intake was linked to lower BMI and WC in TT homozygotes, but not in TG or GG genotypes. These gene-diet interactions were confirmed in the independent ARIC population. Dietary PUFA intake modifies the effect of LPL rs320 on obesity traits, suggesting that gene-diet interactions may influence obesity risk and could be considered in personalized dietary strategies, especially for women.	34
Controlled intervention (8 weeks)	Supplemention with 2g of pure EPA daily.	FABP2 (Ala54Thr)	Hypertriglyceridemia	Iran	N/A or N/S	46	Both	Serum/plasma	Significantly greater reductions in key lipid markers in Thr54 carriers compared to Ala54 carriers: Triacylglycerol, VLDL, ApoCIII, HDLc. No significant changes in total cholesterol, LDLc, or ApoB. EPA levels increased in both groups, more so in Thr54 carriers. EPA supplementation is more effective at improving blood lipid profiles in hypertriglyceridemic individuals with the FABP2 Thr54 genotype than in those with the Ala54 genotype. This suggests that increasing EPA intake could be a targeted strategy for managing triglyceride levels, particularly in individuals with the Thr54 variant.	35
Cross-sectional	Dietary intake was assessed using a validated semiquantitative food frequency questionnaire.	APOB (Ins/Del)	Type 2 Diabetes Mellitus	Iran	N/A or N/S	700	Both	Serum/plasma	Significant interactions between Ins/Del genotype and ω-3 PUFA intake on BMI, WC, and obesity risk. Del allele carriers had lower BMI and WC only when ω-3 PUFA intake was ≥0.6% of energy. With low ω-3 PUFA intake (<0.6%), Del allele carriers had a 1.6-fold higher risk of general obesity, With high ω-3 PUFA intake, the obesity risk was reduced by over half. A similar gene-diet interaction was found for central obesity in men. A high dietary intake of ω-3 PUFA (≥0.6% of energy) significantly reduces the risk of both general and central obesity in carriers of the ApoB Del allele, highlighting a gene x diet interaction relevant to obesity management in type 2 diabetes	36
Cross-sectional	Participants of the Health Survey of Sao Paulo. Individuals were categorized into inflammatory (INF) and noninflammatory (NINF) groups based on biomarker profiles. Information about food intake was obtained using 24-h recall and structured questionnaires. Fatty acid (FA) profile measured in plasma.	TLR4 (rs4986790, rs4986791, rs11536889, rs5030728)	Healthy	Brasil	N/A or N/S	262	Both	Serum/plasma	A significant interaction between rs11536889 and AA/EPA ratio: Individuals with the C allele and a high AA/EPA ratio had increased odds of being in the INF cluster. The plasma fatty acid profile, particularly the AA/EPA ratio, interacts with TLR4 genetic variation (rs11536889) to modulate the risk of systemic inflammation, highlighting a gene x diet interaction in inflammatory status.	37
Cross-sectional	Participants categorized into high or low intake groups based on median intake of PUFAs, MUFAs, and SFAs. Dietary intake assessed using a food frequency questionnaire.	APOA2 (-265 T>C)	Type 2 Diabetes Mellitus	Iran	N/A or N/S	180	Both	Serum/plasma	Subjects with CC genotype are more susceptible to inflammation. The intake of ω-3 poly- and monounsaturated fatty acids reduces the inflammatory effects of CC genotype. Results suggest a significant interaction between apolipoprotein A2 -265 T>C polymorphism and ω-3 PUFA intake on serum level of IL-18. In T2DM patients, anti-inflammatory fatty acids (ω-3 PUFAs and MUFAs) may reduce inflammation particularly in CC genotype carriers of APOA2, while SFA intake may increase inflammation in T-allele carriers, potentially negating any protective effects. These gene x diet interactions suggest a personalized approach to dietary fat intake for managing inflammation in diabetes.	38
Cross-sectional	Participants completed a food frequency questionnaire. Fatty acid intake was estimated based on the interview and a nutrient reference table. Women in the study were categorized in 2 groups	PON1 (T-107C)	Healthy	Brasil	N/A or N/S	39	Women	Serum/plasma	Serum PON1 activity varied significantly by genotype, with the CC genotype showing higher activity. Significant differences in PON1 activity between CC and TT genotypes were found across intake levels of total fat, SFAs, MUFAs, PUFAs, n-3, and n-6. In women with high n-6/n-3 ratio, CC genotype was associated with reduced PON1 activity, while TT genotype was associated with increased activity. A low n-6/n-3 ratio diet led to decreased PON1 activity in CC carriers and increased activity in TT carriers. The C allele of PON1	39

	according to the median nutrient intake.								T(-107)C is generally associated with increased serum PON1 activity, but this benefit may be blunted by high saturated fat intake or a low n-6/n-3 fatty acid ratio, especially in CC genotype women. These findings support a gene x diet interaction in the modulation of antioxidant enzyme activity.	
Cross-sectional	Participants of the Health Survey of Sao Paulo. Information about food intake was obtained using 24-h recall and structured questionnaires.	FADS1 (rs174546), ELOVL2 (rs953413)	Healthy	Brasil	N/A or N/S	226	Both	Serum/plasma	FADS1 SNP (rs174546) T allele carriers showed: Significantly lower plasma HDL and LDL cholesterol levels, higher plasma oleic acid, linoleic and linolenic acid levels, higher stearoyl CoA desaturase enzyme (SDC_18) estimated activity, lower delta-5 and delta-6 desaturase estimated activity. ELOVL2 SNP (rs953413) AG/GG genotypes showed higher plasma oleic acid levels compared to AA genotype. SNPs in FADS1 and ELOVL2 genes showed protective associations for lipid metabolism and could potentially serve as markers of lower cardiometabolic risk	40
Cross-sectional	Dietary data obtained through 24-hour recalls.	FADS2 (rs174593, rs174616, rs174576)	Healthy	Serbia	N/A or N/S	84	Both	Serum/plasma	Gene-fatty acid associations: Addition of FADS2 alternative alleles associated with lower plasma AA, FADS2 alternative alleles associated with lower estimated desaturase-5 activity. rs174576 showed the strongest association with AA. No associations were found between the variants and dietary intake, serum lipids, or obesity. FADS2 variants were inversely associated with plasma AA but not with ω-3 fatty acids. FADS2 gene variants are inversely associated with plasma arachidonic acid levels and estimated desaturase-5 activity in Serbian adults, with rs174576 showing the strongest relationship. These variants did not show significant associations with ω-3 fatty acids, dietary intake, serum lipids, or obesity	41
Randomized placebo-controlled trial (Last two trimesters of pregnancy)	Placebo group (n=96): Given mixed soy and corn oil capsules, Intervention group (n=109): Given 600mg algal DHA daily.	FADS1 (rs174533), FADS2 (rs174575)	Pregnancy	USA	N/A or N/S	205	Women	Serum/plasma and RBC	Baseline findings: Women homozygous for the minor allele of FADS1rs174533 had lower DHA and ARA status. At delivery: In the placebo group, minor allele homozygotes of FADS1rs174533 had lower RBC-DHA compared to major-allele carriers. In the DHA-supplemented group, all genotypes showed higher DHA status compared to baseline, with no significant differences between genotypes. DHA supplementation decreased ARA status in minor allele homozygotes of both FADS SNPs, while ARA status was maintained in major allele homozygotes. DHA supplementation (600mg daily) during pregnancy effectively increases DHA status regardless of FADS genotype. The supplementation has a differential effect on ARA status based on FADS genotype, decreasing ARA levels only in minor allele homozygotes. This suggests that the physiological effects of altering the DHA to ARA ratio through DHA supplementation may be more pronounced in individuals who are minor allele homozygotes for certain FADS SNPs.	42
One-arm intervention (6 weeks)	Fish oil supplementation.	PLA2G4A, PLA2G6	Healthy	Canada	N/A or N/S	191	Both	Serum/plasma	Interaction effects: SNPs and supplementation together modulated total n-6 FAs and CRP levels in both men and women. Gender-specific findings: In men only: Associations were found between SNPs and total n-6 FA levels, and between SNPs and CRP levels, independently of supplementation. Changes in CRP levels correlated positively with changes in total n-6 FAs. Supplementation effects: Fish oil supplementation decreased total n-6 FAs, Supplementation did not affect plasma CRP levels. Total omega-6 fatty acid levels in plasma phospholipids and plasma C-reactive protein levels are modulated by SNPs within PLA2G4A and PLA2G6 genes, either independently or in interaction with fish oil supplementation. The findings suggest gender-specific effects in the relationship between genetic factors, fatty acid metabolism, and inflammatory markers.	43
Cross-sectional	Investigate whether FADS1 rs174547 (T/C) is associated with changes in erythrocyte membrane and plasma phospholipid long-chain polyunsaturated fatty	FADS1 (rs174547)	Healthy	Japan	Japanese	124	Both	Serum/plasma and RBC	FADS1 rs174547 C-allele carriers showed: Significantly lower arachidonic acid levels in both erythrocyte membrane and plasma phospholipids, Higher linoleic acid in both erythrocyte membrane and plasma phospholipids, Higher α-linolenic acid (n-3 PUFA precursor) levels in plasma phospholipids only, No significant changes in EPA or DHA levels in either erythrocyte membrane or	44

	acid (LCPUFA) composition.								plasma phospholipids. These findings suggest a lower conversion rate of linoleic acid to arachidonic acid in C-allele carriers. The FADS1 rs174547 genotype is significantly associated with differences in arachidonic acid composition in the blood of elderly Japanese participants, specifically showing reduced conversion of linoleic acid to arachidonic acid in C-allele carriers, without affecting n-3 LCPUFA (EPA and DHA) levels.	
Longitudinal study (mean follow-up of 3 years)	Plasma PUFA levels were measured via GC-MS.	FADS1 (rs174547)	Overweight	Korea	Japanese	287	Both	Serum/plasma	Significant interaction effects between FADS1 rs174547 T > C genotype and baseline BMI on: Changes in plasma arachidonic acid (AA), eicosapentaenoic acid (EPA)/AA ratio and ba-PWV. Group-specific findings: Normal-weight C allele carriers and overweight TT subjects showed smaller increases in AA levels compared to normal-weight TT subjects. Overweight C allele carriers demonstrated: Greater reductions in plasma EPA/AA ratio, greater increases in ba-PWV (arterial stiffness) compared to the other three groups. The minor allele (C) of the FADS1 rs174547 polymorphism is associated with age-related decreases in the EPA/AA ratio and increases in arterial stiffness (ba-PWV) specifically among overweight subjects, suggesting an interaction between this genetic variant and weight status that affects cardiovascular health markers over time	45
Metabolic tracer study(14 days)	Administration of [U-13C]linoleate (isotope-labeled linoleic acid). Participants divided in two age groups: Young (25-34 y) and Elderly (65-74 y).	FADS1 (rs174547)	Healthy	Japan	N/A or N/S	64	Both	Serum/plasma	Genetic influence on ARA synthesis: AUC of 13C-ARA concentration differed significantly by FADS1 rs174547 genotype: TT genotype: 100% (reference), TC genotype: 57% of TT reference, CC genotype: 37% of TT reference. Age-related differences: Among C allele carriers (TC and CC genotypes), 13C-ARA formation was 32% lower in elderly participants compared to young participants, Age-related decline in LCPUFA biosynthetic capacity was specifically observed in C allele carriers. This is the first study to directly demonstrate that LCPUFA biosynthetic capacity is regulated by FADS1 polymorphisms and is decreased by aging specifically in FADS1 C allele carriers. The findings provide direct evidence of the impact of both genetic factors and aging on the body's ability to synthesize long-chain polyunsaturated fatty acids.	46
Case-control study	Dietary intake through questionaries.	FADS1 (rs174546), FADS2 (rs3834458)	Metabolic Syndrome (postmenopausal)	Poland	N/A or N/S	131	Women	Serum/plasma and RBC	Genetic findings: Participants with at least one minor allele of either FADS1 (rs174546) or FADS2 (rs3834458) polymorphism had lower levels of EPA, lower EPA/AA ratio and higher DHA/EPA ratio in RBCs compared to women with major alleles. Metabolic syndrome is associated with lower levels of fatty acids that have a protective effect on cardiometabolic health. FADS1 and FADS2 polymorphisms are associated with unfavorable fatty acid profiles. The EPA/AA ratio in red blood cells contributes to metabolic syndrome risk, suggesting this may be an important biomarker for cardiometabolic health in postmenopausal women.	47
Case-control study	Self-reported dietary intake. Erythrocyte membrane phospholipid PUFA percentages measured using gas chromatography.	FADS (rs174537)	Healthy	USA	African Americans and European Americans	1733	Both	Serum/plasma and RBC	Genetic associations (GG genotype): Negatively associated with precursor PUFAs (Linoleic acid (LA) and Di-homo-α-linolenic acid (DGLA)). Positively associated with product PUFAs (Arachidonic acid (AA) and Docosahexaenoic acid (DHA), and with product-to-precursor ratio (AA to DGLA), an indirect measure of FADS efficiency. Increased consumption of n-6 PUFA and linoleic acid, resulting in increased arachidonic acid and subsequent inflammation due to more efficient FADS conversion (GG genotype), may be contributing to the increased prevalence of chronic diseases, especially in populations of African descent.	48
Randomized controlled trial (6 months)	Secondary analysis with participants from the seAFOod trial: Daily supplementation of 2 g eicosapentaenoic acid (EPA) or placebo. Daily dietary intake of EPA and DHA (g/day) at baseline was calculated from data	APOE (rs429358, rs7412)	Multiple colorectal polyps	UK	N/A or N/S	584	Both	Serum/plasma and RBC	At baseline, APOE2/2 individuals had lower and APOE4/4 individuals had higher n-3 HUFA levels compared to APOE3/3. Post-supplementation, n-3 HUFA levels did not significantly differ across APOE genotypes. APOE genotype influences baseline n-3 HUFA and 18-HEPE levels in individuals with multiple colorectal polyps.	49

	collected with the European Prospective Investigation into Cancer and Nutrition (EPIC) short-form food frequency questionnaire, which was completed at trial entry. Dietary fish intake was converted into EPA and DHA intake per day using the EPIC-Norfolk fatty acid nutrient database.									
Cross-sectional	Genome-wide interaction study (GWIS) with individuals from the Framingham Heart Study Offspring cohort.	APOE ε4	Cognitive decline	USA	N/A or N/S	1620	Both	Serum/plasma and RBC	22 SNPs showed enhanced cognitive performance with higher ω-3 PUFA in minor allele carriers, 9 SNPs showed benefits for common homozygotes. This GWIS identified 8 genes plausibly linking ω-3 PUFA levels, cognition, and lipid metabolism, suggesting that genetic background may influence cognitive benefits from ω-3 PUFA intake. Replication in diverse, prospective cohorts is recommended.	50
Randomized, double-blind, placebo-controlled trial (6 months)	Supplementation with ω-3 FAs (DHA 0.8 g + EPA 1.7 g daily) or placebo.	APOE ε4	Cognitive decline	Canada	N/A or N/S	189	Both	Serum/plasma	Nonesterified fatty acids (NEFA) pool: EPA and DHA increased significantly after 1 and 6 months, no modulating effects from sex, BMI, age, or APOE ε4. Plasma phospholipids (PL) pool: EPA increased by 387%-463%, DHA by 83%-109%, EPA in PLs was higher in APOE4 carriers vs. noncarriers, Females vs. males and Individuals with BMI ≤25 vs. >25. Plasma phospholipid EPA concentrations are influenced by APOE4 genotype, sex, and BMI, and these variables should be considered in the design and interpretation of ω-3 FA supplementation trials.	51
Case-only genetic interaction study	Cases from a population-based genetic repository.	191 SNPs (55 genes in fatty acid metabolism)	Sudden cardiac arrest	USA	N/A or N/S	1869	Both	RBC	No SNP-fatty acid associations reached significance after multiple comparison correction. Nominal association found for SNP rs4654990 near PLA2G2A: Minor allele linked to lower DHA and EPA, and higher trans-fatty acids. Although not statistically significant after correction, results suggest that the relationship between circulating n-3 and trans-fatty acids and SCA risk may be influenced by the PLA2G2A variant rs4654990, potentially modifying individual susceptibility.	52
Metabolic tracer study (28 days)	Single oral dose of 40 mg [13C]DHA.	APOE ε4	Cognitive decline	Canada	N/A or N/S	40	Both	Serum/plasma	E4+ had 31% lower plasma [13C]DHA than E4-. E4+ showed higher cumulative β-oxidation of [13C]DHA over 28 days. A significant genotype x time interaction for β-oxidation was found. DHA metabolism is altered in APOE E4 carriers, with increased breakdown and lower retention of DHA. This metabolic disturbance may help explain why DHA levels do not correlate with cognitive benefit in E4+ individuals.	53
Cross-sectional	Stratification of participants into inflammatory (INF) and non-inflammatory clusters.	TNF-α (rs361525, rs1800629, rs1799724, rs1799964)	Healthy	Brazil	N/A or N/S	281	Both	Serum/plasma	Allele carriers had higher levels of total PUFA and DHA. Significant gene x FA interactions affecting risk of being in the INF cluster: -857C/T x α-linolenic acid. TNF-a polymorphisms are associated with variations in inflammatory biomarker levels and plasma fatty acid profiles, and gene x FA interactions may influence systemic inflammation risk.	54
Cross-sectional	Using baseline samples from the FINGEN study.	APOE	Healthy	UK	N/A or N/S	306	Both	Serum/plasma	APOE4 allele associated with higher EPA in males, and higher DPA and DHA. Plasma concentrations of EPA, DPA, and DHA in various lipid fractions are influenced by oily fish intake, age, sex, BMI, and APOE genotype, with specific gene x sex interactions. These factors should be considered when interpreting fatty acid biomarkers and formulating dietary recommendations.	55
Cross-sectional	Dietary assessment: 147-item food frequency questionnaire (FFQ).	CAV-1 (rs3807992)	Metabolic Syndrome	Iran	N/A or N/S	404	Women	Serum/plasma	Gene x diet interactions: CAV-1 x PUFA intake interactions were significant for MetS, TAG, glucose, and insulin resistance. Higher PUFA intake appeared to attenuate the negative associations of the A allele with MetS risk. CAV-1 rs3807992 polymorphism is associated with MetS risk and related metabolic traits, and these effects are significantly modified by dietary fatty acid intake. Specifically, high SFA intake exacerbates, while high PUFA intake mitigates, the genetic risk of MetS in A allele carriers.	56
Cross-sectional	Dietary assessment: Semi-quantitative food frequency	PPARG (Pro12Ala,	Type 2 Diabetes	Iran	N/A or N/S	290	Both	Serum/plasma	Diet x gene interaction: Among those with low MUFA and PUFA intake, Ala carriers had higher BMI than non-carriers. A significant	57

	questionnaire assessing intake over the past year.	rs1801282)	Mellitus						interaction between PUFA intake and genotype on triglyceride levels was observed. In participants with high PUFA intake, Ala carriers had lower triglyceride levels than non-carriers. PPARγ Pro12Ala polymorphism is associated with metabolic syndrome traits (BMI, waist circumference), and modifies the effect of dietary fat intake, especially PUFAs on triglyceride levels. These findings highlight the importance of gene x diet interactions in metabolic regulation in individuals with type 2 diabetes.	
Cross-sectional	Dietary intake: Fish consumption assessed via self-reported diet history questionnaire.	FADS (rs28456, rs174576, rs174547)	Bipolar disorder	Japan	N/A or N/S	300	Both	Serum/plasma	Risk variants in FADS SNPs associated with increased n-6 PUFA and higher TNFα. BD is associated with an imbalance in n-3 and n-6 PUFAs and increased inflammation. Genetic variation in the FADS gene cluster and lower fish consumption may contribute to this altered PUFA profile and heightened proinflammatory state in BD. These findings suggest a gene-diet-inflammation interaction that could be relevant for understanding and managing BD.	58
Cross-sectional	Self-reported dietary DHA intake assessed by food frequency questionnaire (FFQ). Individuals from the ALFA study, enriched for APOE-ε4 carriers.	APOE ε4	Alzheimer's Disease	Spain	N/A or N/S	340	Both	Not applicable	Significant association between higher DHA intake and greater cortical thickness in the AD signature region in APOE-ε4 homozygotes. In cognitively unimpaired APOE-ε4 homozygotes, higher dietary DHA intake is associated with brain structural features potentially protective against AD pathology. These findings support the hypothesis that individuals at highest genetic risk for AD may derive the greatest neuroprotective benefit from DHA intake in the preclinical phase.	59
Randomized crossover, controlled trial (4 weeks)	Participants consumed five isoenergetic diets: SFA from cheese, SFA from butter, MUFA, PUFA, High-carbohydrate (CHO).	22 SNPs (lipid and bile acid metabolism)	Elevated waist circumferenc e and low HDL	Multicenter	N/A or N/S	92	Both	Serum/plasma	ABCA1-rs2066714 and APOE isoforms showed consistent significant effects on LDL cholesterol. Other SNPs showed diet-specific associations with changes in LDL and TG. Combinations of genetic variants, rather than individual SNPs alone, are significantly associated with interindividual variability in blood lipid responses to diets differing in fatty acid composition. These findings highlight the value of multigenic models in understanding lipid metabolism and personalizing dietary interventions.	60
Case-control study	Participants from a nested case-control study of coronary artery disease (from Nurses' Health Study and Health Professionals Follow-Up Study. Dietary PUFA intake: Assessed using semiquantitative food-frequency questionnaires.	FADS1 (rs174546)	Coronary Artery Disease	USA	Chinese	2288	Both	Serum/plasma	Each copy of the C allele of rs174546 was associated with: Higher circulating proportions of arachidonic acid, EPA, and DHA, and lower proportions of LA and α-LA. Gene-diet interactions were observed: The positive association between dietary EPA/DHA intake and circulating EPA proportions increased with each copy of the rs174546_T allele. Each 1-SD increment in EPA intake was associated with an average 3.7% increase in circulating EPA for CC genotype carriers versus 7.8% increase for TT genotype carriers. Carriers of the T allele at FADS1 rs174546 may require higher doses of dietary EPA and DHA to achieve the same circulating proportions of EPA as carriers of the C allele.	61
Cross-sectional	Plasma fatty acids were measured from a single sample obtained at baseline in Chinese adults with the use of gas chromatography. Blood lipids were measured at baseline and a second time at the 18-mo follow-up.	FADS1 (rs66698963)	Healthy	China	Chinese	1504	Both	Serum/plasma	FADS1 activity increased in the order of genotypes D/D to I/D to I/I, reflecting a shift from precursors (linoleic acid and α-linolenic acid) to products (AA and EPA). For I/I compared to D/D carriers: Plasma concentrations of n-6 AA and Ratio of AA to n-3 EPA plus DHA were higher. Carriers of the deletion (D) allele of rs66698963 showed: Higher triglycerides and lower HDL cholesterol compared to carriers of the insertion (I) allele. The rs66698963 genotype is significantly associated with arachidonic acid concentrations and AA to EPA+DHA ratio, which reflects the basal risk of inflammatory and related chronic disease phenotypes. The polymorphism is also correlated with the risk of dyslipidemia.	62
Cross-sectional	Subjects from the Metabolic Syndrome in Men cohort (METSIM).	FADS1 (rs174550)	Metabolic Syndrome	Finland	N/A or N/S	1337	Men	Serum/plasma	Besides regulation of proportions of PUFAs in plasma lipids, the FADS1 rs174550 genotype modified concentrations of inflammation-related lipid mediators. Furthermore, responses in concentrations of serum hsCRP and plasma fasting glucose differed between the genotype groups. In addition, correlations between lipid mediators and their substrate fatty acids as well as correlations between lipid mediators and plasma hsCRP concentrations in healthy men were modified by genotype.	63
Intervention study (4 weeks)	Non-randomized, parallel study. 62 Subjects from the	FADS1 (rs174550)	Healthy	Finland	N/A or N/S	62	Men	Serum/plasma	Plasma LA proportion increased in both genotype groups in response to the LA-enriched diet. Significant diet x genotype	63

	METSIM study were devided in 2 groups: homozygotes for either TT or CC genotype of FADS1 rs174550 and consumed a LA-enriched diet (FADSDIET).								interactions were observed for: serum hsCRP concentrations, Plasma fasting glucose concentrations, Arachidonic acid proportion in plasma phospholipids and cholesteryl esters. In TT homozygous subjects, plasma eicosanoid concentrations correlated with arachidonic acid proportion in plasma and with hsCRP. No such correlations were observed in CC genotype subjects. The FADS1 genotype modifies metabolic responses to dietary linoleic acid. This suggests that personalized dietary counseling might need to be modified according to FADS1 genotype, though this concept requires testing in larger randomized trials.	
One arm study (6 weeks)	Participants in the Fatty Acid Sensor (FAS) Study received 5g fish oil daily (containing 1.9-2.2g EPA and 1.1g DHA). A dietitian administrated a validated food-frequency questionnaire (FFQ) before the run-in period to each participant.	GWAS	Overweight	Canada	N/A or N/S	208	Both	Serum/plasma	31 tagging SNPs associated with triglyceride response were identified and used for GRS calculation. The GRS explained 49.73% of triglyceride response variance in the FAS study. Non-responders to omega-3 supplementation had a higher GRS than responders. In the FINGEN replication study, the GRS explained 3.67% of triglyceride response variance. Fine mapping proved to be effective to refine the previous GRS. Carrying increasing numbers of at-risk alleles of 31 SNPs confers a higher risk of being nonresponsive to n-3 FAs. The genetic profile therefore appears to be an important determinant of the plasma TG response to an n-3 FA supplementation and could be used to target those most likely to gain clinical benefit.	64
Cross-sectional	Volumetric magnetic resonance imaging. Measurements of serum DHA were taken. For spatial navigation assessment, an independent population of APOE genotyped adults (n=46) completed a novel virtual reality diagnostic test for Alzheimer's disease.	APOE ε4	Healthy (cognitively normal)	Australia/UK	N/A or N/S	53	Both	Serum/plasma	Greater serum DHA was associated with increased entorhinal cortex volume, but not hippocampal volume, in non-APOE ε4 carriers. APOE interacted with serum lysophosphatidylcholine DHA to predict hippocampal volume. APOE genotype modulated DHA associations with spatial navigation performance. DHA was inversely associated with path integration performance in APOE ε4 carriers only. Interventions aiming to increase DHA blood levels to protect against cognitive decline should consider APOE ε4 carrier status	65
Randomized, double-blind, placebo-controlled, multicenter trial (21 days)	Secondary analysis of the OMEGA trial.	FADS1 (rs174537)	ARDS/Acute lung injury	USA	N/A or N/S	214	Both	Serum/plasma	All individuals receiving omega-oil showed significantly higher concentrations of GLA, EPA, and DHA, but they did not vary by genotype at rs174537. Statistically significant SNP-diet interactions were observed on circulating DHA concentrations in African Americans. African American T-allele carriers on placebo illustrated elevated DHA concentrations. No significant SNP-diet interactions were detected on pulmonary functional metrics, clinical outcomes, and mortality. The study highlights the importance of genetic and racial contributions to PUFA metabolism and inflammation. SNP rs174537 had a significant impact on circulating DHA and urinary isoprostane concentrations	66
Randomized, double-blind, placebo-controlled, 2x2 factorial trial (2 years)	Ancillary study within a completed 2 x 2 factorial trial testing vitamin D3 (2,000 IU per day), omega-3s (1 g per day), and/or placebos.	APOE ε4	Cognitive decline (older adults)	USA	N/A or N/S	743	Both	Serum/plasma	APOE-ε4 did not significantly modify effects of vitamin D3 or omega-3s, compared to placebo, on change in global cognition, episodic memory, or executive function/attention. APOE-ε4 was associated with worse cognition but did not modify overall effects of vitamin D3 or omega-3 supplementation on cognition over 2 years.	67
Case control	Nested case-control study design in the multicentre Studies of the Etiology of RA (SERA) cohort includes RA-free subjects who are first-degree relatives of RA probands or are enriched with the HLA-DR4 allele. Anti-CCP2 status, self-reported ω-3 FA supplement use and ω-3 FA % in RBCs were obtained from a single visit.	HLA-DR4	Rheumatoid arthritis	USA	N/A or N/S	77	Both	RBC	Anti-CCP2 positive cases were less likely than controls to report omega-3 FA supplement use (odds ratio: 0.14, 95% CI 0.03, 0.68). In addition, the likelihood of anti-CCP2 positivity was inversely associated with total omega-3 FA % in RBCs (odds ratio: 0.47, 95% CI 0.24, 0.92, for a s.d. increase). The inverse association between anti-CCP2 positivity and self-reported omega-3 FA supplement use and omega-3 FA % in RBCs suggests that omega-3 FAs may protect against the development of RA-related autoimmunity in pre-clinical RA.	68

Case control	Nested case-control study within two prospective cohorts (Nurses' Health Study and NHS II). Dietary intake was assessed by food questionnaires, four years prior to diagnosis.	CYP4F3 (rs4646904, rs1290617, rs3794987, rs2683037), FADS1 (rs174561, rs174556), FADS2 (rs3834458, rs174575)	Inflammatory Bowel Disease	USA	N/A or N/S	735	Women	Serum/plasma	High n3:n6 PUFA intake was associated with a reduced risk of UC in individuals with the GG/AG genotype at a single nucleotide polymorphism in CYP4F3 (OR 0.57, 95% CI, 0.32-0.99) but not those with the AA genotype (OR 0.95, 95% CI, 0.47-1.93). No gene-diet interactions were noted for CD. Genetic variation at the CYP4F3 locus may modify the protective effect of dietary n3:n6 PUFA intake on ulcerative colitis risk. Further gene-environment interaction studies are needed to explore diet's role in inflammatory bowel disease (IBD) risk.	69
Cross-sectional	The Toon Genome Study is a cohort study of Japanese community-dwelling subjects. Each nutrient intake was assessed using the semiquantitative food frequency questionnaire and categorized into the quartiles (Q1-Q4).	Resistin SNP-420 (rs1862513)	Healthy	Japan	Japanese	1981	Both	Serum/plasma	The inverse association between serum resistin and n-3 PUFA was significant and most pronounced in individuals with the G/G genotype of SNP-420. higher intake of n-3 PUFA was associated with lower serum resistin levels, particularly in individuals with the G/G genotype of SNP-420. This suggests a gene-diet interaction influencing resistin levels.	70
Case-control study	Dietary intake was assessed using a validated 168-item food frequency questionnaire (FFQ).	FTO (rs9939609)	Breast cancer	Iran	N/A or N/S	540	Women	Not applicable	No significant association was observed between dietary intake and breast cancer in individuals without the FTO risk allele. A positive association between ω-6 fatty acid intake and breast cancer risk was found only in individuals with the FTO risk allele. The presence of the FTO rs9939609 risk allele may modify the effect of dietary ω-6 fatty acid intake on breast cancer risk.	71
Cross-sectional	Plasma ALA/LA ratio was measured as an objective marker of dietary fatty acid intake, instead of using questionnaires or dietary records.	FADS1 (rs174546), FADS2 (rs174602, rs2072114)	Type 2 Diabetes Mellitus	Taiwan	Chinese	816	Both	Serum/plasma	A significant gene-diet interaction was observed between rs2072114 and low α-linolenic acid/linoleic acid ratio, where G allele carriers had lower LDLc levels. A marginal interaction was also noted for rs174602 (P = 0.063) with the same fatty acid ratio. The study demonstrates that dietary n-3/n-6 fatty acid ratios can modify the genetic impact of FADS polymorphisms on LDLc levels in patients with type 2 diabetes. These findings support the development of personalized dietary strategies for managing dyslipidemia and cardiovascular risk in this population.	72
Observational prospective cohort study	Long-term (~10 years) changes in BMI and body weight were assessed in relation to dietary intake of n-3 PUFAs and fish. Dietary fatty acids, fish and adiposity measures were self-reported, measurement errors in these variables are inevitable.	FADS (rs174570)	Healthy	Multicenter	European ancestry	29674	Both	Not applicable	Significant gene-diet interactions were found between FADS rs174570 and n-3 PUFA intake on BMI change in NHS, HPFS, WHI, and SCHS cohorts. Fish intake also strengthened the association between rs174570 and long-term BMI change. Among T allele carriers of rs174570, higher intake of long-chain n-3 PUFAs was associated with greater increases in BMI, compared to non-T carriers. The study provides consistent and replicable evidence across diverse cohorts that genetic variation in the FADS cluster (rs174570) interacts with n-3 PUFA and fish intake to influence long-term weight gain. These findings support the potential for personalized dietary recommendations based on genetic makeup and warrant further validation in additional populations.	73
Cross-sectional	Food consumption was assessed using three 24h records collected within seven days.	PPARG (Pro12Ala, rs1801282), IL6 (-174G>C)	Obesity (severe)	Brazil	N/A or N/S	150	Both	Serum/plasma	Individuals with ProAla + AlaAla and GC + CC genotypes had higher BMI and greater PUFA intake. In severely obese individuals, the Ala allele of the PPARG2 Pro12Ala polymorphism is associated with increased adiposity and elevated blood pressure. No significant effects were observed for the IL6 -174G>C variant alone, but gene-gene and gene-diet interactions may influence obesity-related traits.	74
Cross-sectional	Energy, macro- and micronutrient intake was assessed by a validated food frequency questionnaire (FFQ).	ADRB2 (rs1042713)	Obesity	Malasia	Malaysian	178	Both	Serum/plasma	Gene-diet interactions in GG genotype carriers: Lower fasting glucose with low saturated fatty acid intake (<7.3% of TE/day), lower fasting glucose with high PUFA ratio (≥0.8/day), lower HOMA-IR and fasting insulin levels with high PUFA intake (≥6% of TE/day). These effects were not observed in non-carriers (AA genotype). G allele carriers of ADRB2 rs1042713 were associated with increased odds of insulin resistance. Obese G allele carriers showed compromised blood lipid profiles. Although it is premature to report gene-diet interaction on the regulation of glucose and insulin levels in Malaysians, authors suggest that higher quantity of PUFA-rich food	75

									sources in regular diet may benefit overweight and obese Malaysian adults metabolically.	
Cross-sectional	Food intake was not assessed. Serum levels of PUFA-containing TGs were assessed.	APOC3 (rs4225, rs4520, rs5128, rs2070666, rs207066)	Non-Alcoholic Fatty Liver Disease	China	N/A or N/S	34	Both	Serum/plasma	The A allele at rs2070667 (compared to G allele) exhibited downregulatory effect on triacylglycerols containing polyunsaturated fatty acids (PUFA-containing TGs): TG 54:7, TG 54:8, and TG 56:9. Low levels of PUFA-containing TGs were associated with high-grade lobular inflammation. The A allele at APOC3 rs2070667 has an inhibitory effect on serum levels of PUFA-containing TGs. Lower levels of these PUFA-containing TGs are associated with higher-grade lobular inflammation in NAFLD patients. This suggests a potential mechanistic link between APOC3 genetic variants, lipid metabolism alterations, and NAFLD pathological features	76
Randomized, Double-Blind, Placebo-Controlled Clinical Trial (8 weeks)	Subjects were classified as Ala carriers or non-Ala carriers. Participants from both groups were randomly assigned to receive either DHA-rich fish oil supplementation (containing 2400 mg/d fish oil, DHA: 1450 mg and eicosapentaenoic acid: 400 mg) or Placebo.	PPARG (Pro12Ala)	Type 2 Diabetes Mellitus	Iran	N/A or N/S	72	Both	Serum/plasma	No gene-diet interaction was found between PPAR γ Pro12Ala polymorphism and DHA-rich fish oil supplementation effects on body composition, adiponectin level, PPAR γ gene expression. DHA-rich fish oil supplementation favorably modulated body composition in patients with T2DM and could be useful to reduce visceral obesity. However, the PPAR γPro12Ala polymorphism did not influence the changes in the desired variables.	77
One arm intervention study (6 weeks)	Based on previous genome-wide association study (GWAS) by the same group that identified 13 loci associated with plasma TG response to n-3 FA supplementation. Intervention: n-3 FA supplementation (5 g/day of fish oil) containing 1.9-2.2 g of EPA and 1.1 g of DHA.	GWAS (67 SNPs in IQCJ, NXPH1, PHF17, MYB)	Overweight	Canada	N/A or N/S	208	Both	Serum/plasma	Gene-diet interactions (effect on TG response to supplementation): 10 SNPs of IQCJ gene, 4 SNPs of NXPH1 gene and 3 SNPs of MYB gene. Fine mapping in GWAS-associated loci identified specific SNPs that partly explain the large interindividual variability in plasma TG response to n-3 FA supplementation. These findings help explain why some individuals respond differently to omega-3 supplementation in terms of triglyceride reduction	78
Open-label intervention study (4 weeks)	PNPLA3 p.148I wild-type individuals vs. Homozygous carriers of the PNPLA3 p.148M variant. Intervention: 4g ω-3 fatty acids (1,840 mg EPA) and 1,520 mg DHA) daily. Serum free fatty acids (FFA) were determined.	PNPLA3 (p.I148M)	Non-Alcoholic Fatty Liver Disease	Germany	N/A or N/S	20	Both	Serum/plasma	FFA concentrations: Risk group (PNPLA3 p.148M carriers) had significantly lower baseline FFA, which increased by 9.1% after intervention. Wild-type group FFA decreased significantly by 28.3% after intervention. Short-term omega-3 fatty acid supplementation did not significantly alter hepatic steatosis in either genotype group. Different metabolic responses were observed between genotypes, particularly in free fatty acid concentrations.	79
One arm intervention study (6 weeks)	Based on the Fatty Acid Sensor (FAS) Study: n-3 PUFA supplementation with 5 g/day of fish oil (providing 1.9-2.2 g of EPA + 1.1 g of DHA). Based on changes in HOMA-IR, participants were categorized as high-risk or low-risk.	GWAS (ADGRL2 rs72723587, LOC101929563 rs77850702, rs72703546, PTPRO rs17174795, TPM1 rs12437986, RPH3AL rs55842940, rs6001872)	Overweight	Canada	N/A or N/S	138	Both	Serum/plasma	A significantly higher HOMA-IR change was observed in the high-risk group, as compared to the low-risk group following the n-3 PUFA supplementation. Results suggest that the genetic background has a relevant role in the interindividual variability observed in the insulin sensitivity response following an n-3 PUFA supplementation. Subjects being at risk of insulin sensitivity lowering following an n-3 PUFA supplementation may be identified using genetic-based precision nutrition approaches.	80
Cross-sectional	7-day dietary records. Determine the relationships among genetic variation, dietary fat intake, and blood lipid concentrations (HDL and triglycerides).	23 SNPs (15 lipid metabolism genes)	Overweight/ Obesity	USA	N/A or N/S	101	Both	Serum/plasma	The interaction between ANGPTL3-rs10889337 and PUFA intake was significant for the genotypic mode of inheritance (interaction p = 0.031, R2 = 0.353). Interactions between dietary intake and genes in lipid metabolism pathways were found to be associated with blood lipid concentrations in adults with overweight and obesity. Fatty acid intake may not modulate blood lipid concentrations uniformly across all individuals.	81

Cross-sectional	Measurements included plasma lipids, fatty acid profiles, physiological parameters, and lifestyle factors (via questionnaire).	APOE (ε2, ε3, ε4)	Cardiovascular Disease	Finnish	N/A or N/S	211	Both	Serum/plasma	LDL and total cholesterol levels were lower in the ε2 carriers than in the ε3 or ε4 groups. Proportions of plasma saturated fatty acids (SFAs) were higher, and omega-6 fatty acids lower in the ε2 carriers compared with the ε4 group. The ε2 carriers had a higher percentage of 22:4n-6 and 22:5n-6 and a lower percentage of 24:5n-3 and 24:6n-3 than individuals without the ε2 allele. Carriers of the APOE ε2 allele exhibit favorable lipid profiles (lower LDL and total cholesterol), suggesting a lower CVD risk compared to ε4 carriers. They also show distinct fatty acid compositions, with elevated SFAs and altered long-chain omega-3 and omega-6 profiles—novel findings that warrant further investigation into their physiological significance.	82
Cross-sectional	Genetic analysis: Array-based and targeted genotyping, assessing 233 serum metabolic phenotypes.	CPT1A (rs80356779, p.Pro479Leu)	Healthy	Canada	Inuit people	1570	Both	Serum/plasma	rs80356779 (L479 allele) was strongly associated with degree of unsaturation, n-3 fatty acid levels, PUFA and DHA relative to total fatty acids. A common missense mutation (rs80356779) in CPT1A is highly prevalent in Greenlanders and is strongly associated with fatty acid metabolism and reduced height, likely reflecting adaptation to a traditional marine-based diet. These results underscore the value of studying isolated populations to understand gene-environment interactions and their public health implications.	83
Cross-sectional	Genetic analysis: Assessed associations between variants in FADS1, FADS2, and ELOVL2 and BMI, obesity risk, lipid profiles, and specific fatty acid concentrations and enzyme activity indices.	FADS1, FADS2, ELOVL2	Overweight/ Obesity	Tunisia	Tunisian	628	Both	Serum/plasma	Allele-specific effects on fatty acids: FADS1 C allele: Associated with lower DHA levels. FADS2 C allele: Lower stearic acid, EPA, and elongase activity. ELOVL2 C allele: Lower ALA, EPA, DPA, and D6D activity. Variants in FADS1, FADS2, and ELOVL2 genes are significantly associated with BMI, obesity risk, and circulating fatty acid composition. These genes may influence metabolic pathways central to metabolic syndrome and related diseases, underscoring their potential as targets for precision nutrition or therapeutic strategies.	84
Cross-sectional	Measured plasma levels of AA and DGLA, and calculated AA/DGLA ratio (a proxy for FADS1 enzymatic efficiency).	FADS (80 SNPs, including rs174537)	Healthy	USA	African Americans	329	Both	Serum/plasma	rs174537 G allele—associated with higher enzymatic conversion of DGLA to AA—was more common in African Americans (79–82% homozygous) than in European Americans (42–45%). FADS genetic variants, especially rs174537, strongly influence PUFA metabolism, particularly AA levels. The greater prevalence of the G allele in African Americans explains their higher AA levels and suggests genotype-driven differences in desaturase activity between populations. This highlights the importance of ancestry-specific genetic background in lipid metabolism and potential dietary or therapeutic recommendations.	85
One arm study (8 weeks)	Intervention:diet high in saturated fat plus 3.45 g/day DHA. Fatty acids quantified via gas chromatography. Lipoprotein fractions analyzed: Sf >400 (chylomicrons), Sf 60–400 (VLDL1), Sf 20–60 (VLDL2).	APOE ε4	Healthy	Canada	N/A or N/S	23	Both	Serum/plasma	Fasting state: E4+ had 2× higher EPA/AA ratio and a trend toward higher EPA % in Sf >400 fraction. No APOE-related differences in total n-3 PUFA in VLDL1 or VLDL2 fractions. Postprandial state (5h): Trend toward genotype × time interaction for EPA in Sf >400 ($P = 0.081$). Among those with high baseline EPA, postprandial EPA (%) significantly decreased. Baseline EPA predicted postprandial EPA only in E4+ subjects. E4+ individuals may have altered postprandial n-3 PUFA metabolism, particularly regarding EPA clearance, despite low EPA content in the DHA supplement. These findings suggest that APOE genotype modifies fatty acid handling, highlighting a potential need for genotype-specific dietary strategies involving omega-3 supplementation.	86
One arm study (6 weeks)	Supplementation with 5 g/day fish oil (1.9–2.2 g EPA and 1.1 g DHA).	MGLL (18 SNPs)	Healthy	Canada	N/A or N/S	210	Both	Serum/plasma	Significant gene-diet interaction effects observed on LDLc: SNPs rs782440, rs6776142, rs555183, rs6780384, rs6787155, rs1466571, and on LDL particle size: SNPs rs9877819, rs13076593. Genetic variation in the MGLL gene may partly explain the interindividual variability in LDLc response and particle size changes after omega-3 PUFA supplementation, indicating the potential value of personalized nutrition based on MGLL genotype.	87
Cross-sectional	Food frequency questionnaire (147 items) to assess dietary intake.	CRY1 (rs2287161)	Overweight/ Obesity	Iran	N/A or N/S	377	Women	Not applicable	Significant interaction between CC + CG group genotype and PUFA intake on Resting Metabolic Rate (RMR) per BMI, RMR per kg, RMR per body surface area. The study emphasizes the importance of considering dietary compositions, gene variants, and their interactions in understanding lower resting metabolic rate,	88

									particularly in women with overweight or obesity.	
Cross-sectional	Food intake: 147-item semi-quantitative food frequency questionnaire. Fat quality indices: Cholesterol-saturated fat index (CSI) and ω-6/ω-3 ratio. Genetic risk score (GRS) calculated using three single nucleotide polymorphisms: Total average GRS value: 2, Sum of risk alleles: 6.	CAV-1 (rs3807992), CRY1 (rs2287161), MC4R (rs17782313)	Overweight/ Obesity	Iran	N/A or N/S	279	Women	Serum/plasma	Waist Circumference (WC): Positive interaction between T2 of GRS and T2 of N6/N3 ratio. Diastolic Blood Pressure (DBP): Positive interaction between T3 of GRS and T2 of N6/N3 ratio. Fasting Blood Sugar (FBS): Positive interaction between T3 of GRS and T2 of N6/N3 ratio. Triglycerides (TG): Positive interaction between T3 of GRS and T3 of N6/N3 ratio. The interaction between genetic risk score and fatty acid quality indices is positively associated with several metabolic syndrome components. Highlights the importance of considering gene-diet interactions. Suggests that genetic heterogeneity across ethnic groups may explain conflicting evidence in previous studies on fat intake, obesity, and cardiovascular diseases. Recommends future studies to consider the synergistic effect of genetic and dietary intakes	89
Cross-sectional	Food intake: 147-item semi-quantitative food frequency questionnaire. Fat quality indices: Cholesterol-saturated fat index (CSI) and ω-6/ω-3 ratio. Genetic risk score (GRS) calculated using three single nucleotide polymorphisms: Total average GRS value: 2, Sum of risk alleles: 7.	CAV-1 (rs3807992), CRY1 (rs2287161), MC4R (rs17782313)	Overweight/ Obesity	Iran	N/A or N/S	279	Women	Serum/plasma	Significant interactions between GRS and N6/N3 in the adjusted model controlling for confounding factors (age, body mass index, energy, and physical activity) (β = 2.26, 95% CI: 0.008 to 4.52, P = 0.049). This study highlights the importance of personalized nutrition and recommends further study of widely varying fat intake based on the findings on gene-N6/N3 PUFA interactions	90
One arm intervention study (6 weeks)	Intervention: 3 g/day of n-3 PUFA supplementation.	PLA2G2A (5 SNPs), PLA2G2C (6 SNPs), PLA2G2D (8 SNPs), PLA2G2F (6 SNPs), PLA2G4A (22 SNPs), PLA2G6 (5 SNPs), PLA2G7 (9 SNPs)	Overweight	Canada	N/A or N/S	208	Both	Serum/plasma	Genotype × Supplementation Interaction Effects: observed for rs1805018 in PLA2G7 and rs10752979, rs10737277, rs7540602, and rs3820185 in PLA2G4A. These results suggest that, SNPs in PLA2 genes may influence plasma TG levels during a supplementation with n-3 PUFA.	91
Cross-sectional	Gas chromatography for plasma phospholipid FA composition.	FADS1 (rs174547)	Healthy	China	N/A or N/S	67	Both	Serum/plasma	The rs174547 C minor allele was associated with a higher proportion of linoleic acid, lower arachidonic acid and docosahexaenoic acid, as well as lower delta-6-desaturase and delta-5-desaturase activity. Study confirmed association between FADS1 rs174547 and Plasma phospholipid fatty acid composition. Suggests potential for personalized nutritional and metabolic interventions based on genetic variations.	92
Randomized, single-blinded, parallel dietary intervention (16 weeks)	Dietary Intervention and VAScular function (DIVAS) study. Participants received one of three isoenergetic diets: high in Saturated Fatty Acids (SFA), high in MUFA or high in n-6 PUFA.	LPL (rs320, rs328), APOE (rs405509, rs769450, rs439401, rs445925, rs405697, rs1160985, rs1064725)	Cardiovascular Disease risk (moderate)	UK	N/A or N/S	120	Both	Serum/plasma	For the APOE SNP rs1064725, only TT homozygotes showed a significant reduction in total cholesterol after the MUFA diet (n = 33, -0.71 ± 1.88 mmol/l) compared to the SFA (n = 38, 0.34 ± 0.55 mmol/l) or n-6 PUFA diets (n = 37, -0.08 ± 0.73 mmol/l). greater sensitivity of the APOE SNP rs1064725 to dietary fat composition, with a total cholesterol lowering effect observed following substitution of SFA with MUFA but not n-6 PUFA. Further large intervention studies incorporating prospective genotyping are required to confirm or refute our findings	93
Cross-sectional	Subgroup analysis of participants from the Shanghai Obesity Study (SHOS), a community-based, prospective cohort study to investigate the occurrence and	FADS1, FADS2, C11orf10 (rs174546, rs174547, rs174550, rs174570,	Metabolic Syndrome	China	Chinese	304	Both	Serum/plasma	Strong associations between SNPs in FADS region and multiple PUFA. Minor allele of rs174570 was associated with decreased FADS1 and FADS2 expression levels. Methylation levels at four CpG sites in FADS1, one CpG site in intragenic region, and three CpG sites in FADS2 were strongly associated with rs174570. Genetic variants in FADS region are major regulators of fatty acid metabolism. Regulation occurs through complex epigenetic	94

	development of metabolic syndrome and its related diseases.	rs1535, rs174583, rs102275)							mechanisms. Involves intricate interactions between: Genetic variations, DNA methylation and Gene expression	
Randomized, double-blind, placebo-controlled trial (18 months)	Alzheimer's Disease Cooperative Study-sponsored DHA clinical trial. Participants were randomly allocated to placebo or 2 g of DHA. Phospholipid DHA was assayed in the plasma of 384 participants and CSF of 70 participants at baseline. Forty-four of the 70 participants completed the 18-month follow-up visit after allocation to placebo (n = 15) or DHA (n = 29).	APOE ε4	Alzheimer's Disease	USA	N/A or N/S	44	Both	Serum/plasma	At baseline, there were no significant differences between CSF or plasma phospholipid DHA levels by CSF Aβ42 tertiles or ε4 status. After 18 months of DHA supplementation, participants at the lowest Aβ42 tertile had significantly lower CSF DHA levels and lower CSF-to-plasma DHA ratios compared to the other tertiles. Participants carrying the ε4 allele demonstrated a less pronounced increase in CSF DHA level compared with noncarriers, with a possible interaction effect between treatment and APOE genotype (p = 0.07). APOE ε4 allele and lower CSF Aβ42 levels were associated with less transport of DHA to CSF. Brain amyloid pathology may limit the delivery of DHA to the brain in AD. Suggests importance of personalized nutritional interventions, genetic screening for DHA transport efficiency, and targeted approaches for individuals with APOE ε4 allele.	95
Cohort	22 PUFA concentrations measured by gas chromatography.	FADS1 (rs174537, rs174545, rs174546, rs174553, rs174556, rs174561, rs174568, rs99780)	Healthy	USA	Geographically isolated population (Tangier Island, Virginia)	224	Both	Serum/plasma	rs174537, rs174545, rs174546, rs174553, rs174556, rs174561, rs174568, and rs99780 were strongly associated with arachidonic acid (AA) among other PUFAs, but the strongest associations were with the ratio measuring FADS1 activity in the ω-6 series. The minor allele across all SNPs was consistently associated with decreased ω-6 PUFAs, with the exception of dihomo-gamma-linoleic acid (DHGLA), where the minor allele was consistently associated with increased levels. findings in a geographically isolated population with a homogenous dietary environment suggest that variants in the Δ-5 desaturase enzymatic step likely regulate the efficiency of conversion of medium-chain PUFAs to potentially inflammatory PUFAs, such as AA.	96
Randomized, double-masked, parallel intervention trial (6 weeks)	Intervention: Fish oil (5.0 g daily, containing 2.0 g EPA and 1.0 g DHA) vs placebo oil (5.0 g corn/soy mixture). The objective of this study was to determine whether 5-lipoxygenase (ALOX5) gene variants associated with cardiovascular disease affect eicosanoid production by monocytes.	ALOX5 (promoter variants)	Healthy	USA	African American ancestry	98	Both	Serum/plasma and PBMCs	Subjects with "55" genotype had higher levels of several metabolites compared to "d5" and "dd" genotypes, including arachidonic acid-derived: 5-HETE, 6-trans-LTB4, 5-oxo-ETE, 15-HETE, and 5,15-diHETE, EPA-derived: 5-HEPE and 15-HEPE, DHA-derived: 17-HDoHE. Regarding fish oil supplementation EPA-derived metabolites (5-HEPE and 15-HEPE) increased more in "55" genotype than other genotypes, and 5-oxo-ETE decreased more in "55" genotype than other genotypes. The differential eicosanoid response observed across ALOX5 genotypes is consistent with previous findings showing an interaction between these genetic variants and dietary omega-3 fatty acid intake in predicting cardiovascular disease risk	97
Cross-sectional	FADS1 genetic variant rs174550 in relation to blood PUFA and lipid levels, examining erythrocyte PUFA levels and their interactions with the genetic variant.	FADS1 (rs174550)	Healthy	China	Han people	321	Both	Serum/plasma and RBC	The C-allele of rs174550 was significantly associated with erythrocyte PUFA levels in both upstream and downstream pathways of Δ-5 desaturase. The rs174550 C-allele was associated with lower HDL cholesterol levels in the total population. In Beijing residents specifically, the C-allele was associated with higher triglyceride levels. Erythrocyte levels of 18:2n-6 and 18:3n-3 modified the genetic effect on HDL cholesterol, with stronger associations between the C-allele and lower HDL cholesterol when these PUFA levels were low. FADS1 genetic variants are associated with circulating PUFA and lipid levels in Han Chinese populations, and the effect of these variants on HDL cholesterol levels depends on an individual's PUFA status.	98
Cross-sectional	Participants from the Three-City study, aged 65 years and over, with 19% being APOE4 carriers.	APOE ε4	Alzheimer's Disease	France	N/A or N/S	1135	Both	Serum/plasma	Fish consumption was positively associated with plasma DHA regardless of APOE genotype, but the association was stronger in APOE4 non-carriers than carriers. Plasma DHA increased significantly with age in APOE4 non-carriers only. Dietary habits, gender, and APOE4 genotype should be considered when designing interventions to increase n-3 PUFA blood levels in older people.	99
Cross-sectional	Participants from the LIPGENE dietary cohort.	GCKR (rs1260326, P446L)	Metabolic Syndrome	Spain	N/A or N/S	379	Both	Serum/plasma	Among subjects with n-3 PUFA levels below the population median: carriers of the common C/C genotype had significantly higher plasma concentrations of fasting insulin, C-peptide, HOMA-IR, and CRP compared to subjects carrying the minor T-allele (Leu446).	100

									Among homozygous C/C carriers with n-3 PUFA levels above the median: showed lower plasma concentrations of fasting insulin, C-peptide, HOMA-IR, and CRP compared to individuals with the T-allele. This represents an opposite pattern of associations depending on n-3 PUFA status. interaction between the GCKR rs1260326-P446L polymorphism and plasma n-3 PUFA levels modulating insulin resistance and inflammatory markers in MetS subjects.	
Case-control	440 CAD patients and 838 healthy controls in a middle-aged and elderly Chinese population. Dietary EPA and DHA intakes were assessed using a validated quantitative frequency food questionnaire.	FADS1 (rs174547)	Coronary Artery Disease	China	Costa Rican	1278	Both	Serum/plasma	The minor T allele of FADS1 rs174547 increased CAD risk. Significant interaction was observed between rs174547 and dietary EPA intakes on CAD. The T-allele was associated with higher CAD risk only among individuals with lower dietary EPA intakes, but not with higher EPA intakes. Similar significant interaction was observed between rs174547 and dietary DHA intakes on CAD. High n-3 LCPUFA intake appeared to negate the adverse genetic effect. Dietary n-3 LCPUFA intakes could modulate the association between FADS1 rs174547 polymorphism and CAD. High dietary n-3 LCPUFA intakes could negate the unfavorable effect of genetic variation in FADS1 on CAD in middle-aged and elderly Chinese population.	101
Randomized, placebo-controlled, double-blind, parallel, comparative study (3 years)	To investigate whether genotype could influence response to DHA supplementation in the occurrence of choroidal new vessels (CNV), as genetic susceptibility could be modified by environmental factors and may influence differential responses to treatments for age-related macular degeneration (AMD). Patients were randomized to receive either 3 daily fish-oil capsules (each containing 280 mg DHA, 90 mg EPA, and 2 mg Vitamin E) or placebo.	CFH (Y402H)	Age-related Macular Degeneration	France	N/A or N/S	250	Both	Serum/plasma and RBC	A significant interaction was observed between CFH Y402H and DHA supplementation. Among homozygous non-risk patients, a protective effect of DHA supplementation was observed: CNV occurrence was 38.2% in placebo group versus 16.7% in DHA group. Genetic predisposition to AMD conferred by the CFH Y402H variant limits the benefit provided by DHA supplementation. The protective effect of DHA supplementation appears to be restricted to patients without the genetic risk variant, suggesting that genetic testing could inform treatment decisions for AMD prevention.	102
Cross-sectional	Dietary assessment was conducted using a validated food frequency questionnaire (FFQ).	MC4R (rs17782313), TCF7L2 (rs12255372, rs7903146)	Type 2 Diabetes Mellitus	India	Costa Rican	1882	Both	Serum/plasma	Secondary analysis showed significant interaction between rs12255372 and polyunsaturated fatty acids (PUFA, g/day) on HDLc, minor allele carriers had higher HDLc in the lowest PUFA tertile and lower HDLc in the highest PUFA tertile than GG homozygotes. The association between TCF7L2 SNP rs12255372 and HDL cholesterol may be modified by dietary fat intake in this Asian Indian population. The findings suggest that genetic effects on lipid metabolism are modulated by specific dietary components, particularly total fat and PUFA intake, indicating the importance of considering gene-diet interactions in this population.	103
Cross-sectional	Erythrocyte n-3 PUFAs were measured as suitable markers of dietary fatty acid intake.	APOC3 (T-455C)	Heart Disease	Italy	N/A or N/S	848	Both	Serum/plasma and RBC	In the total population, apo C-III concentrations were significantly inversely correlated with total erythrocyte PUFAs, but this correlation was not significant in -455CC homozygous individuals alone. In the total population and in -455TT and -455CT genotype subgroups: the proportion of individuals with elevated apo C-III (above 75th percentile) decreased progressively as n-3 PUFA and DHA concentrations increased. In the homozygous -455CC subgroup: the opposite pattern was observed, with increasing erythrocyte n-3 PUFA and DHA concentrations associated with higher proportions of individuals with high apo C-III. A formal interactive effect between genotype and n-3 PUFAs was confirmed after adjustment for confounding variables using logistic models. Patients homozygous for the -455C APOC3 variant are poorly responsive to the apo C-III-lowering effects of n-3 PUFAs. This suggests that genetic variation	104

									in the APOC3 gene modulates the cardiovascular benefits typically associated with n-3 PUFA intake, indicating the need for personalized nutrition approaches based on genetic profile.	
Cross-sectional	Non-Hispanic whites with histologically confirmed NAFLD who completed a Food Frequency Questionnaire within 6 months of their liver biopsy.	PNPLA3 (rs738409)	Non-Alcoholic Fatty Liver Disease	USA	Non-Hispanic whites	452	Both	Not applicable	PNPLA3 rs738409 significantly modulated the relationship between several dietary factors (including PUFA) and fibrosis severity in a dose-dependent, genotype-specific manner. PUFAs had larger and significant effects on fibrosis severity among rs738409 G-allele carriers. Among G-allele carriers only, significant associations remained for n-3 PUFAs. NPLA3 rs738409 G-allele might modulate the effect of specific dietary nutrients on risk of fibrosis in patients with NAFLD. The gene-diet interaction study suggests that genetic variation influences how dietary factors affect liver disease progression, with G-allele carriers being more responsive to both protective and harmful dietary influences on fibrosis development.	105
Randomized controlled trial (3 months)	Participants were allocated to one of two diets: Diet P (enriched in polyunsaturated fatty acids) vs. Diet M (enriched in monounsaturated fatty acids).	ADIPOQ (rs822393)	Obesity	Spain	N/A or N/S	381	Both	Serum/plasma	After Diet P, non-T allele carriers showed significant improvements in: HDLc, serum adiponectin, and adiponectin/leptin ratio. These parameters remained unchanged in T-allele carriers for both diets. After two different hypocaloric diets, obese subjects with the T allele of rs822393 did not improve their adiponectin levels, adiponectin/leptin ratio, and HDLc, despite achieving weight loss. This suggests that genetic variation influences the metabolic response to dietary interventions beyond simple weight reduction effects	106
Cross-sectional	Dietary intake was assessed by validated three-day food consumption records.	APOE (ε2, ε3, ε4)	Type 2 Diabetes Mellitus	Mexico	N/A or N/S	224	Both	Serum/plasma	Carriers of the APOE ε4 allele with a high ω-6:ω-3 PUFA ratio in the diet had higher %HbA1c blood concentrations. The findings indicate that genetic variation modulates how dietary fat composition affects metabolic outcomes in T2D patients.	107
One arm intervention study (12 weeks)	Hypocaloric diet with a Mediterranean pattern enriched in ω-6 PUFA.	APOA5 (-1131C, rs662799)	Obesity	Spain	N/A or N/S	362	Both	Serum/plasma	Both genotype groups showed improvements in adiposity parameters, systolic blood pressure, total cholesterol, LDLc, leptin, adiponectin, and leptin/adiponectin ratio. Non-C allele carriers showed significantly greater improvements in insulin levels, HOMA-IR, and triglyceride levels. C allele carriers showed minimal or no improvement in these metabolic parameters. The minor C allele of the APOA5 gene (rs662799) produces a worse response in triglyceride levels, insulin levels, and HOMA-IR after a ω-6 PUFA enriched hypocaloric diet with Mediterranean pattern. This suggests that genetic variation influences the metabolic benefits obtained from this specific dietary intervention, indicating the need for personalized nutrition approaches based on genetic profile	108
Randomized controlled trial (18 months)	DHA supplementation (2 g per day) or placebo.	APOE ε4/ε4	Alzheimer's Disease	USA	N/A or N/S	275	Both	Serum/plasma	After intervention, DHA-treated APOE ε3/ε3 and APOE ε2/ε3 carriers demonstrated significantly greater increase in plasma DHA/AA compared to ε4/ε4 carriers. APOE ε2/ε3 carriers had greater increase in plasma EPA/AA and less decline in left and right hippocampal volumes compared to ε4/ε4 carriers. Greater baseline and increase in plasma EPA/AA was associated with lower decrease in right hippocampal volume, but only in APOE ε4 non-carriers. APOE ε4/ε4 carriers showed reduced response to DHA supplementation in terms of both plasma fatty acid ratios and brain outcomes. The lower increase in plasma DHA/AA and EPA/AA in APOE ε4/ε4 carriers after DHA supplementation reduces brain delivery and affects the efficacy of DHA supplementation. This suggests that genetic variation in APOE influences the metabolism and brain uptake of ω-3 fatty acids, potentially explaining differential responses to DHA supplementation for cognitive health and neurodegeneration prevention.	109
Observational	Blood levels of omega-3 (n-3) and omega-6 (n-6) PUFAs were measured using gas chromatography.	FADS1 (rs174546, rs174547, rs174550)	MAFLD/MetS/T2DM/Dyslipidemia risk	Germany	N/A or N/S	85	Both	Serum/plasma	Homozygous ancestral genotype was associated with significantly lower blood levels of n-6 PUFA arachidonic acid (AA). No significant differences in n-3 PUFAs (EPA and DHA). No significant differences in liver fat content or AA-derived lipid mediators (e.g., TXB2), though a trend toward lower levels in the homozygous ancestral group was observed. FADS1 genotypes influence blood levels of n-6 PUFAs but not n-3 PUFAs. Variations in fatty acid levels associated with genotype do not appear to significantly affect liver fat content or	110

									inflammatory lipid mediators in this cohort, although trends observed warrant further investigation into potential cardiometabolic implications	
One arm intervention study (6 weeks)	Participants received 3 g/day of omega-3 fatty acids (1.9–2.2 g EPA and 1.1 g DHA).	FFAR4 (12 SNPs)	Healthy	Canada	N/A or N/S	210	Both	Serum/plasma and PBMCs	Major allele homozygotes of FFAR4 rs11187537, rs17108973, rs7081686, and rs17484310 had more favorable insulin-related responses to ω-3 supplementation compared to minor allele carriers. FFAR4 genetic variants modulate individual responses to omega-3 fatty acid supplementation with respect to insulin sensitivity. Major allele homozygotes show greater improvements in glycemic control-related traits, highlighting the potential for personalized nutrition strategies based on FFAR4 genotype.	111
One arm intervention study (6 weeks)	To refine a previously developed genetic risk score (GRS) for plasma triglyceride (TG) response to omega-3 fatty acid supplementation and to test its association with TG response in young Mexican adults who had to take three capsules a day, providing 2.7 g/day of DHA/EPA.	103 SNPs (quantitative PCR)	Healthy	Mexico	N/A or N/S	191	Both	Serum/plasma and RBC	Five lead SNPs were selected for the GRS model. The refined GRS explained 11.01% of the variance in TG response to ω-3 supplementation in the Mexican cohort. Allele frequency differences were observed between Canadian and Mexican populations, suggesting population-specific genetic effects. The refined GRS demonstrates a significant association with triglyceride response to omega-3 supplementation in young Mexican adults, explaining 11.01% of the response variance. These results underscore the role of genetic factors in modulating individual lipid responses to dietary interventions and support the relevance of population-specific genetic risk models.	112
One arm intervention study (7 or 16 weeks)	This interventional study had a pre- and post-supplementation design to assess the changes in O3I status from baseline (pre-supplementation) to 7-week or 16-week supplements (post-supplementation). Thus, each participant served as their own control. Participants received a personalized dose of ω-3 supplements based on their baseline O3I. Secondary aim: To identify if changes in O3I levels would be associated with either of the two FADS1/2 variants.	FADS1/2 (2 variants)	Healthy	USA	N/A or N/S	90	Both	Serum/plasma	Although O3I changes were not associated with FADS variants, the issues of compliance may have confounded our results. O3I was significantly increased following omega-3 supplementation. However, it was not possible to conclude whether the two FADS1/2 variants led to differential increases in OI3.	113
Cross-sectional	Subjects were asked to record their daily dietary intake for 3 days, including a weekend day.	MLXIPL (rs17145750, rs3812316)	Healthy	Mexico	Mestizos	587	Both	Serum/plasma	Association of rs3812316 on triglycerides was only observed in patients with inadequate alpha-linolenic acid intake (1.97 ± 0.03 vs. 2.11 ± 0.01 log mg/dL, $p < 0.001$)	114
Cross-sectional	Dietary data were collected using a 116-item semi-quantitative food frequency questionnaire (FFQ).	SIDT2 (rs17120425, rs1784042), ABCA1 (rs9282541)	Healthy	Mexico	Mestizos	1982	Both	Serum/plasma	Premenopausal women who carried at least one rs17120425-A allele and consumed high dietary fat, protein, monounsaturated, or polyunsaturated fatty acids levels had higher HDL-c levels than the non-carriers. association between the genetic variants on SIDT2 and ABCA1 with HDL-c levels and suggest gene-gene and gene-diet interactions over HDL-c concentrations in Mexican adults	115
Cross-sectional	Genome-wide association studies (GWAS) to screen for COPD-associated variants.	FAM13A (rs1585258), CAV1 (rs1997571), CPD (rs719601), PEPD (rs10405598), ITGA1 (rs889294)	Chronic Obstructive Pulmonary Disease	Korea	Chinese	8840	Both	Serum/plasma	PRS interacted with omega-3 fatty acid intake and exercise. Increased COPD incidence in individuals with higher PRS, particularly those with Low omega-3 fatty acid consumption. In conclusion, adults with a high-PRS are susceptible to COPD risk, and w-3 fatty acid intake and exercise may impact the risk of developing COPD, potentially applying to formulate precision medicines to prevent COPD.	116
Randomized, double-blind, placebo-	Randomized to receive either 2000 mg omega-3 fatty acids daily, or placebo	PPARG	Elevated LDL cholesterol	Russia	N/A or N/S	99	Both	Serum/plasma	In the omega-3 group with PPARG polymorphisms, LDLc was reduced by 15.4% compared with a 2.6% decrease in the placebo group. In the omega-3 group without PPARG polymorphisms,	117

controlled trial (90 days)	daily.								reduction in LDLc was not significantly different from placebo. The reduction in LDLc was 11.7% greater in those with PPARG polymorphisms than in those without. Triglycerides decreased by 21.3% in ω-3 recipients with PPARG polymorphisms, with no significant changes in HDLc, total cholesterol, or hsCRP levels in any groups. ω-3 fatty acids significantly reduce LDLc and triglycerides in carriers of PPARG polymorphisms, underlining the potential for genetic-driven personalization of cardiovascular interventions.	
Case-cohort	Using data of participants with incident MI from the Danish Diet, Cancer and Health study.	ALOX5	Myocardial Infarction	Danish	Danish	3089 (cases) and 3000 (controls)	Both	Serum/plasma and adipose tissue	Adipose tissue EPA and AA and the ALOX-5 tandem repeat polymorphism did not significantly interact to affect the risk of MI	118
Randomized controlled trial, parallel design, double-blind (12 months)	Doses of 0.45, 0.9, and 1.8 g/d 20:5n3 and 22:6n3 (1.51:1), or placebo for 12 mo.	ADIPOQ (rs17300539, rs266729, rs182052, rs2241766, rs1501299)	Healthy	UK	N/A or N/S	367	Both	Serum/plasma	The study revealed that the -11391 A-allele is associated with higher serum adiponectin levels at baseline. For participants over 58 years old, researchers found a significant interaction between treatment and age in determining adiponectin levels. Additionally, they observed a nominally significant interaction between the +45 T/G polymorphism, treatment, and age in determining serum adiponectin levels, after adjusting for BMI, gender, and ethnicity. Notably, individuals over 58 who were homozygous for the +45 T-allele experienced a 22% increase in adiponectin concentration following treatment with the highest dose. The researchers suggest that if these findings are confirmed in a larger sample, a diet high in ω-3 PUFA might be beneficial for older individuals, particularly those with the +45 TT genotype. This group has been reported to have an increased risk of hypoadiponectinemia, type 2 diabetes, and obesity, making the potential dietary recommendation especially relevant for them.	119
Placebo controlled trial, double-masked (6 weeks)	5 g/d fish oil (FO) (2 g EPA, 1 g DHA) or 5 g/d corn/soy oil (Placebo).	ALOX5 (promoter variants)	Healthy	USA	African American	98	Both	Serum/plasma and RBC	Researchers observed significant genotype-dependent variations in response. The investigation revealed that individuals with the low cardiovascular disease (CVD) risk genotypes "d5" and "55" exhibited marked increases in erythrocyte levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and total omega-3 polyunsaturated fatty acids (PUFAs) when supplemented with FO, compared to placebo (PL). Concurrently, these genotypes demonstrated a reduction in the ratio of omega-6 to omega-3 PUFAs. In contrast, the high-risk "dd" genotype did not manifest these changes. Furthermore, the study noted a decrease in high-density lipoprotein (HDL) particle concentration in the "d5" and "55" genotypes following FO supplementation, an effect not observed in the "dd" genotype. Plasma triglyceride (TG) concentrations showed a significant reduction in the "d5" genotype with FO supplementation, but this effect was not replicated in the "dd" and "55" genotypes. Notably, the research found no significant alterations in low-density lipoprotein (LDL) particle or cholesterol concentrations, heart rate, or blood pressure across any genotypes. These findings suggest that the efficacy of fish oil supplements may be influenced by an individual's ALOX5 genotype, highlighting the potential importance of genetic factors in determining the response to omega-3 fatty acid supplementation.	120
Observational	To examine the interaction of MTHFR variants with dietary fatty acids influencing plasma Hcy.	MTHFR	Hypertension / CVD	USA	Puerto Rico ancestry	995	Both	Serum/plasma	This study on Boston Puerto Rican adults investigated the relationship between dietary polyunsaturated fatty acids (PUFAs), genetic variants of the MTHFR gene, and plasma homocysteine (Hcy) levels. The researchers found a negative correlation between plasma Hcy and both ω-3 PUFA intake and the ratio of omega-3 to omega-6 PUFAs in the diet. Two MTHFR gene variants (1298A>C and 677C>T) were associated with increased risk of hypertension, and the 1298A>C variant was also linked to cardiovascular disease risk. Importantly, the effect of the 1298A>C variant on plasma Hcy levels was modulated by PUFA intake. Carriers of the 1298C risk allele showed higher plasma Hcy only when consuming a high-PUFA diet. Additionally, individuals with specific combined	121

									genotypes of both variants showed lower plasma Hcy when consuming high levels of ω-3 PUFAs compared to those with the same genotypes but low ω-3 PUFA intake. These findings suggest that dietary PUFA intake can modulate the effects of MTHFR genetic variants on plasma Hcy levels in this population.	
Cohort	Data were collected from 1083 European Americans participating in the Genetics of Lipid Lowering Drugs and Diet Network Study.	TCF7L2 (rs7903146, rs12255372)	Diabetes/ Metabolic Syndrome	USA	European Americans	1083	Both	PBMCs	High (n-6) PUFA intakes (≥6.62% of energy intake) were associated with atherogenic dyslipidemia in carriers of the minor T allele at the TCF7L2rs7903146 SNP and may predispose them to MetS, diabetes, and cardiovascular disease	122
Randomized, double-blind, placebo-controlled (6 weeks)	Either 1.7 g DHA and 0.6 g EPA or placebo daily.	DNA methylation (4 CpG sites, LINE-1)	Alzheimer's Disease	Sweden	N/A or N/S	63	Both	PBMCs	Supplementation with n-3 FA for 6 mo was associated with global DNA hypomethylation in PBLs	123
Case-control	Cross-sectional data from 1932 case subjects with a first nonfatal MI and 2055 population-based control subjects who were living in Costa Rica to examine potential gene-environment interactions.	PCSK9 (rs11206510)	Myocardial Infarction (with controls)	Costa Rica	Costa Rican Hispanics	1932	Both	PBMCs	LC n–3 PUFA intake is associated with a lower risk of nonfatal MI in C-allele carriers of PCSK9 rs11206510 (n = 799) but not in non–C-allele carriers (n = 3188).	124
Prospective intervention (8 weeks)	Part of the SATgenε trial. 41 APOE4 carriers and 41 APOE4 noncarriers. Intervention protocol: Phase 1: High-saturated fat diet (HSF diet) for 8 weeks, Phase 2: HSF diet + DHA/EPA supplementation for 8 weeks (3.45 g DHA/day and 0.5 g EPA/day). Plasma total lipids separated into free FAs, neutral lipids (NLs), and phospholipids using solid-phase extraction, FA profiles quantified by gas chromatography.	APOE	Overweight	UK	N/A or N/S	82	Both	Serum/plasma	Plasma FA response to HSF + DHA diet was correlated with BMI in APOE4 carriers but not in noncarriers. APOE4 carriers were lower plasma responders to DHA supplement than noncarriers, but only in the high-BMI group (≥25.5 kg/m²). Apolipoprotein E genotype and BMI are important variables that determine the plasma long-chain PUFA response to dietary fat manipulation. APOE4 carriers with BMI ≥25.5 kg/m² may need higher intakes of DHA for cardiovascular or other health benefits than noncarriers. This suggests that both genetic background and body weight status should be considered when making DHA supplementation recommendations.	125
Randomized trial (4 months)	Two groups: omega-3 (1.5 g of n-3/day) and placebo (1.5 g of sunflower oil/day).	FADS1 (rs174547)	Obesity	Mexico	N/A or N/S	74	Both	PBMCs	Subjects carrying the CC genotype showed significant differences (minor increase) in n-6, n-3, total PUFA, EPA, DHA, and the O3I in RBCs compared to TT genotype carriers in the n-3 group	126
Cross-sectional	To investigate whether methylation quantitative loci (mQTL) change the relationship between dietary nutrient intake and leukocyte DNA methylation (DNAm) levels, using the example of estimated fatty acid intake and the ATP-binding cassette transporter A1 (ABCA1) gene.. Dietary fatty acid intake estimated using validated food frequency questionnaire.	ABCA1 (rs1800976)	Healthy	Japan	N/A or N/S	231	Both	PBMCs	Higher dietary n-3 PUFA intake was associated with lower ABCA1 DNAm levels. The interaction between mQTL and dietary n-3 PUFA intake on DNAm levels was not significant. This result suggested that dietary n-3 PUFA intake would be an independent predictor of DNAm levels in ABCA1 gene after adjusting for individual genetic background. Considering mQTL need to broaden into other genes and nutrients for deeper understanding of DNA methylation, which can contribute to personalized nutritional intervention.	127
Cross-sectional observational	Serum fatty acid analysis by gas chromatography-flame ionization detection (GC-FID). Measured 37 fatty acids including ARA, DGLA, EPA, DHA.	FADS1/2/3 (rs174537, rs174538, rs174546, rs174547, rs174548,	81% overweight/obese; 45% hyperglycemia; metabolic syndrome	Arizona, USA	Latino/Mexican American	493	Both (35% male)	Serum/plasma	FADS ancestral haplotype alleles associated with: decreased ARA (8-20% per allele), increased DGLA (10-14% per allele), decreased EPA (11-25% per allele), decreased DHA (6-9% per allele), increased triglycerides (7-14% per allele), increased VLDL (7-13% per allele), increased fasting insulin and HOMA-IR (rs174455: 43-45% increase). ELOVL2/5 variants associated with increased	128

		rs174554, rs1535, rs174576, rs174594, rs174602, rs174455); ELOVL2 (rs3734398, rs2281591, rs3798713, rs953413, rs1570069, rs3798719); ELOVL5 (rs7744440, rs9357760, rs2397142)	features						glucose, insulin, and HOMA-IR. rs174537 TT genotype shows 33% lower ARA, 38% lower EPA (mean 3.03 ng/mL, suggesting n-3 deficiency), and ARA/EPA ratio ~30:1.	
Cross-sectional, observational GWIS	Fish oil supplements (FOS) assessed via touchscreen FFQ. NMR-measured 14 plasma PUFA traits: total PUFAs, total MUFAs, omega-3, omega-6, LA, DHA, and their percentages (PUFAs%, MUFAs%, omega-3%, omega-6%, LA%, DHA%), plus ratios (PUFAs:MUFAs, omega-6:omega-3). All phenotypes rank-based inverse normal transformed.	Genome-wide interaction study (GWIS). Lead SNPs: FADS1-FADS2 locus (rs35473591, rs174535); GPR12 locus (rs1752653). Gene-level: FADS1, FADS2, FADS3, TMEM258, MYRF, FEN1, RAB3IL1, GPR12, BEST1, FTH1.	Generally healthy UK Biobank participants	United Kingdom (UK Biobank)	European ancestry	200,060 (FOS users: 63,711; non-users: 136,349)	Both (53.5% female)	Plasma	FADS1-FADS2×FOS interactions for omega-3% ($p=2.50\times10^{-23}$), omega-6:omega-3 ratio ($p=1.09\times10^{-20}$), total omega-3 ($p=2.74\times10^{-17}$), DHA ($p=1.56\times10^{-12}$), DHA% ($p=4.11\times10^{-8}$). Lead SNP rs35473591: genetic effect reduced from β=0.42 (no FOS) to β=0.35 (with FOS) on omega-3%; FOS effect varied by genotype (β=0.45, 0.50, 0.59 in C/C, C/CT, CT/CT). GPR12×FOS interactions for PUFAs% and PUFAs:MUFAs ratio (gene-level significant, $p<2.66\times10^{-6}$). Gene×FOS interactions explain 0.53-1.51% phenotypic variance (significant in 10/14 traits).	129
Case-cohort (EPIC-InterAct) + RCT (PREDIMED, 1 year intervention)	EPIC-InterAct: Dietary LA/ALA intake (FFQ), plasma phospholipid FA (GC-FID), nut consumption. PREDIMED: MedDiet+Nuts intervention (30g/d: 15g walnuts, 7.5g almonds, 7.5g hazelnuts) vs control diet. Plasma phospholipid FA (GC-FID) at baseline and 1 year.	FADS1 rs174547 (T>C)	EPIC-InterAct: Type 2 diabetes cases and subcohort; PREDIMED: High CVD risk (T2D or multiple CVD risk factors)	Europe (8 countries) + Spain	European	EPIC-InterAct: 17,128 (7,498 T2D cases, 10,087 subcohort); PREDIMED: 928 (492 MedDiet+Nuts, 436 control)	Both	Plasma	Nut consumption × FADS1 rs174547: (1) C-allele carriers showed greater 1-year increases in plasma LA (+0.24 vs -0.01 SD, p=0.003) and ALA (+0.29 vs +0.08 SD, p=0.015) with nut intervention; (2) Stronger inverse association with AA in C-allele carriers (p-interaction=0.030 EPIC, 0.003 PREDIMED); (3) Greater decline in D6D activity in C-allele carriers (p-interaction=0.007). T2D risk: Suggestive stronger protection in CC genotype (HR=0.73, 0.54-1.00) vs CT (0.94, 0.81-1.10) or TT (0.90, 0.78-1.05), but interaction NS (p=0.638 additive model). No significant interactions for dietary LA/ALA intake or plasma LA/ALA biomarkers with T2D risk (all p>0.14).	130
Case-control	Serum omega-3 PUFAs (ALA, SDA, ETA, EPA, DHA) and omega-6 PUFAs (LA, GLA, DGLA, AA) measured via gas chromatography and ELISA. D5D and D6D enzyme levels assessed via ELISA.	FADS1 (rs174547, T>C)	Type 2 diabetes mellitus (newly diagnosed)	Iraq	Iraqi (Middle Eastern)	120 (60 T2DM, 60 controls)	Both (39M/21F in T2DM; 33M/27F in controls)	Serum/plasma	FADS1 rs174547 C allele significantly associated with increased T2DM risk (OR=3.051, 95%CI 1.259-7.395, p=0.014). All omega-3 and omega-6 PUFAs significantly lower in T2DM patients (p<0.001). TC genotype showed significantly higher ALA levels vs TT in T2DM patients (2.67±0.24 vs 2.46±0.21%, p=0.016). No significant genotype effects on D5D/D6D enzyme levels or activity ratios within T2DM group. Association remained significant after adjusting for sociodemographic factors, lipid profile, and inflammatory markers.	131
Prospective cohort (16 years, 2006-2022)	Blood PUFA biomarkers measured by NMR spectroscopy: DHA (0.23 mmol/L), N3FA (0.51	APOE genotypes (rs429358, rs7412): High	Hypertensive adults (SBP≥140 and/or	UK (UK Biobank)	Predominantly White (94.1%), Other races	123,235 (full cohort); 25,902	Both (47.9% female, 52.1%	40-69 years (mean 63.5 years)	Dementia incidence (ICD-10: F01.1, F01.9, F03, G30.0, G30.1, G30.9), dementia mortality, all-cause mortality	132

mmol/L), N6FA (4.48 mmol/L), LA (3.40 mmol/L), total PUFA (5.02 mmol/L), N6FA/N3FA ratio (8.72). Observational study examining associations with dementia outcomes.	risk (ε4/ε4, ε3/ε4) vs Low-to-moderate risk (ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4). Polygenic risk scores (PRS) for Alzheimer's disease and PUFAs (total, N3FA, N6FA, DHA) in subgroup (n=25,902).	DBP≥90 mmHg, or antihypertensive medication use, or self-reported/diagnosed hypertension)	(5.9%)	(PRS subgroup)	male)

Legend: AA, arachidonic acid; AD, Alzheimer's disease; ADCS, Alzheimer's disease cooperative study; ALA, alpha-linolenic acid; AMD, age-related macular degeneration; ANCOVA, analysis of covariance; APOE, apolipoprotein e; ARDS, acute respiratory distress syndrome; ARIC, atherosclerosis risk in communities; AUC, area under the curve; BMI, body mass index; BPRHS, Boston puerto rican health study; CAD, coronary artery disease; CNV, choroidal new vessels; COPD, chronic obstructive pulmonary disease; CRP/hsCRP, c-reactive protein/high-sensitivity c-reactive protein; CSF, cerebrospinal fluid; CSI, cholesterol-saturated fat index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DGLA, dihomo-gamma-linolenic acid; DHA, docosahexaenoic acid; DHQ, diet history questionnaire; E-%, energy percent; EPA, eicosapentaenoic acid; EPIC, European prospective investigation into cancer and nutrition; FA, fatty acid; FADS, fatty acid desaturase; FBS, fasting blood sugar; FFA, free fatty acids; FFQ, food frequency questionnaire; GC-MS, gas chromatography-mass spectrometry; GLA, gamma-linolenic acid; GRS, genetic risk score; GWAS, genome-wide association study; GWIS, genome-wide interaction study; HDLc, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; HSF, high-saturated fat; HUFA, highly unsaturated fatty acids; IBD, inflammatory bowel disease; LA, linoleic acid; LCPUFA/LC-PUFA, long-chain polyunsaturated fatty acids; LDLc, low-density lipoprotein cholesterol; LFHCC, low-fat, high-complex carbohydrate; MCI, mild cognitive impairment; MESA, multi-ethnic study of atherosclerosis; MetS, metabolic syndrome; METSIM, metabolic syndrome in men study; MI, myocardial infarction; mQTL, methylation quantitative trait loci; MUFA, monounsaturated fatty acids; N/A, not applicable; N/S, not specified; NAFLD, non-alcoholic fatty liver disease; NEFA, non-esterified fatty acids; NHS, nurses' health study; O3I, omega-3 index; OR, odds ratio; OSCC, oral squamous cell carcinoma; PBMCs, peripheral blood mononuclear cells; PPOL, potentially malignant oral lesions; PRS, polygenic risk score; PUFA, polyunsaturated fatty acids; RA, rheumatoid arthritis; RBC, red blood cells; RMR, resting metabolic rate; SCA, sudden cardiac arrest; SERA, studies of the etiology of rheumatoid arthritis; SFA, saturated fatty acids; SNP, single nucleotide polymorphism; SQFFQ, semi-quantitative food frequency questionnaire; T2DM, type 2 diabetes mellitus; TE, total energy; TG, triglycerides; UC, ulcerative colitis; UDS, uniform data set; WC, waist circumference.

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