Lipids in Health and Disease

RESEARCH

Open Access

The influence of FADS1 and ELOVL2 genetic polymorphisms on polyunsaturated fatty acid composition in response to fish oil supplementation

Alessandro Medoro[1], Francesca Graziano[2,3], Gaetano Cardinale[4], Serena Voccola[5], Tiziana Zotti[6], Mariano Intrieri[1], Giovanni Scapagnini[1*] and Sergio Davinelli[1]

Abstract

Background Unhealthy dietary habits have been recognized as key contributors to the increasing incidence of non-communicable diseases. Among the healthy nutrients studied, omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have received considerable attention for their benefits in cardiovascular health and inflammation management. Their synthesis is regulated by enzymes encoded by *FADS1* and *ELOVL2* genes. Single nucleotide polymorphisms (SNPs) within these genes can modify the efficiency of fatty acid conversion, thereby influencing the Omega-3 Index, which reflects omega-3 status, particularly EPA and DHA. This study aimed to assess the impact of *FADS1* (rs174537) and *ELOVL2* (rs953413) polymorphisms on the effects on fatty acids profiles of fish oil supplementation in healthy individuals.

Methods Eighty-six healthy adults aged 20–70 participated in a quasi-experimental intervention involving a 4-week fish oil supplementation rich in EPA and DHA. Dried-blood spots (DBS) were collected before and after the intervention to evaluate lipid profiles. Genotyping for *FADS1* and *ELOVL2* SNPs was performed using high-resolution melting analysis.

Results Post-supplementation, the percentage of EPA and DHA increased significantly ($p < 0.001$), leading to an improved Omega-3 Index. Baseline omega-3 percentages did not differ significantly between *FADS1* and *ELOVL2* genotypes. However, individuals with the *ELOVL2* minor allele (GA + AA) genotype benefited more from the fish oil supplementation with increased EPA and DBS Omega-3 Index, indicating a more favorable metabolic response.

Conclusions Genetic variability may influence the metabolic response to fish oil supplementation. These findings underscore the importance of personalized nutrition strategies to optimize health outcomes and prevent non-communicable diseases.

Keywords Polyunsaturated fatty acids, Omega-3, Omega-6, Omega-3 index, FADS1, ELOVL2, Single nucleotide polymorphisms

*Correspondence:
Giovanni Scapagnini
giovanni.scapagnini@unimol.it

Full list of author information is available at the end of the article

Introduction

Unhealthy dietary habits have been widely recognized as key contributors to the increasing incidence of non-communicable diseases, such as obesity, diabetes, cardiovascular diseases, and cancers. Current public health strategies and individualized care approaches are focused on preventing and managing disease risks, particularly emphasizing the role of lifestyle factors—especially diet and nutrient intake—in the onset and progression of these diseases [1, 2]. These strategies often operate under the assumption that a single, standardized dietary recommendation can be universally applied across all individuals within a population. However, despite extensive research linking diet to disease, many dietary interventions produce only modest and limited improvements in health outcomes. This limitation highlighted the inadequacy of "one-size-fits-all" strategies and the necessity of understanding how individual genetic profiles can influence metabolism and overall health outcomes [3–6].

Among the nutrients being studied, polyunsaturated fatty acids (PUFA), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have received considerable attention for their benefits in cardiovascular health, cognitive function, and inflammation management [7–9]. The anti-inflammatory properties of EPA and DHA arise in part from their role as precursors to specialized pro-resolving mediators, including resolvins, protectins, and maresins. These bioactive compounds play a crucial role in resolving inflammation, promoting tissue healing, and restoring homeostasis following inflammatory responses. The combined percentage levels of EPA and DHA are represented by the Omega-3 Index, a biomarker that emerged as an indicator of omega-3 status and potential disease risk. Therefore, this biomarker assesses the omega-3 status of an individual by measuring the incorporation of EPA and DHA into red blood cell membranes, a process influenced by factors such as diet, genetics, age, sex, and weight. An increase in the Omega-3 Index can be achieved through dietary modifications (e.g., increased consumption of oily fish) or supplementation with products containing EPA and DHA [10]. An Omega-3 Index below 4% is associated with an increased risk of cardiovascular disease, sudden cardiac death, inflammation, cognitive dysfunction, depression, sleep apnea, and diabetes, reflecting a significant deficiency in omega-3 fatty acids. Conversely, maintaining an Omega-3 Index above 8%, ideally within the range of 8–12%, is considered optimal, as it correlates with reduced inflammation and lower risks for these conditions, thereby supporting overall health and well-being [11, 12].

The complex metabolic pathways responsible for synthesizing and elongating these essential fatty acids are shared between omega-3 and omega-6 PUFA involving a series of desaturation and elongation steps catalyzed by specific enzymes, such as desaturase FADS1 and elongase ELOVL2. The enzyme encoded by the *FADS1* gene is known as Δ5 desaturase. It specifically catalyzes the insertion of a double bond at the Δ-5 position in fatty acids, playing a crucial role in the biosynthesis of important polyunsaturated fatty acids such as AA and EPA. Likewise, the enzyme encoded by the *ELOVL2* gene is known as ELOVL fatty acid elongase 2 and catalyzes the elongation PUFA, particularly converting EPA to docosapentaenoic acid (DPA), which can then be further processed into DHA [13, 14].

Single nucleotide polymorphisms (SNPs) in the genes encoding these enzymes may influence the efficiency of converting precursor fatty acids into their longer-chain, more biologically active forms and impact the Omega-3 Index, potentially affecting also the inflammatory status and disease risk [15]. Among these SNPs, rs174537 in *FADS1* has been extensively studied and is located within a gene region identified as a strong genetic proxy for DNA methylation. Specifically, it is located within a putative promoter region of the FADS gene cluster, and the methylation status of this locus can directly influence gene expression [16]. The relationship between rs174537 and concentrations of EPA and DHA is often contradictory. While many studies indicate that individuals carrying the minor T allele at rs174537 have lower plasma and serum EPA concentrations than those with the major G allele [17–21], other studies have failed to observe this association [22–27]. Three independent studies linked blood DHA concentrations to rs174537. In a healthy cohort studied by Hilal et al., minor allele carriers exhibited lower DHA concentrations in plasma [19]. Conversely, two additional studies involving East Asian participants with coronary artery disease or type 2 diabetes (T2D) showed that carriers of the minor allele exhibited higher DHA concentrations compared to those with the major allele [21, 28]. These inconsistent findings may be explained by population differences in allele frequencies. Indeed, allele frequencies of the *FADS1* gene can vary significantly between different ethnicities, particularly in relation to genetic variants that influence the biosynthesis of PUFA. The genetic variations within *FADS1* reflect adaptations influenced by dietary patterns and evolutionary pressures across different human populations [29–31]. For example, for rs174537 (G/T), the allele frequencies in Europeans are G = 65% and T = 35%, whereas in East Asians, they are G = 43% and T = 57% (https://www.ncbi.nlm.nih.gov/snp/rs174537, accessed on 11 January 2025). On the other hand, rs953413 is another extensively studied SNP located in *ELOVL2*. Variations in *ELOVL2* can lead to differences in enzyme activity, affecting the composition of long-chain PUFA. Individuals with the minor allele (A) exhibited significantly lower

DHA and higher EPA concentrations in different cohorts [18, 32].

This genetic variability presents a significant challenge for standardized dietary recommendations for EPA and DHA intake, as individuals with different genetic backgrounds may respond differently to the same supplementation dose. However, the complex relationship between *FADS1* and *ELOVL2* polymorphisms and the response to fish oil supplementation remains poorly understood [19, 32, 33]. To address this gap, this study aimed to analyze the relationship between a 4-week supplementation with fish oil rich in EPA and DHA, measured as the Omega-3 Index in dried blood spots (DBS), and genetic polymorphisms in the desaturase enzyme FADS1 (rs174537) and the elongase enzyme ELOVL2 (rs953413).

Materials and methods

Study design and participants

This study is a quasi-experimental intervention, with pre- and post-evaluations, of fish oil rich in EPA and DHA supplementation in healthy Italian individuals. Eighty-six caucasian volunteers were recruited from Centro Delta srl, in Apollosa, Benevento (Italy) between January 2021 and February 2021 based on the following inclusion criteria: (I) healthy male and female subjects; (II) age range of 18–70 years; (III) subjects who have not participated in similar studies in the last 3 months; (IV) absence of diagnosis of eating disorders; (V) subjects who have not regularly taken dietary omega-3 EPA + DHA supplements for at least 3 months. Exclusion criteria were as follows: (I) subjects receiving pharmacological therapy, either oral or topical, such as nonsteroidal anti-inflammatory drugs, lipoxygenase inhibitors, statins, and anticoagulants, that directly or indirectly interfere with the biochemical pathways of omega-3 supplementation; (II) diagnosis of acute or chronic conditions, such as cardiovascular disease (CVD), metabolic syndrome, neurocognitive disorders, liver disease, cancer, or fish allergy, that may significantly alter the parameters under analysis; (III) surgical interventions in the last thirty days; (IV) chemotherapy, immunotherapy, or radiotherapy in the previous six months. Moreover, participants were instructed to avoid consuming omega-3-rich foods throughout the intervention period. Compliance was checked by asking participants to return all unused packages of the product. All included participants were assessed for body mass index (BMI) and, after venous blood sampling, for blood glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the institutional review board of the University of Molise (Prot. n. 22/2019–23 September 2019). The protocol complied with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials and was registered on the Open Science Framework https://osf.io/mgwyj/?view_only=147cf3bdf02e426bb9765c3df603222e (accessed on 3 January 2025). Written informed consent was obtained from all participants before the study began.

Dietary supplementation

Participants received three times a day for one month 5 ml of a nutraceutical formulation with fish oil containing 740 mg of EPA and 460 mg of DHA (in triglyceride form), 14 mg of vitamin E (d-alpha-tocopherol emulsion), and excipients including lime oil, rosemary oil, soy lecithin, and ascorbyl palmitate (Pufagenics Liquido, Metagenics Italia, Milan, Italy). Participants were instructed to consume the fish oil supplement along with meals.

Analysis of fatty acids composition in dried blood spots

The analysis of fatty acids composition in DBS was performed as previously described [34, 35]. Briefly, DBS were collected by fingerstick. Following disinfection of the volunteer finger and application of the lancet, the first drop of blood was discarded. Subsequent blood drops were deposited onto the spot card (BioSample TFN cards, Ahlstrom, Bärenstein, Germany), which was then air-dried for 12 h at room temperature in the dark. To prevent lipid peroxidation, the spot cards were pre-treated with an antioxidant (butylated hydroxytoluene, BHT). The DBS cards were stored at 4 °C until further processing.

Sample preparation was performed as previously described [36]. Briefly, each DBS was placed in a 10-mL headspace vial with a sealing cap, and 2 mL of BF_3–MeOH reagent (12% w/v) was added. The vials were sealed and heated at 100 °C for 60 min in a convectional block heater to achieve direct transesterification of fatty acids to fatty acid methyl esters. After cooling to 25 °C, 2 mL of n-hexane was added, and the mixture was vortexed for 1 min, resulting in a transparent n-hexane layer containing the fatty acid methyl esters. The organic layer was transferred into a fresh 2-mL glass vial, air-dried in the dark, then redissolved in 400 µL of n-hexane, and subsequently injected into the gas chromatography with flame ionization detection (GC-FID) for analysis. As a control, five batches of a commercial standard mixture containing 22 fatty acid methyl esters (Nu-Chek-Prep, MN, USA) were prepared in n-hexane at various concentrations before GC-FID. The DBS Omega-3 Index, defined as the percentage of EPA and DHA relative to total fatty acids, was calculated using the formula: DBS Omega-3 Index = (EPA + DHA) / Total Fatty Acids × 100.

Genetic profiling

Participants were genotyped for polymorphisms in the desaturase gene *FADS1* (rs174537, alleles G-T) and

elongase gene *ELOVL2* (rs953413, alleles G-A). DNA extractions were performed using the DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany) with modifications based on the method described by Choi et al. [37]. Briefly, DBSs were cut with sterile scissors and placed into wells of 24-well plates. The samples were rehydrated in phosphate-buffered saline (PBS) for 3 h to facilitate cell release from the filter paper. The PBS containing the cells was then transferred to sterile 1.5 ml microcentrifuge tubes containing proteinase K and RNase A. One set of samples underwent an additional incubation at 95 °C for 15 min to enhance extraction efficiency, as recommended by Choi et al. [37]. Subsequent steps followed the manufacturer's protocol. After extraction, genomic DNA from each sample was purified using spin columns, washed with 70% ethanol to remove residual salts, and eluted in 100 µl of sterile milli-Q water. DNA concentration and purity were assessed using a NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA, USA) by measuring absorbance at 260 nm and calculating the 260/280 and 260/230 ratios to evaluate the quality of the extracted DNA. High-resolution melt analysis (HRM analysis) was assessed by a real-time PCR detection system (CFX96 Touch Real-Time PCR Detection System, BioRad, Hercules, CA, USA) to quantify the melt curves of product DNA fragments following PCR amplification according to the manufacturer protocol (SsoFastTM EvaGreen, Bio-Rad, Hercules, CA, USA). The following primers (Eurofins Scientific, Luxembourg) were used:

- *FADS1* (rs174537): forward 5'-TCGCCCTGCAGAAGAGAC-3', reverse 5'-GTGCGTCTGTGATGTGGTTT-3'.
- *ELOVL2* (rs953413): forward 5'-AAAACGCTAAAGGTCACAAAGC-3', reverse 5'-TTCTGCCCTTCTTCCACTGT-3'.

For the analysis, the genotypes were grouped as follows: GT+TT vs. GG for rs174537 and GA+AA vs. GG for rs953413, with GT/TT and GA/AA considered the minor alleles, respectively. One patient could not be genotyped for the FADS1 rs174537 polymorphism, and three patients could not be genotyped for the ELOVL2 rs953413 polymorphism. Consequently, they were excluded from the correlation analyses between SNPs and fatty acid percentages at baseline and post-supplementation.

Table 1 (**A**) BMI and metabolic parameters (glycemia, total cholesterol, LDL cholesterol, and HDL cholesterol) of all the participants. (**B**-**C**) distribution of age and sex within each genotype group of *FADS1* rs174537 *and ELOVL2* rs953413. Data are expressed as mean ± SD and frequency (and percentage, %)

A. Total participants		
n	86	
BMI	23.3 ± 1.3	
Glycemia (mg/dl)	83.9 ± 10.3	
Total cholesterol (mg/dl)	188.5 ± 36.0	
LDL cholesterol (mg/dl)	108.5 ± 27.8	
HDL cholesterol (mg/dl)	58.3 ± 11.1	
B.*FADS1*rs174537		
	GG	**GT + TT**
n	49	36
Age	37.2 ± 11.2	44.5 ± 14.2
Female (%)	18 (36.7)	15 (41.7)
Male (%)	31 (63.3)	21 (58.3)
C.*ELOVL2*rs953413		
	GG	**GA + AA**
n	24	59
Age	38.9 ± 13.6	40.4 ± 12.9
Female (%)	10 (41.7)	22 (37.3)
Male (%)	14 (58.3)	37 (62.7)

Statistical analysis

Baseline characteristics of the study population, including the distribution of the DBS Omega-3 Index, and the frequency of *FADS1* and *ELOVL2* genotypes, were described as means, medians, standard deviations, I-III quartile for continuous, and absolute and relative frequencies for categorical variables.

Post-intervention change from baseline was calculated for fatty acid composition and DBS Omega-3 Index. A t-test was used to evaluate the differences in the fatty acid profile changes between the two genes (*FADS1* and *ELOVL2* genotypes). The paired t-test was used to compare differences between baseline and endpoint values. Finally, linear regression models were performed to assess the association between the two genes (*FADS1* and *ELOVL2* genotypes) on the delta DBS Omega-3 Index. All models were adjusted also for gender and age, and significant differences were established at $p < 0.05$. Since some analyses involved multiple tests, the p-values were adjusted with a Benjamini and Hochberg (BH) correction. All analyses were performed using SPSS Statistics software version 26.0 (IBM Corp., 139 Armonk, NY, USA) and R (version 4.3.1).

Results

Participant baseline characteristics

From a total of 94 volunteers enrolled in the study, 86 participants, 53 males (61.6%) and 33 females (38.4%), met the inclusion and exclusion criteria, completed the survey, and were analyzed. The mean age was 40.39 ± 12.92 years. Table 1 summarizes the characteristics of the participants, such as body mass index (BMI), metabolic parameters, and the distribution of age and sex within each genotype group of *FADS1* rs174537 *and ELOVL2* rs953413. No patient reported experiencing adverse events related to the supplementation.

Effects of fish oil rich in EPA and DHA supplementation on fatty acid changes of dried blood spots.

All the fatty acids profiles before and after 1-month of supplementation with the omega-3-based nutraceutical formulation were reported in Table 2. Among the omega-3 fatty acids, α-linolenic acid slightly increased from 0.23 ± 0.11% to 0.25 ± 0.12% ($p < 0.001$). EPA, n-3 docosapentaenoic, and DHA substantially increased ($p < 0.001$).

For omega-6 fatty acids, linoleic acid, γ-linolenic acid, and eicosadienoic acid showed a non-significant increase. In contrast, the percentages levels of dihomo-γ-linolenic acid, AA, and docosatetraenoic acid significantly decreased ($p = 0.013$, $p < 0.001$, and $p < 0.001$, respectively), while the percentage of docosapentaenoic n-6 acid remained relatively unchanged.

At baseline, the DBS Omega-3 Index is very low in the studied population (3.14 ± 0.81%) with only 3 volunteers with a DBS Omega-3 Index > 5. Compared with baseline, a 1-month treatment with the omega-3-based nutraceutical formulation led to a statistically significant increase in EPA and DHA percentageand the DBS Omega-3 Index (1.56 ± 0.90%; $p < 0.001$).

Effects of FADS1 rs174537 and ELOVL2 rs953413 SNPs at baseline and after fish oil supplementation

The analysis of the *FADS1* rs174537 polymorphism compared two groups: 49 individuals with the major allele (GG) and 36 with the minor allele (GT + TT), as shown in Table 3. At baseline, no significant differences were observed between the groups in the percentage of α-linolenic acid, EPA, DHA, n-3 docosapentaenoic acid, or linoleic acid. A significant difference was found in dihomo-γ-linolenic acid percentage, which was higher in the GT + TT group ($p = 0.028$). The DBS Omega-3 Index was nearly identical between the groups. Post-supplementation, only eicosadienoic acid showed a statistically significant difference, with a higher percentage in GT + TT carriers compared to GG carriers ($p = 0.027$). No other fatty acids evaluated differ significantly between the two genotypic groups after supplementation. Similarly, from the analysis of pre- to post-supplementation differences for the *FADS1* rs174537 polymorphism, no significant differences emerged between the major and minor alleles.

For the ELOVL2 rs953413 polymorphism, participants were categorized into the GA + AA ($n = 59$) and GG ($n = 24$) groups. No significant differences were found in the percentage of α-linolenic acid, EPA, DHA, linoleic acid, γ-linolenic acid, or eicosadienoic acid. However, the percentages of n-3 docosapentaenoic acid and DHA were slightly higher in the GA + AA group, although the difference was not statistically significant. The DBS Omega-3 Index was slightly lower in the GG group, but this difference did not reach significance ($p = 0.079$). Carriers of the GA + AA genotype of *ELOVL2* rs953413 exhibited a significantly higher post-supplementation omega-3 fatty acid percentage compared to those with the GG genotype. In particular, EPA was 1.28 ± 0.57% in GA + AA vs. 0.67 ± 0.35% in GG ($p < 0.001$), docosapentaenoic-n3 acid was 0.85 ± 0.24% vs. 0.67 ± 0.21% ($p = 0.002$), DHA was 2.82 ± 0.66% vs. 2.33 ± 0.54% ($p = 0.002$), and the DBS Omega-3 Index was 5.06 ± 1.16% vs. 3.83 ± 0.81% ($p < 0.001$). No statistically significant differences were observed for the other fatty acids evaluated.

Based on the analysis of pre- to post-supplementation differences for the *ELOVL2* rs953413 polymorphism, minor-allele carriers showed more pronounced, statistically significant changes for EPA ($p < 0.001$), docosapentaenoic acid n-3 ($p = 0.008$), DHA ($p = 0.042$),

Table 2 Changes in PUFA percentage after supplementation with EPA- and DHA-rich fish oil. A paired t-test was used for the comparison. Data are expressed as mean ± sd. *p*-value was adjusted using BH correction

	Baseline	After supplementation	Mean difference (after supplementation-baseline)	*p*-value
Omega-3 (%)				
α-linolenic acid (18:3n3)	0.23 ± 0.11	0.25 ± 0.12	+ 0.025 ± 0.05	**< 0.001**
Eicosapentaenoic acid (EPA, 20:5n3)	0.39 ± 0.20	1.09 ± 0.59	+ 0.70 ± 0.52	**< 0.001**
n-3 Docosapentaenoic acid (22:5n3)	0.65 ± 0.21	0.80 ± 0.25	+ 0.15 ± 0.15	**< 0.001**
Docosahexaenoic acid (DHA, 22:6n3)	1.89 ± 0.57	2.68 ± 0.67	+ 0.79 ± 0.48	**< 0.001**
Omega-6 (%)				
Linoleic acid (18:2n6)	20.06 ± 2.98	20.44 ± 2.58	+ 0.37 ± 1.90	1
γ-linolenic acid (18:3n6)	0.18 ± 0.08	0.21 ± 0.09	+ 0.04 ± 0.08	0.065
Eicosadienoic acid (20:2n6)	0.28 ± 0.08	0.30 ± 0.11	+ 0.02 ± 0.10	1
Dihomo-γ-linolenic acid (20:3n6)	1.29 ± 0.33	1.13 ± 0.24	-0.16 ± 0.30	**0.013**
Arachidonic acid (AA, 20:4n6)	9.30 ± 1.36	8.45 ± 1.07	-0.85 ± 0.94	**< 0.001**
Docosatetraenoic acid (22:4n6)	1.12 ± 0.41	0.87 ± 0.37	-0.24 ± 0.35	**< 0.001**
n-6 Docosapentaenoic acid (22:5n6)	0.19 ± 0.06	0.20 ± 0.09	+ 0.01 ± 0.08	1
DBS Omega-3 Index (%)	3.14 ± 0.81	4.69 ± 1.20	+ 1.56 ± 0.90	**< 0.001**

Table 3 Baseline and post-supplementation fatty acid profiles (%) stratified by (**A**) *FADS1* rs174537 and (**B**) *ELOVL2* rs953413 SNPs. A t-test was used for the comparison between the two groups

A. FADS1 rs174537									
	Baseline			**Post**			**Mean difference (after supplementation-baseline)**		
	GG	**GT + TT**	***p*-value**	**GG**	**GT + TT**	***p*-value**	**GG**	**GT + TT**	***p*-value**
n	**49**	**36**		**49**	**36**		**49**	**36**	
α-linolenic acid (18:3n3)	0.24 ± 0.12	0.21 ± 0.10	0.257	0.27 ± 0.13	0.23 ± 0.09	0.086	+ 0.03 ± 0.05	+ 0.02 ± 0.05	0.164
Eicosapentaenoic acid (EPA, 20:5n3)	0.38 ± 0.18	0.41 ± 0.23	0.493	1.06 ± 0.54	1.15 ± 0.64	0.484	+ 0.68 ± 0.47	+ 0.74 ± 0.59	0.602
Docosapentaenoic-n3 acid (22:5n3)	0.64 ± 0.23	0.67 ± 0.20	0.429	0.79 ± 0.26	0.83 ± 0.23	0.467	+ 0.15 ± 0.17	+ 0.15 ± 0.12	0.949
Docosahexaenoic acid (DHA, 22:6n3)	1.90 ± 0.59	1.86 ± 0.54	0.742	2.70 ± 0.70	2.65 ± 0.64	0.737	+ 0.80 ± 0.51	+ 0.79 ± 0.44	0.935
Linoleic acid (18:2n6)	20.15 ± 2.78	19.96 ± 3.30	0.774	20.78 ± 2.63	19.98 ± 2.50	0.159	+ 0.63 ± 1.71	+ 0.02 ± 2.13	0.144
γ-linolenic acid (18:3n6)	0.16 ± 0.07	0.20 ± 0.09	0.082	0.21 ± 0.08	0.22 ± 0.09	0.396	+ 0.04 ± 0.08	+ 0.03 ± 0.09	0.379
Eicosadienoic acid (20:2n6)	0.27 ± 0.05	0.29 ± 0.10	0.348	0.28 ± 0.08	0.33 ± 0.13	**0.027**	0.00 ± 0.08	+ 0.04 ± 0.12	0.085
Dihomo-γ-linolenic acid (20:3n6)	1.21 ± 0.32	1.37 ± 0.30	**0.028**	1.10 ± 0.21	1.17 ± 0.28	0.171	-0.12 ± 0.30	-0.20 ± 0.28	0.215
Arachidonic acid (AA, 20:4n6)	9.55 ± 1.45	9.00 ± 1.17	0.062	8.56 ± 1.11	8.33 ± 1.01	0.330	-0.99 ± 0.96	-0.67 ± 0.89	0.115
Docosatetraenoic acid (22:4n6)	1.14 ± 0.45	1.08 ± 0.36	0.536	0.85 ± 0.39	0.90 ± 0.34	0.621	-0.28 ± 0.36	-0.19 ± 0.35	0.213
Docosapentaenoic-n6 acid (22:5n6)	0.20 ± 0.06	0.19 ± 0.0	0.643	0.20 ± 0.09	0.20 ± 0.08	0.892	0.00 ± 0.07	+ 0.01 ± 0.08	0.597
DBS Omega-3 Index	3.13 ± 0.84	3.15 ± 0.80	0.891	4.67 ± 1.25	4.75 ± 1.15	0.779	+ 1.55 ± 0.99	+ 1.60 ± 0.79	0.804
B.*ELOVL2*rs953413									
	Baseline			***Post***			***Mean difference (after supplementation-baseline)***		
At baseline (%)	**GG**	**GA + AA**	***p-value***	**GG**	**GA + AA**	***p-value***	**GG**	**GA + AA**	***p-value***
n	**24**	**59**		**24**	**59**		**24**	**59**	
α-linolenic acid (18:3n3)	0.21 ± 0.10	0.23 ± 0.12	0.559	0.23 ± 0.10	0.26 ± 0.13	0.317	+ 0.02 ± 0.05	+ 0.03 ± 0.05	0.317
Eicosapentaenoic acid (EPA, 20:5n3)	0.38 ± 0.22	0.40 ± 0.19	0.665	0.67 ± 0.35	1.28 ± 0.57	**< 0.001**	+ 0.29 ± 0.23	+ 0.89 ± 0.51	**< 0.001**
Docosapentaenoic-n3 acid (22:5n3)	0.58 ± 0.19	0.67 ± 0.21	0.076	0.67 ± 0.21	0.85 ± 0.24	**0.002**	+ 0.09 ± 0.12	+ 0.18 ± 0.15	**0.008**
Docosahexaenoic acid (DHA, 22:6n3)	1.71 ± 0.52	1.96 ± 0.56	0.064	2.33 ± 0.54	2.82 ± 0.66	**0.002**	+ 0.62 ± 0.29	+ 0.86 ± 0.54	**0.042**
Linoleic acid (18:2n6)	19.55 ± 2.94	20.38 ± 2.94	0.244	20.09 ± 2.11	20.72 ± 2.72	0.313	+ 0.54 ± 1.87	+ 0.33 ± 1.93	0.655
γ-linolenic acid (18:3n6)	0.16 ± 0.06	0.18 ± 0.09	0.184	0.21 ± 0.08	0.22 ± 0.09	0.879	+ 0.06 ± 0.09	+ 0.03 ± 0.08	0.227
Eicosadienoic acid (20:2n6)	0.28 ± 0.07	0.28 ± 0.07	0.787	0.30 ± 0.11	0.29 ± 0.10	0.754	+ 0.02 ± 0.10	+ 0.01 ± 0.10	0.881
Dihomo-γ-linolenic acid (20:3n6)	1.20 ± 0.30	1.31 ± 0.34	0.179	1.19 ± 0.27	1.10 ± 0.23	0.097	-0.01 ± 0.24	-0.21 ± 0.31	**0.004**
Arachidonic acid (AA, 20:4n6)	9.22 ± 1.31	9.32 ± 1.39	0.779	8.75 ± 1.16	8.30 ± 1.00	0.085	-0.47 ± 0.67	-1.01 ± 1.01	**0.019**
Docosatetraenoic acid (22:4n6)	1.13 ± 0.46	1.10 ± 0.40	0.746	0.87 ± 0.41	0.86 ± 0.36	0.915	-0.26 ± 0.39	-0.24 ± 0.34	0.790
Docosapentaenoic-n6 acid (22:5n6)	0.19 ± 0.08	0.19 ± 0.06	0.861	0.19 ± 0.08	0.20 ± 0.09	0.561	0.00 ± 0.04	+ 0.01 ± 0.09	0.612
DBS Omega-3 Index	2.89 ± 0.77	3.23 ± 0.80	0.079	3.83 ± 0.81	5.06 ± 1.16	**< 0.001**	+ 0.94 ± 0.49	+ 1.83 ± 0.92	**< 0.001**

dihomo-γ-linolenic acid ($p = 0.004$), arachidonic acid ($p = 0.019$), and the Omega-3 Index ($p < 0.001$). No statistically significant differences were observed for the other fatty acids.

The results of the linear regression analysis for *FADS1* rs174537 and *ELOVL2* rs953413 are illustrated in Fig. 1, showing the changes observed (delta) before and after one month of fish oil supplementation for the GG group (major allele) and the combined GT + TT group (minor allele) adjusted for sex and age for the main fatty acids investigated (EPA, DHA, AA and DBS Omega-3 Index). Regarding *FADS1* rs174537, no statistically significant differences were observed between the groups for any of the parameters. Specifically, the difference between the two groups in the change of EPA percentage was minimal (0.02 ± 0.10, $p = 0.84$). Similarly, the GT + TT group did not exhibit significant differences in the changes for DHA (-0.03 ± 0.11, $p = 0.770$), and the DBS Omega-3 Index (-0.004 ± 0.19, $p = 0.981$). A small effect was observed for AA, where the GT + TT group showed a slight change (+0.39 ± 0.22), though this was not statistically significant ($p = 0.081$). Regarding the ELOVL2 rs953413, the GG group exhibited a lower change in EPA compared to the GA + AA group (-0.57 ± 0.10, $p < 0.001$). Significant reductions were also observed in the DBS Omega-3 Index for the GG group compared to GA + AA (-0.86 ± 0.20, $p < 0.001$). While the change for DHA was different in the two groups. In particular, greater change was observed in the GG group compared to GA + AA (-0.23 ± 0.12, $p = 0.053$). Regarding the percentage of AA a greater change was observed in the GG group (+0.55 ± 0.23, $p = 0.019$) compared to the GA + AA group. Gender and age did not significantly affect the changes for any of the parameters analyzed.

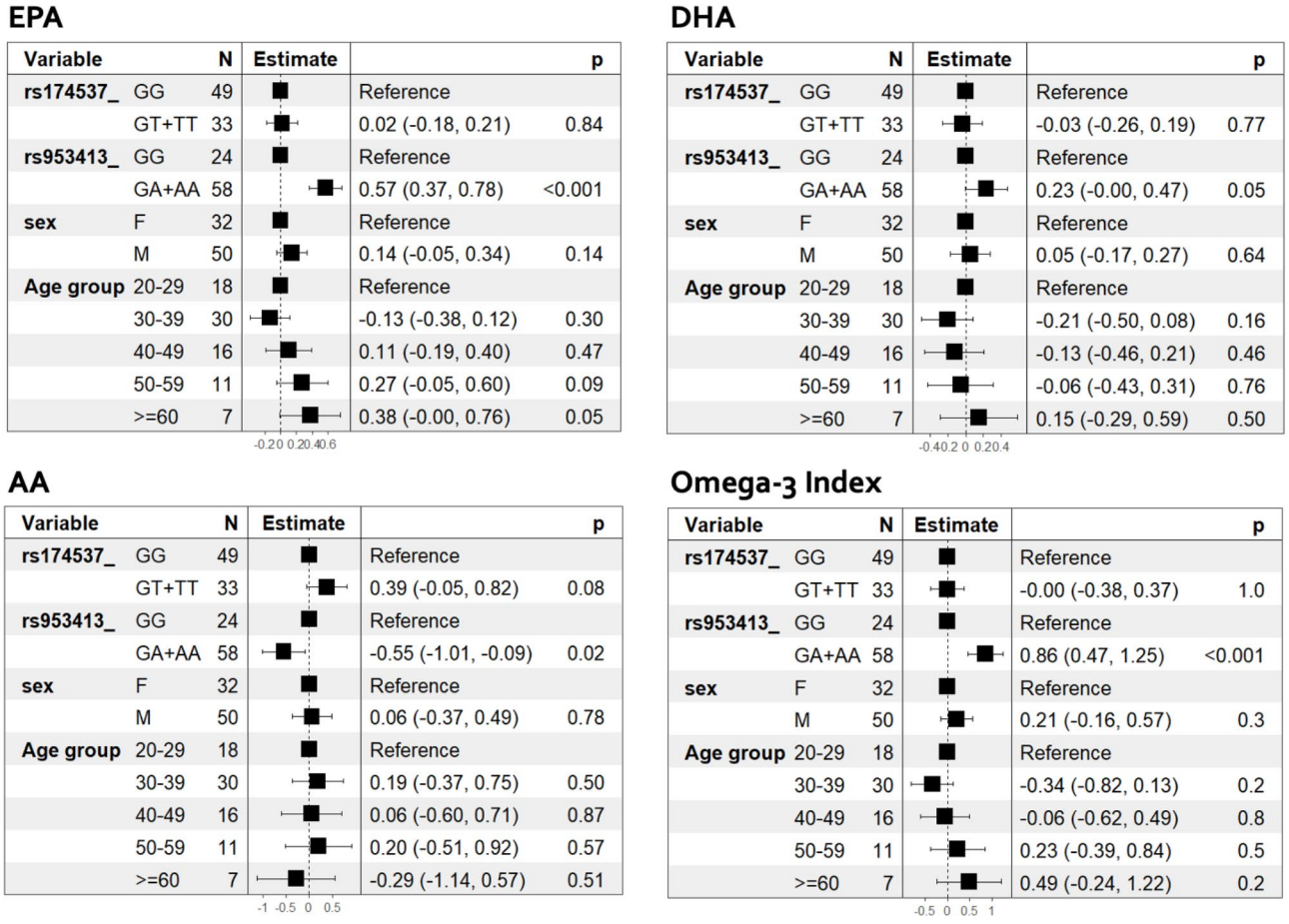

Fig. 1 Forest plots illustrating the results of linear regression analyses examining associations of genotype, sex, and age group with changes (delta) in key fatty acid composition and DBS Omega-3 Index. Forest plots showing the estimated effects of *FADS1* (rs174537) and *ELOVL2* (rs953413) genotypes, sex (F, M), and age groups (20–29, 30–39, 40–49, 50–59, ≥ 60) on changes in EPA, DHA, AA, and DBS Omega-3 Index, following supplementation. Reference groups for each variable are indicated in the legend

Discussion

The metabolism of omega-3 fatty acids, particularly EPA and DHA, is influenced by enzymes encoded by the *FADS* and *ELOVL* gene families. The *FADS1* gene encodes Δ5 desaturase, which is crucial for converting ALA to EPA, while the *ELOVL2* gene encodes an elongase enzyme (i.e., ELOVL fatty acid elongase 2) involved in converting EPA to DHA. Genetic polymorphisms in these genes can lead to variations in enzyme activity, affecting the percentages of EPA, DHA, and other related fatty acids. The evaluation of baseline fatty acid percentages in relation to the *FADS1* (rs174537) and *ELOVL2* (rs953413) genetic variants found no significant differences in baseline EPA and DHA percentages between individuals with different genotypes at these loci. This represents one of the main findings of the study and highlights the genetic and metabolic complexity of this topic. As expected, individuals with the minor allele at *FADS1* rs174537 did not differ significantly from major allele carriers in their baseline omega-3 PUFA concentrations, including EPA and DHA percentages. Indeed, since the fish oil supplement used primarily contains EPA and DHA, genetic variants in *FADS1* are unlikely to influence the effects of dietary EPA and DHA supplementation, given its role in the biosynthesis pathway before EPA and DHA. However, differently from our study, previous research has reported lower baseline EPA and DHA levels in minor allele carriers, although data about EPA levels are often contradictory [17–27].

Although no significant differences in baseline omega-3 percentages were observed between individuals with different genotypes for the *ELOVL2* rs953413 polymorphism, this SNP demonstrated a more substantial impact. The carriers of the minor allele (GA + AA) may have more benefits from the fish oil supplementation in terms of increasing EPA and DBS Omega-3 Index. Consequently, the major allele of rs953413 in *ELOVL2* is associated with a less favorable response to EPA and DHA supplementation, which may influence the balance between omega-3 and omega-6 fatty acids and the inflammatory status.

The experimental data from our study are in line with the findings of two previous studies, where carriers of the minor allele of the ELOVL2 gene (specifically rs953413) showed a more pronounced benefit from supplementation with fish oil rich in EPA and DHA. This pattern is consistent with the results of previous studies, where minor allele carriers had higher plasma concentrations of EPA and DHA in plasma after fish oil (especially at high doses) or EPA supplementation. However, our study did not find sex-based differences in the response to fish oil supplementation, which contrasts with the findings of Metherel et al., in which only female participants showed a greater increase in DHA percentage. This study also differed from ours in that it utilized a supplementation regimen that exclusively contained EPA. These differences in supplementation and study design could explain the absence of sex-related differences in our results, as the effect of EPA alone might vary compared to a supplementation of omega-3 [38, 39].

Personalized nutrition, which tailors dietary recommendations based on individual genetic, phenotypic, and environmental factors, is increasingly recognized as a key approach to optimizing health outcomes. The differential response to fish oil supplementation observed in this study, influenced by genetic variants, suggests that uniform dietary guidelines may not adequately address the needs of diverse populations, underscoring the need for a more personalized approach [40, 41]. These fatty acids involve numerous physiological processes, including inflammation regulation, cardiovascular health, and neuroprotection [42]. However, the efficacy of supplementation can vary significantly depending on an individual genetic makeup. For instance, individuals with certain *ELOVL2* polymorphisms may need higher doses of EPA and DHA to achieve the same anti-inflammatory effects as those without these variants. Moreover, the balance between omega-3 and omega-6 fatty acids is crucial for maintaining health, with a lower omega-6 to omega-3 ratio associated with reduced inflammation and a lower risk of chronic diseases. Genetic variants that affect the metabolism of these fatty acids can influence this balance, potentially altering the risk profile for conditions such as CVD, T2D, and inflammatory disorders [17, 43–45].

Future studies should investigate the long-term health outcomes of personalized omega-3 supplementation in diverse populations. This includes exploring the interactions between genetic variants and other factors such as diet, lifestyle, and the microbiome, which may also influence the metabolism and efficacy of EPA and DHA [46]. Understanding these interactions could lead to more refined and effective personalized nutrition strategies. Expanding research to include other relevant genes involved in fatty acid metabolism, such as those encoding enzymes in the β-oxidation pathway, could provide a more comprehensive understanding of how genetic factors influence lipid profiles and health outcomes.

Although this study offers some interesting insights, it is important to acknowledge its limits. The main limitations include the relatively short duration of omega-3 supplementation, which may not fully capture long-term metabolic adaptations associated with dietary interventions. However, the one-month period was intentionally chosen to enhance treatment compliance and accurately assess the initial incorporation kinetics of omega-3 fatty acids in relation to *FADS1* and *ELOVL2* SNPs.

The sample size, while adequate for detecting significant differences in certain parameters, may limit the generalizability of the findings and the ability to identify more subtle associations. Additionally, the study focused on specific genetic polymorphisms (*FADS1* rs174537 and *ELOVL2* rs953413), which may not account for the broader genetic variability influencing PUFA metabolism. Finally, another important limitation is the absence of a prescribed standardized diet and the control of consumed fatty fish or omega-3-rich foods. However, one of the goals of the study was to assess whether the addition of omega-3 fatty acids from fish oil to the habitual diet of participants would influence the outcomes. This approach is consistent with a free-living population model and enhances the real-world applicability of our findings.

In conclusion, this study highlights the critical role of genetic variability in influencing the response to fish oil supplementation and underscores the importance of personalized nutrition. Although baseline differences in fatty acid percentages between genotypes were not significant, the findings suggest that genetic factors still play a crucial role in determining the effectiveness of fish oil supplementation. As our understanding of the genetic determinants of nutrient metabolism grows, it will become increasingly feasible to tailor dietary recommendations to individual needs, thereby maximizing the health benefits of supplementation.

Acknowledgements

This work was partially supported by the European Union—NextGenerationEU, under the National Recovery and Resilience Plan (NRRP) of the Italian Ministry of University and Research, Project "D34 Health: Digital Driven Diagnostics, Prognostics, and Therapeutics for Sustainable Healthcare." Additional support was provided by NextGenerationEU, within the NRRP, Investment PE8–Project Age-It: "Ageing Well in an Ageing Society." This resource was co-financed by NextGenerationEU [DM 1557, 11.10.2022]. We thank all volunteers for their participation in this study.

Author contributions

Study conception and design: G.S. and S.D.; methodology: G.C., S.V., T.Z.; formal analysis: G.C., S.V., and T.Z.; investigation: G.C., S.V., and M.I.; data curation: A.M., and F.G.; writing—original draft: A.M., and F.G.; writing—review and editing: M.I., G.S., and S.D.; supervision: G.S., and S.D. All authors have read and agreed to the published version of the manuscript.

Funding
This research was funded by Horizon 2020-PON 2014/2020 (CUP: B38I17000310008) and "F.F.I.N—Functional Foods Italy Network" (POS TR5—Piano Operativo Salute Traiettoria 5) of the Italian Ministry of Health (CUP H33C22000780008).

Data availability
The datasets used in the present study are available from the corresponding author on reasonable request.

Declarations

Competing interests
The authors declare no competing interests.

Informed consent
The study by the institutional review board of the University of Molise (Prot. n. 22/2019–23 September 2019). Written informed consent was obtained from all participants involved in this study.

Author details
[1]Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Via F. De Sanctis, s.n.c, Campobasso 86100, Italy
[2]Biostatistics and Clinical Epidemiology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[3]Bicocca Bioinformatics Biostatistics and Bioimaging Center B4, School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy
[4]Tecnobios srl, Apollosa, Benevento, Italy
[5]Centro Delta srl, Apollosa, Benevento, Italy
[6]Genus Biotech, University of Sannio, Benevento, Italy

Received: 15 January 2025 / Accepted: 4 March 2025
Published online: 20 March 2025

References

1. Afshin A, Sur PJ, Fay KA, Cornaby L, Ferrara G, Salama JS, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2019;393:1958–72.
2. Cena H, Calder PC. Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. Nutrients. 2020;12.
3. Verma M, Hontecillas R, Tubau-Juni N, Abedi V, Bassaganya-Riera J. Challenges in personalized nutrition and health. Front Nutr. 2018;5.
4. Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French TAC, Tai ES, et al. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. J Nutrigenet Nutrigenomics. 2011;4:69–89.
5. van Ommen B, van den Broek T, de Hoogh I, van Erk M, van Someren E, Rouhani-Rankouhi T, et al. Systems biology of personalized nutrition. Nutr Rev. 2017;75:579–99.
6. Celis-Morales C, Lara J, Mathers JC. Personalising nutritional guidance for more effective behaviour change. Proc Nutr Soc. 2015;74:130–8.
7. von Schacky C. Omega-3 index and cardiovascular health. Nutrients [Internet]. 2014 [cited 2024 Apr 9];6:799–814. Available from: https://pubmed.ncbi.nlm.nih.gov/24566438/
8. Von Schacky C. Omega-3 fatty acids in cardiovascular disease–an uphill battle. Prostaglandins Leukot Essent Fatty Acids [Internet]. 2015 [cited 2024 Apr 9];92:41–7. Available from: https://pubmed.ncbi.nlm.nih.gov/24935800/
9. Davinelli S, Medoro A, Intrieri M, Saso L, Scapagnini G, Kang JX. Targeting NRF2–KEAP1 axis by Omega-3 fatty acids and their derivatives: Emerging opportunities against aging and diseases. Free Radic Biol Med [Internet]. 2022;193:736–50. Available from: https://doi.org/10.1016/j.freeradbiomed.2022.11.017
10. Dempsey M, Rockwell MS, Wentz LM. The influence of dietary and supplemental omega-3 fatty acids on the omega-3 index: A scoping review. Front Nutr [Internet]. 2023 [cited 2025 Feb 13];10. Available from: https://pubmed.ncbi.nlm.nih.gov/36742439/
11. Harris WS, Von Schacky C. The Omega-3 Index: A new risk factor for death from coronary heart disease? Prev Med (Baltim) [Internet]. 2004 [cited 2024 Apr 5];39:212–20. Available from: https://pubmed.ncbi.nlm.nih.gov/15208005/
12. Davinelli S, Intrieri M, Corbi G, Scapagnini G. Metabolic indices of polyunsaturated fatty acids: current evidence, research controversies, and clinical utility. Crit Rev Food Sci Nutr [Internet]. 2021 [cited 2025 Feb 13];61:259–74. Available from: https://pubmed.ncbi.nlm.nih.gov/32056443/
13. Lattka E, Illig T, Koletzko B, Heinrich J. Genetic variants of the FADS1 FADS2 gene cluster as related to essential fatty acid metabolism. Curr Opin Lipidol [Internet]. 2010 [cited 2025 Jan 11];21:64–9. Available from: https://journals.lww.com/co-lipidology/fulltext/2010/02000/genetic_variants_of_the_fads1_fads2_gene_cluster.11.aspx
14. Alsaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TAB, O'Dell SD. ELOVL2 gene polymorphisms are associated with increases in plasma eicosapentaenoic and docosahexaenoic acid proportions after fish oil supplement. Genes Nutr [Internet]. 2014 [cited 2025 Jan 11];9:1–9. Available from: https://link.springer.com/articles/https://doi.org/10.1007/s12263-013-0362-6
15. Loukil I, Mutch DM, Plourde M. Genetic association between FADS and ELOVL polymorphisms and the Circulating levels of EPA/DHA in humans: a scoping review. Genes Nutr. 2024;19.
16. Howard TD, Mathias RA, Seeds MC, Herrington DM, Hixson JE, Shimmin LC et al. DNA methylation in an enhancer region of the FADS cluster is associated with FADS activity in human liver. PLoS One [Internet]. 2014 [cited 2025 Feb 7];9. Available from: https://pubmed.ncbi.nlm.nih.gov/24842322/
17. Roke K, Mutch DM. The role of FADS1/2 polymorphisms on cardiometabolic markers and fatty acid profiles in young adults consuming fish oil supplements. Nutrients. 2014;6:2290–304.
18. Tanaka T, Shen J, Abecasis GR, Kisialiou A, Ordovas JM, Guralnik JM, et al. Genome-Wide association study of plasma polyunsaturated fatty acids in the InCHIANTI study. PLoS Genet. 2009;5:1000338.
19. Al-Hilal M, AlSaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TAB, et al. Genetic variation at the FADS1-FADS2 gene locus influences delta-5 desaturase activity and LC-PUFA proportions after fish oil supplement. J Lipid Res. 2013;54:542–51.
20. Metelcová T, Vaňková M, Zamrazilová H, Hovhannisyan M, Staňková B, Tvrzická E, et al. FADS1 gene polymorphism(s) and fatty acid composition of serum lipids in adolescents. Lipids. 2021;56:499–508.
21. Li SW, Lin K, Ma P, Zhang ZL, Zhou YD, Lu SY, et al. FADS gene polymorphisms confer the risk of coronary artery disease in a Chinese Han population through the altered desaturase activities: based on High-Resolution melting analysis. PLoS ONE. 2013;8:55869.
22. Cribb L, Murphy J, Froud A, Oliver G, Bousman CA, Ng CH, et al. Erythrocyte polyunsaturated fatty acid composition is associated with depression and FADS genotype in Caucasians. Nutr Neurosci. 2018;21:589–601.
23. Kim OY, Lim HH, Yang LI, Chae JS, Lee JH. Fatty acid desaturase (FADS) gene polymorphisms and insulin resistance in association with serum phospholipid polyunsaturated fatty acid composition in healthy Korean men: cross-sectional study. Nutr Metab (Lond). 2011;8.
24. Huang MC, Chang WT, Chang HY, Chung HF, Chen FP, Huang YF et al. FADS gene polymorphisms, fatty acid desaturase activities, and HDL-C in type 2 diabetes. Int J Environ Res Public Health. 2017;14.
25. Puentes ADLG, Goyanes RM, Tonato AMC, Torres-Espínola FJ, García MA, De Almeida LD et al. Association of maternal weight with FADS and ELOVL genetic variants and fatty acid levels- the PREOBE follow-up. PLoS ONE. 2017;12.
26. Hong SH, Kwak JH, Paik JK, Chae JS, Lee JH. Association of polymorphisms in FADS gene with age-related changes in serum phospholipid polyunsaturated fatty acids and oxidative stress markers in middle-aged Nonobese men. Clin Interv Aging. 2013;8:585–96.
27. Murff HJ, Shrubsole MJ, Cai Q, Su T, Dooley JH, Cai SS, et al. N-3 long chain fatty acids supplementation, fatty acids desaturase activity, and colorectal Cancer risk: A randomized controlled trial. Nutr Cancer. 2022;74:1388–98.
28. Huang T, Sun J, Chen Y, Xie H, Xu D, Huang J, et al. Genetic variants in desaturase gene, erythrocyte fatty acids, and risk for type 2 diabetes in Chinese Hans. Nutrition. 2014;30:897–902.
29. Merino DM, Johnston H, Clarke S, Roke K, Nielsen D, Badawi A et al. Polymorphisms in FADS1 and FADS2 alter desaturase activity in young Caucasian and Asian adults. Mol Genet Metab [Internet]. 2011 [cited 2025 Feb 13];103:171–8. Available from: https://pubmed.ncbi.nlm.nih.gov/21414826/
30. Mathias RA, Sergeant S, Ruczinski I, Torgerson DG, Hugenschmidt CE, Kubala M et al. The impact of FADS genetic variants on ω6 polyunsaturated fatty acid metabolism in African Americans. BMC Genet [Internet]. 2011 [cited 2025 Feb 13];12. Available from: https://pubmed.ncbi.nlm.nih.gov/21599946/

31. Buckley MT, Racimo F, Allentoft ME, Jensen MK, Jonsson A, Huang H et al. Selection in Europeans on Fatty Acid Desaturases Associated with Dietary Changes. Mol Biol Evol [Internet]. 2017 [cited 2025 Feb 13];34:1307–18. Available from: https://pubmed.ncbi.nlm.nih.gov/28333262/
32. Alsaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TAB, O'Dell SD. ELOVL2 gene polymorphisms are associated with increases in plasma eicosapentaenoic and docosahexaenoic acid proportions after fish oil supplement. Genes Nutr. 2014;9.
33. Fujii TM, de Norde M, Fisberg MM, Marchioni RM, Ordovás DML, Rogero JM. FADS1 and ELOVL2 polymorphisms reveal associations for differences in lipid metabolism in a cross-sectional population-based survey of Brazilian men and women. Nutr Res. 2020;78:42–9.
34. Ali S, Intrieri M, Pisanti A, Cardinale G, Corbi G, Scapagnini G, et al. Determination of n-3 index and arachidonic acid/eicosapentaenoic acid ratio in dried blood spot by gas chromatography. Biotechniques. 2022;73:25–33.
35. Harris WS, Polreis J. Measurement of the Omega-3 Index in Dried Blood Spots. Ann Clin Lab Res [Internet]. 2016 [cited 2025 Feb 28];4:4. Available from: http://www.imedpub.com/
36. Metherel AH, Hogg RC, Buzikievich LM, Stark KD. Butylated hydroxytoluene can protect polyunsaturated fatty acids in dried blood spots from degradation for up to 8 weeks at room temperature. Lipids Health Dis [Internet]. 2013 [cited 2025 Jan 12];12:1–10. Available from: https://link.springer.com/articles/https://doi.org/10.1186/1476-511X-12-22
37. Choi EH, Lee SK, Ihm C, Sohn YH. Rapid DNA extraction from dried blood spots on filter paper: potential applications in biobanking. Osong Public Health Res Perspect. 2014;5:351–7.
38. Alsaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TAB, O'Dell SD. ELOVL2 gene polymorphisms are associated with increases in plasma eicosapentaenoic and docosahexaenoic acid proportions after fish oil supplement. Genes Nutr [Internet]. 2014 [cited 2025 Jan 5];9. Available from: https://pubmed.ncbi.nlm.nih.gov/24292947/
39. Metherel AH, Irfan M, Klingel SL, Mutch DM, Bazinet RP. Higher Increase in Plasma DHA in Females Compared to Males Following EPA Supplementation May Be Influenced by a Polymorphism in ELOVL2: An Exploratory Study. Lipids [Internet]. 2021 [cited 2025 Jan 5];56:211–28. Available from: https://pubmed.ncbi.nlm.nih.gov/33174255/
40. Adams SH, Anthony JC, Carvajal R, Chae L, Khoo CSH, Latulippe ME, et al. Perspective: guiding principles for the implementation of personalized nutrition approaches that benefit health and function. Adv Nutr. 2020;11:25.
41. Clemente-Suárez VJ, Peris-Ramos HC, Redondo-Flórez L, Beltrán-Velasco AI, Martín-Rodríguez A, David-Fernandez S, et al. Personalizing nutrition strategies: bridging research and public health. J Personalized Med 2024. 2024;14:14:305.
42. Davinelli S, Intrieri M, Corbi G, Scapagnini G. Metabolic indices of polyunsaturated fatty acids: current evidence, research controversies, and clinical utility. Crit Rev Food Sci Nutr. 2021;61:259–74.
43. Yuan S, Bäck M, Bruzelius M, Mason AM, Burgess S, Larsson S. Plasma phospholipid fatty acids, FADS1 and risk of 15 cardiovascular diseases: A Mendelian randomisation study. Nutrients. 2019;11.
44. Roke K, Ralston JC, Abdelmagid S, Nielsen DE, Badawi A, El-Sohemy A, et al. Variation in the FADS1/2 gene cluster alters plasma n-6 PUFA and is weakly associated with HsCRP levels in healthy young adults. Prostaglandins Leukot Essent Fat Acids. 2013;89:257–63.
45. Aiello A, Medoro A, Accardi G, Calabrò A, Carru C, Cannavo A, et al. Polyunsaturated fatty acid status and markers of oxidative stress and inflammation across the lifespan: A cross-sectional study in a cohort with long-lived individuals. Exp Gerontol. 2024;195:112531.
46. Rittenhouse M, Sambuughin N, Deuster P. Optimization of Omega-3 index levels in athletes at the US naval academy: personalized Omega-3 fatty acid dosage and molecular genetic approaches. Nutrients. 2022;14.

Publisher's note