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<thead>
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<th>The impact of fatty acid desaturase genotype on fatty acid status and cardiovascular health in adults</th>
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<td>O'Neill, Colette M.; Minihane, Anne-Marie</td>
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The impact of fatty acid desaturase genotype on fatty acid status and cardiovascular health in adults

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2Cork Centre for Vitamin D and Nutrition Research, School of Food and Nutritional Sciences, University College Cork, Ireland

The aim of this review was to determine the impact of the fatty acid desaturase (FADS) genotype on plasma and tissue concentrations of the long-chain (LC) n-3 PUFA, including EPA and DHA, which are associated with the risk of several diet-related chronic diseases, including CVD. In addition to dietary intakes, which are low for many individuals, tissue EPA and DHA are also influenced by the rate of bioconversion from α-linolenic acid (αLNA). Δ-5 and Δ-6 desaturase enzymes, encoded for by FADSI and FADS2 genes, are key desaturation enzymes involved in the bioconversion of essential fatty acids (αLNA and linoleic acid (LA)) to longer chained PUFA. In general, carriers of FADS minor alleles tend to have higher habitual plasma and tissue levels of LA and αLNA, and lower levels of arachidonic acid, EPA and also to a lesser extent DHA. In conclusion, available research findings suggest that FADS minor alleles are also associated with reduced inflammation and CVD risk, and that dietary total fat and fatty acid intake have the potential to modify relationships between FADS gene variants and circulating fatty acid levels. However to date, neither the size-effects of FADS variants on fatty acid status, nor the functional SNP in FADSI and 2 have been identified. Such information could contribute to the refinement and targeting of EPA and DHA recommendations, whereby additional LC n-3 PUFA intakes could be recommended for those carrying FADS minor alleles.


Plasma and tissue long-chain (LC) PUFA concentrations are associated with the risk of several diet-related chronic diseases, including CVD. Therefore it is important that the determinants of LC-PUFA metabolism, and concentrations in the circulation and in target tissues are fully understood. n-3 Fatty acids are PUFA, which contain the first double bond at the third carbon atom from the methyl end of the fatty acid. There are three major LC n-3 PUFA in the human diet and mammalian tissues, namely α-linolenic acid (αLNA), EPA and DHA. Although the most effective means to increase EPA and DHA status is through increased consumption of fish, bioconversion from the essential fatty acid, αLNA, represents a significant source and in particular in non–fish/EPA plus DHA supplement consumers who have 57–80% lower intakes than fish eaters, with EPA and DHA derived from the sequential desaturation and elongation from αLNA.

The potential health benefits associated with consumption of EPA and DHA are numerous, with the most studied and accepted being a reduction in CVD risk. As summarised in several systematic reviews and meta-analysis of prospective epidemiological studies and randomised controlled trials, the ability of LC n-3 PUFA to reduce all-cause mortality and cardiovascular mortality has been widely described. However,
it should be noted that this is not a fully consistent finding, with the heterogeneity in responsiveness as yet not fully understood\(^9,26\). Consumption of EPA and DHA has also been shown to be associated with many other diseases, for example, autoimmune diseases such as rheumatoid arthritis, cancer, diabetes, respiratory diseases, gastrointestinal diseases, Alzheimer’s disease, depression, as well as psychotic disorders, for example schizophrenia\(^11-14\).

The current recommended intakes for EPA plus DHA in the UK are $\geq 450$ mg/d\(^19\). This recommendation is based largely on the cardiovascular benefits of these fatty acids and can be achieved by consuming two portions of fish per week, one of which should be oily\(^15\). However, the estimated EPA and DHA consumption in adults in the UK is approximately 270 mg/d for men and 220 mg/d for women, which is far below the recommended minimal intake\(^6\). Furthermore, mean population intakes are known to be highly skewed, with a large proportion of the population who do not consume fish or an EPA/DHA-containing supplement having a typical EPA plus DHA intake of $<50$ mg/d\(^16\).

\(\textit{n-6}\) PUFA, including linoleic acid (LA) and arachidonic acid (AA), contain the first double bond at the sixth carbon atom from the methyl end of the fatty acid. LA is an essential fatty acid that is found in vegetable oils and is the most abundant PUFA in the modern Western diet\(^17\). LA can be metabolised to AA, which in turn, is a precursor of eicosanoids, such as PG, thromboxanes and leukotrienes. These eicosanoids tend to be pro-inflammatory and therefore may negatively impact the development of CVD\(^18\).

There is now a large published literature reporting on the impact of individual gene variants on LC-PUFA metabolism and CVD incidence and biomarker profiles. This review will focus on the fatty acid desaturase (\textit{FADS}) genotypes, which are emerging as the most significant common genetic determinants identified to date. Accumulating evidence suggests that the locus may, in the future, be useful in stratification and targeting of LC-PUFA recommendations towards individuals likely to be deficient and responsive.

### PUFA bioconversion and the fatty acid desaturase genotype

In addition to dietary intake, tissue EPA and DHA is influenced by the rate of bioconversion from \(\gamma\)LNA, which involves multiple desaturation and elongation steps (Fig. 1). The \(\Delta-5\) and \(\Delta-6\) desaturase enzymes are the key rate-limiting enzymes in this pathway\(^19\). The human desaturase complementary DNA were first cloned in 1999 by Cho \textit{et al.}\(^20,21\) and were later identified as \textit{FADS1} and \textit{FADS2} in the human genome\(^22\), located in a cluster on chromosome 11 (11q12–13.1). \(\Delta-5\) desaturase and \(\Delta-6\) desaturase are found in many human tissues, but the liver is the site at which they are most highly expressed\(^22,23\). LA and \(\gamma\)LNA are metabolised by the same series of enzymes. EPA and DHA are produced at limited conversion rates of 0.2–6% for EPA and <0.1% for DHA in human males and post-menopausal females, with higher rates evident in pre-menopausal females\(^23\). The more efficient EPA and DHA synthesis in pre-menopausal women is thought to be an evolutionary adaptation, so that younger females have sufficient LC-PUFA to meet the demands of pregnancy and the developing fetus. As will be described, variation across the \textit{FADS} gene region appears to be important in modulating LC-PUFA status. The functional SNP in \textit{FADS1} and \(\Delta-3\) have not yet been identified.

### Impact of fatty acid desaturase genotype on PUFA status

Using both a candidate gene (Table 1) and a genome wide association study (Table 2) approach, numerous studies have reported associations between variations in the \textit{FADS} locus and desaturase activity and fatty acid status in human subjects. Desaturase activity can be approximated by calculating the product-to-precursor ratio of fatty acids. In 2006, Schaeffer \textit{et al.}\(^24\) analysed eighteen SNP and reconstructed haplotypes in the \textit{FADS1}–2 cluster in 727 adults. A five-locus \textit{FADS} haplotype accounted for 27.7, 5.2 and 1.4% of the variation in AA, EPA and DHA in serum phospholipids, respectively. The minor alleles were associated with higher \(\alpha\)LNA and LA and lower \(\gamma\)-linolenic acid, AA, EPA and \(n-3\) docosapentaenoic acid concentrations, with no significant impact on DHA\(^24\). More recently, Ameur \textit{et al.}\(^25\) performed genome wide genotyping in 5652 individuals, and targeted resequencing (\(n\) 960) of the \textit{FADS} region, across five European population cohorts and reported that present-day human subjects have two common \textit{FADS} haplotypes, which are defined by twenty-eight closely linked SNP, one of which was considered to be more efficient in relation to the biosynthesis of LC-PUFA\(^25\). This \textit{FADS} haplotype was associated with lower levels of LA (borderline significant) and \(\alpha\)LNA and higher levels of EPA, \(\gamma\)-linolenic acid, DHA and AA. Over the last decade, a number of other candidate gene approach studies, as well as genome wide association studies, have been conducted and the association between \textit{FADS} SNP/haplotypes and PUFA status, as well as desaturase activities, in plasma have been confirmed and extended to tissue fatty acid composition (Tables 1 and 2). However, information on how factors, including \(n-3\) PUFA intakes, health status and ethnicity, may influence the penetrance of the \textit{FADS} genotype, and in turn the effect size, is relatively unknown. Further research, expanding on the recent research by Wang \textit{et al.}\(^26\), is also required to determine the functional SNP, as well the molecular mechanism(s) responsible for the effect of the \textit{FADS} genotype on EPA and DHA status. Wang \textit{et al.}\(^26\) examined the association between six \textit{FADS} SNP and the lipidomic profile and \textit{FADS1}–3 expression in liver samples (\(n\) 154) and reported all six alleles to be associated with \textit{FADS1} (but not \textit{FADS2} and \(\Delta-3\)) gene expression and protein levels, suggesting that the causal variant(s) may be located at \textit{FADS1}\(^26\). In addition, twenty out of forty-two highly linked SNP
were located in the transcription factor-binding sites of the locus. Although it is unclear exactly which SNP is causal and exactly how the SNP influences transcription factor binding and activation of FADS1, the findings add considerable credibility to the observations that FADS genotypes influence EPA and DHA status.

**Impact of fatty acid desaturase genotype on cardiovascular health**

The majority of studies to date suggest that FADS minor alleles (associated with decreased desaturase activity) are associated with reduced inflammation, total cholesterol, LDL-cholesterol and coronary artery disease risk (Tables 1 and 2)\(^{18,27-31}\). In the Verona Heart Study (2008), a coronary artery disease incidence of 84 v. 66% was evident in individuals with six to seven v. two to three risk alleles and a higher AA:LA ratio was an independent risk factor for coronary artery disease \(^{\text{(18)}}\). A potential reason for these findings could involve the high LA intakes in the Western diet, resulting in reduced synthesis of LC n-3 PUFA from αLNA \(^{\text{(32)}}\). The higher n-6 conversion also leads to increased levels of AA, which is a direct precursor of many pro-inflammatory eicosanoids \(^{\text{(33,34)}}\). Hester et al. \(^{\text{(33)}}\) recently showed that subjects with the major allele for FADS SNP rs174537 had significantly higher levels of pro-inflammatory eicosanoids, LTB4 and 5-HETE, compared with minor allele carriers \(^{\text{(33)}}\). However, a few studies have reported contradictory results \(^{\text{(35-37)}}\) which could be due to the ethnicity of the participants or differences in the n-6 : n-3 PUFA content of the habitual diet. For example, two studies carried out in a Chinese-Han population reported the frequency of the rs174556 minor allele to be significantly higher in cases of both coronary artery disease and acute coronary syndrome compared with control groups \(^{\text{(35,37)}}\).

**Impact of diet composition on the relationship between the fatty acid desaturase genotype and PUFA and cardiovascular health status**

There have been a number of studies that show that diet composition can influence the relationship between FADS genotype and plasma fatty acid and lipid status (Table 3). In 2012, Hellstrand et al. reported that the
Table 1. Candidate gene studies: associations between fatty acid desaturase SNP and fatty acid status and cardiovascular health

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Age (mean (SD or range))</th>
<th>Sex</th>
<th>SNP</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
</table>
| Schaeffer et al.
(24) | n 727                     | 41.6 (12.3 years, 20-64 years) | Both | rs99780, rs174544, rs174545, rs174546, rs174553, rs174556, rs174561, rs174568, rs174570, rs174583, rs174589, rs174602, rs174620, rs2072114, rs3834458, rs482548, rs526126, rs968567 | Fatty acids in serum phospholipids | SNP showed strongest associations with AA ($P < 10^{-15}$), also with LA, αLNA, EPA ($P < 0.001$) |
| Baylin et al.
(49) | n 1694 MI cases, n 1694 controls | 58 (11 years)      | Both | rs3834458                                  | PUFA in plasma and adipose tissue. Risk of MI                           | EPA, LA and AA were significantly decreased in adipose tissue and plasma with increasing copy number of variant alleles ($P < 0.05$ for all). No association with MI |
| Malerba et al.
(52) | n 658                     | 59.7 (11.1 years)        | Both | rs174545, rs174556, rs174561, rs174570, rs174583, rs174589, rs174611, rs174827, rs498793, rs1000778, rs2524299, rs3834458, rs17831757 | Fatty acids in serum phospholipids and erythrocytes                      | SNP strongly associated with AA ($P < 10^{-5}$) in both serum and erythrocytes. Significant associations were also observed for LA and αLNA ($P < 0.05$) |
| Martinelli et al.
(53) | n 266 CAD cases, n 610 controls | 59 (10 years)          | Both | rs174545, rs174556, rs174561, rs174570, rs174583, rs174589, rs174611, rs174627, rs498793, rs1000778, rs2524299, rs3834458, rs17831757 | Serum lipids and other CAD risk factors, including hs-CRP              | Increases in hs-CRP concentrations and CAD risk were associated with FADS haplotypes ($P < 0.04$) |
| Rzhak et al.
(54) | n 163 (plasma) + n 535 (erythrocytes) | 13–80 years             | Both | rs174556, rs174561, rs3834458               | Fatty acids in serum phospholipids and erythrocyte membranes            | SNP strongly associated with EDA ($P = 7.9 \times 10^{-10}$ for rs3834458) and AA ($P = 1.1 \times 10^{-3}$ for rs174561) in erythrocytes |
| Mathias et al.
(55) | n 224                     | 46.7 (21.2 years)        | Both | rs99780, rs174537, rs174545, rs174546, rs174553, rs174556, rs174561, rs174568, rs174570, rs174575, rs174583, rs174611, rs174827, rs498793, rs1000778, rs2524299 | Serum n-6 fatty acids                                                   | Cluster of SNP in LD (rs174537, rs174545, rs174546, rs174553, rs174556, rs174561, and rs174568, and rs99780) associated with AA ($P = 5.8 \times 10^{-7}$) among other PUFA. FADS1 activity ratio associated with the –6 series ($P = 2.1 \times 10^{-13}$) for rs174546 related to estimated D6D activity ($\nu^2 = 0.052$) and D5D activity ($\nu^2 = 0.231$). Genetic effect on D5D activity and DGLA modified by the dietary n-6:n-3 ratio ($P$-values for interaction: 0.008 and 0.002) rs174547 associated with AA:LA in both Caucasians ($P = 4.0 \times 10^{-5}$) and Asians ($P = 5.0 \times 10^{-3}$). Although the minor allele for this SNP differed between Caucasians (T) and Asians (C), carriers of the C allele had a lower desaturase activity than carriers of the T allele in both groups |
| Zietemann et al.
(56) | n 2066                    | 35–65 years in women, 40–65 years in men | Both | rs174546                                  | n-6 PUFA composition in erythrocyte membranes                          | Genetic effect on n-6 PUFA activity and DGLA modified by the dietary n-6:n-3 ratio ($P$-values for interaction: 0.008 and 0.002) rs174547 associated with AA:LA in both Caucasians ($P = 4.0 \times 10^{-5}$) and Asians ($P = 5.0 \times 10^{-3}$). Although the minor allele for this SNP differed between Caucasians (T) and Asians (C), carriers of the C allele had a lower desaturase activity than carriers of the T allele in both groups |
| Merino et al.
(57) | Caucasian: n 78, Asian: n 69 | 20–29 years             | Both | rs174547, rs174570, rs174576, rs174579, rs174593, rs174602, rs174611, rs174827, rs412334, rs482548, rs498793, rs526126, rs695867, rs968567, rs17831757, rs2072114, rs2845573 | Plasma fatty acids                                                     | The frequency of rs174556 minor allele was significantly higher in the case than control group ($P = 0.039$) |
| Qin et al.
(35) | n 199 CAD cases, n 192 controls | 62.5 (20-4 years)        | Both | rs174556, rs174617                        | Distribution of FADS genotype in CAD cases and controls                | The frequency of rs174556 minor allele was significantly higher in the case than control group ($P = 0.039$) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Age (mean (or range))</th>
<th>Sex</th>
<th>SNP</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al. (36)</td>
<td>n 1860</td>
<td>47.5 (7-9 years, 45-85 years)</td>
<td>Both</td>
<td>rs17454</td>
<td>Distribution of FADS genotype and PUFA in incident CHD cases and controls at follow-up</td>
<td>rs174547 major allele was associated with increased plasma levels of AA, EPA and DHA and increased desaturase activity, but not with CHD risk. High baseline desaturase activity was associated with reduced CHD risk ($P$ for trend = 0.02), especially among those carrying the major allele (HR 95% CI = 0.35 (0.15, 0.81) for comparing the extreme quintiles)</td>
</tr>
<tr>
<td>Freemantle et al. (55)</td>
<td>n 61</td>
<td>18-58 years</td>
<td>Male</td>
<td>rs174546, rs174548, rs174549, rs174555</td>
<td>Fatty acid composition in cortical brain tissue</td>
<td>Association of the minor haplotype with estimated fatty acid desaturase activity ($P$ = 0.04). No significant association of the impact of variants on expression and alternative transcripts of FADS1 and FADS2. Significant interaction between haplotype and age on LA and AA</td>
</tr>
<tr>
<td>Song et al. (37)</td>
<td>n 249 ACS cases, n 240 controls</td>
<td>62.5 (20.4 years)</td>
<td>Both</td>
<td>rs174556, rs174617</td>
<td>Distribution of FADS genotype in ACS cases and controls</td>
<td>The frequency of rs174556 minor allele was higher in the case group than the control group ($P$ = 0.036)</td>
</tr>
<tr>
<td>Li et al. (28)</td>
<td>n 505 CAD cases, n 510 controls</td>
<td>33-85 years</td>
<td>Both</td>
<td>rs174460, rs174537, rs174550, rs174611, rs174616</td>
<td>Plasma fatty acids</td>
<td>D6D activity (AA/LA), was higher in CAD patients ($P$ &lt; 0.001). rs174537 minor allele associated with lower risk of CAD (OR 0.743, 95% CI (0.624, 0.884), $P$ = 0.001). Carriers of the rs174460 minor allele were associated with a higher risk of CAD (OR 1.357, 95% CI (1.106, 1.665), $P$ = 0.003). rs174537 showed strongest association; minor allele did not show the age-associated increases in AA ($P$ = 0.022) and D5D activity ($P$ = 0.007) seen with the rs174537 major genotype</td>
</tr>
<tr>
<td>Hong et al. (56)</td>
<td>n 122</td>
<td>35-59 years</td>
<td>Male</td>
<td>rs1000778, rs174537, rs174575, rs2727270</td>
<td>Serum phospholipid PUFA, oxidative stress markers over 3 years</td>
<td>rs174537 showed strongest association; minor allele did not show the age-associated increases in AA ($P$ = 0.022) and D5D activity ($P$ = 0.007) seen with the rs174537 major genotype</td>
</tr>
<tr>
<td>Roke et al. (57)</td>
<td>n 878</td>
<td>20-29 years</td>
<td>Both</td>
<td>Nineteen SNP were genotyped in all subjects and six (rs174579, rs174593, rs174626, rs526126, rs988567 and rs17831757) were further analysed</td>
<td>Plasma fatty acids and hs-CRP</td>
<td>All six SNP that were further analysed significantly associated with AA levels and desaturase indices. Inverse association between FADS1 desaturase index and hs-CRP ($P$ = 4.41 × 10^-6)</td>
</tr>
<tr>
<td>Hester et al. (58)</td>
<td>n 30</td>
<td>21-65 years</td>
<td>Female</td>
<td>rs174537</td>
<td>Serum fatty acids. Eicosanoids: leukotriene, HETE, PG and thromboxane biosynthesis in stimulated whole blood</td>
<td>Associations between rs174537 and desaturase activity ($P$ = 0.035), leukotriene B4 ($P$ = 0.001), and 5-HETE ($P$ = 0.048)</td>
</tr>
<tr>
<td>Wang et al. (26)</td>
<td>n 154</td>
<td>No data</td>
<td>Both</td>
<td>rs1535, rs102275, rs174537, rs174546, rs174556, rs174576</td>
<td>Hepatic lipid composition</td>
<td>Minor alleles associated with the accumulation of VLCFA, increased ratios between the more saturated and relatively less saturated forms of VLCFA and increased total hepatic fat content ($P$ &lt; 0.05)</td>
</tr>
</tbody>
</table>
Horiguchi et al. (56) n 124 ≥65 years Both rs17454 Erythrocyte membrane and plasma phospholipid LCPUFA rs174547 minor allele associated with lower AA and higher LA levels in erythrocyte membrane and plasma phospholipid (P < 0.001)

Vattinen et al. (55) n 89 at baseline and n 64 at follow-up 46.3 (8.8 years) Both rs174547, rs174616 Surgery-induced weight loss, Adipose tissue fatty acids and inflammation (IL-1 and NFκB) SNP associated with estimated desaturase activity at baseline and follow-up (P < 0.006) and adipose tissue inflammation at follow-up (P < 0.03)

Li et al. (56) n 872 59.3 (10.8 years) Both rs174450, rs174616 Plasma fatty acid and lipid composition T2D, CAD, both T2D and CAD, compared with healthy controls T2D patients with rs174537 major allele were at risk of developing T2D and CAD (OR 1.763; 95% CI 1.143, 2.718; P = 0.010), with elevated plasma LDL-C, AA, and desaturase activity

Schuchardt et al. (60) n 111 69 (7.6, 50–80 years) Both rs1535, rs174546, rs174449, rs174455, rs174574, rs174575, rs174576, rs174578, rs174579, rs526126, rs3834458 Erythrocyte membrane LC-PUFA Minor allele carriers of several SNP had higher LA and αLNA, lower AA levels in erythrocyte membranes compared with the major allele carriers (P < 0.001)

AA, arachidonic acid; LA, linoleic acid; αLNA, alpha-linolenic acid; MI, myocardial infarction; CAD, coronary artery disease; hs-CRP, high sensitivity C-reactive protein; EDA, eicosadienoic acid; LD, linkage disequilibrium; D6D, Δ-6-desaturase; D5D, Δ-5-desaturase; DGLA, dihomo-γ-linolenic acid; HR, hazard ratio; ACS, acute coronary syndrome; VLCFA, very long-chained fatty acids; T2D, type 2 diabetes.

Table 2. Genome wide association studies: associations between fatty acid desaturase SNP and fatty acid status and cardiovascular health

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Age (mean (SD or range))</th>
<th>Sex</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gieger et al. (61)</td>
<td>n 284</td>
<td>35–79 years</td>
<td>Male</td>
<td>363 metabolites in serum and blood lipids</td>
<td>Association between rs174548 and PC C36:4 (P = 4.52 × 10⁻⁶) and D5D product-substrate ratio (P = 2.4 × 10⁻²²)</td>
</tr>
<tr>
<td>Tanaka et al. (62)</td>
<td>n 1210 + 1076 (replication)</td>
<td>12–102 years</td>
<td>Both</td>
<td>Fatty acids in plasma and lipids</td>
<td>Associations between rs174537 and AA (P = 5.95 × 10⁻⁴⁶), TC (P = 2.7 × 10⁻³), LDL-C (P = 1.1 × 10⁻⁴)</td>
</tr>
<tr>
<td>Aulchenko et al. (28)</td>
<td>n 17797–22 562</td>
<td>18–104 years</td>
<td>Both</td>
<td>Blood lipid parameters</td>
<td>Associations between rs174570 and TC (P = 1.5 × 10⁻¹⁸) and LDL-C (P = 4.4 × 10⁻¹³)</td>
</tr>
<tr>
<td>Sabatti et al. (21)</td>
<td>n 4763</td>
<td>31 years</td>
<td>Both</td>
<td>Metabolic traits (TAG, cholesterol, etc.)</td>
<td>Associations between rs174546, rs10275, rs174537, rs174548, rs174449, rs174555, rs174574, rs174575, rs174576, rs174578, rs174579, rs526126, rs3834458</td>
</tr>
<tr>
<td>Kathiresan et al. (63)</td>
<td>n 19840 + 22 562 (replication)</td>
<td>All ages</td>
<td>Both</td>
<td>Blood lipid parameters</td>
<td>Associations between rs174547 and TAG (P = 2.0 × 10⁻¹⁴) and HDL-C (P = 2.0 × 10⁻¹⁰)</td>
</tr>
<tr>
<td>Ameur et al. (25)</td>
<td>Genome-wide genotyping (n 5652) and targeted resequencing (n 960) five European population cohorts</td>
<td>All ages</td>
<td>Both</td>
<td>Fatty acid in blood phospholipid</td>
<td>FADS haplotype associated with lower levels of LA (P = 0.052) and αLNA (P = 0.024) and higher levels of EPA (P = 1.1 × 10⁻⁴), GLA (P = 1.3 × 10⁻¹⁸), DHA (P = 8.3 × 10⁻⁵) and AA (P = 5.2 × 10⁻¹⁸)</td>
</tr>
<tr>
<td>Guan et al. (64)</td>
<td>n 8631</td>
<td>60.3 years</td>
<td>Both</td>
<td>Plasma n-6 PUFA composition</td>
<td>FADS cluster associated with LA, AA, GLA, DGLA and arachid acid</td>
</tr>
<tr>
<td>Mozaffarian et al. (63)</td>
<td>n 8013</td>
<td>45.6 (3.4–75.0 (5–1 years)</td>
<td>Both</td>
<td>Phospholipid trans-fatty acids</td>
<td>Thirty-one FADS SNP associated with cis/trans-LA. No significant association was identified for other TFA</td>
</tr>
</tbody>
</table>

PC, phosphatidylcholine; D5D, Δ-5-desaturase; AA, arachidonic acid; TC, total cholesterol; LA, linoleic acid; αLNA, alpha-linolenic acid; GLA, γ-linolenic acid; DGLA, dihomo-γ-linolenic acid; TFA, trans-fatty acid. Impact of FADS genotype on fatty acid status and cardiovascular health in adults.
Table 3. Diet–gene interactions: impact of dietary intakes/interventions on associations between fatty acid desaturase genotype and fatty acid status and cardiovascular health

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Age (mean (SD or range))</th>
<th>Sex</th>
<th>SNP</th>
<th>Intakes/intervention</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al. (66)</td>
<td>n 3575</td>
<td>46.7 (9-8 years)</td>
<td>Both</td>
<td>rs174546, rs174570, rs482548</td>
<td>Dietary intakes of n-3 and n-6 PUFA</td>
<td>Plasma TC, HDL-C, and non-HDL-C</td>
<td>rs174546 major allele associated with high TC and non-HDL-C in high n-3 PUFA group (≥0.51 % of total energy; P = 0.006 and 0.047, respectively) and with high HDL-C in the group with a high intake of n-6 PUFA (≥0.26 % of total energy, P = 0.004)</td>
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<tr>
<td>Hellstrand et al. (38)</td>
<td>n 4635</td>
<td>45–68 years</td>
<td>Both</td>
<td>rs174547</td>
<td>PUFA intakes</td>
<td>Blood lipids concentrations</td>
<td>rs174547 minor allele associated with lower LDL-C (P = 0.03) and with lower LDL-C in the lowest tertile of LC n-3 PUFA intake (P &lt; 0.001). An interaction was observed between rs174547 and the ratio of αLNA and LA intakes on HDL-C (P = 0.03)</td>
</tr>
<tr>
<td>Cormier et al. (67)</td>
<td>n 208</td>
<td>18–50 years</td>
<td>Both</td>
<td>rs174448, rs174456, rs174546, rs174570, rs174579, rs174602, rs174611, rs174616, rs174627, rs482548, rs48793, rs968567, rs2072114, rs2845573, rs7394871, rs7935946, rs7942717, rs12807005, rs74823126</td>
<td>3 g/d supplement of n-3 PUFA for 6 weeks</td>
<td>Blood lipid concentrations</td>
<td>SNP rs174546 was associated (P = 0.02) with TAG, pre- and post-supplementation; no significant genotype by supplementation interaction was observed</td>
</tr>
<tr>
<td>Gillingham et al. (40)</td>
<td>n 36</td>
<td>18–65 years</td>
<td>Both</td>
<td>rs174537, rs174545, rs174561, rs174583, rs953413</td>
<td>Three isoenergetic diets with either 20·6, 2·4 or 1·3 g αLNA/d for 4 weeks</td>
<td>Plasma fatty acids and 13C-labelled αLNA (at 0, 24 and 48 h) in hyper-lipidaemic subjects</td>
<td>20·6 g αLNA/d increased (P &lt; 0.001) plasma αLNA, EPA and DPA. At 24 and 48 h, 13C-labelled αLNA recovered as plasma 13C-EPA and 13C-DPA were lower (P &lt; 0.001) after the 20·6 g αLNA/d diet. Minor allele homozygotes of rs174545, rs174583, rs174561 and rs174537 had lower (P &lt; 0.05) plasma EPA, AA and desaturase ratio compositions, and lower (P &lt; 0.05) plasma 13C-EPA enrichment at 24 and 48 h in comparison with carriers of the major allele after all diets</td>
</tr>
<tr>
<td>Al-Hilal et al. (68)</td>
<td>n 310</td>
<td>45–70 years</td>
<td>Both</td>
<td>rs174537, rs174561, rs3834458</td>
<td>Supplementation with EPA and DHA at three doses (0·45, 0·9 and 1·8 g/d)</td>
<td>LC-PUFA and desaturase activities estimated in plasma and erythrocytes</td>
<td>Minor alleles associated with decreased desaturase activities of (5·84 × 10−10 ≤ P ≤ 4·2 × 10−7). Interaction of rs174537 genotype with treatment was a determinant of desaturase activity estimated in plasma (P = 0.05)</td>
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<tr>
<td>Study</td>
<td>n</td>
<td>Age (years)</td>
<td>Gender</td>
<td>rs IDs</td>
<td>Intervention</td>
<td>Enrichment</td>
<td>Outcomes</td>
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<tr>
<td>-----------------------</td>
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<tr>
<td>Porenta et al.</td>
<td>108</td>
<td>53.0 (11.6)</td>
<td>Both</td>
<td>rs174537, rs174556, rs174561, rs3834458</td>
<td>Mediterranean diet intervention for 6 months</td>
<td>Fatty acids in serum and colonic mucosa in those at increased risk of colon cancer</td>
<td>No diet by genotype effect of the intervention on serum fatty acid status. Significant diet by genotype interaction for AA in the colon; subjects with all major alleles for FADS SNP and were following the Mediterranean diet had 16% lower AA compared with control subjects. Minor allele carriers for both SNP had greater increases in erythrocyte EPA following supplementation ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Roke &amp; Mutch</td>
<td>12</td>
<td>18-25</td>
<td>Male</td>
<td>rs174537, rs174576</td>
<td>12-week fish-oil supplementation, providing 1200 mg EPA and 600 mg DHA/d</td>
<td>FA levels in serum and erythrocytes. TAG, TC, LDL-C, HDL-C, glucose, insulin, HbA1c and hs-CRP</td>
<td>Impact of FADS genotype on fatty acid status and cardiovascular health in adults</td>
</tr>
<tr>
<td>Hellstrand et al.</td>
<td>24032</td>
<td>44-74</td>
<td>Both</td>
<td>rs174546</td>
<td>PUFA intakes</td>
<td>CVD incidence</td>
<td>αLNA:LA intake ratio inversely associated with CVD risk minor allele (HR for quintile 5 v. quintile 1 = 0.72; 95% CI 0.50, 1.04; $P$-trend = 0.049). Interaction between αLNA and rs174546 and ischaemic stroke incidence ($P = 0.03$); αLNA was inversely associated with ischaemic stroke only among minor allele carriers (HR for quintile 5 v. quintile 1 = 0.50; 95% CI 0.27, 0.94; $P$-trend = 0.02)</td>
</tr>
<tr>
<td>Cormier et al.</td>
<td>208</td>
<td>18-50</td>
<td>Both</td>
<td>rs174448, rs174456, rs174546, rs174570, rs174579, rs174602, rs174611, rs174616, rs174627, rs482548, rs498793, rs968567, rs2072114, rs2845573, rs7394871, rs7935946, rs7942717, rs12807005, rs74823126</td>
<td>3 g/d supplement of n-3 PUFA for 6 weeks</td>
<td>Estimated desaturase activities</td>
<td>Desaturase indexes were significantly different following the 6-week n-3 supplementation. The index of D5D activity increased by 25.7 (28.8%) ($P &lt; 0.0001$), whereas the index of D6D activity decreased by 17.7 (18.2%) ($P &lt; 0.0001$) post supplementation</td>
</tr>
</tbody>
</table>

TC, total cholesterol; LC, long chained; αLNA, alpha-linolenic acid; LA, linoleic acid; DPA, docosapentaenoic acid; hs-CRP, high sensitivity C-reactive protein; HR, hazard ratio; D5D, Δ-5-desaturase; D6D, Δ-6-desaturase; LDL-C, LDL-cholesterol.
**FADS** rs174547 minor allele was associated with lower LDL-cholesterol among individuals in the lowest tertile of LC n-3 PUFA intakes. A significant interaction between rs174547 and the ratio of aLNA and LA intakes on HDL-C was also observed. More recently, a 14-year follow-up in 24,032 participants reported that the aLNA:LA intake ratio was inversely associated with CVD risk only among participants homozygous for the rs174547 minor allele. aLNA intakes were also inversely associated with ischaemic stroke in this genotype group. In addition to observational analysis, the impact of **FADS** variants on response to LC-PUFA supplementation has also been examined. Gillingham et al. carried out a randomised crossover trial in thirty-six hyperlipidemic subjects in which three diets (enriched with flaxseed oil or high-oleic acid canola oil compared with a typical Western diet) were consumed for 4 weeks and five **FADS** SNP were analysed. Subjects with minor allele variants (rs174545, rs174583, rs174561, rs174537) had decreased desaturase activity, but an increase in aLNA intake resulted in greater increases in plasma EPA than in major allele homozygotes consuming aLNA intakes typical of a Western diet. Cormier et al. conducted a study in 208 subjects examining the impact of fish-oil supplementation (1·9–2·2 g/d EPA and 1·1 g/d DHA) for 6 weeks and nineteen **FADS** SNP on plasma TAG and reported that rs174546 was associated with TAG, but no significant genotype by supplementation interaction was observed. In terms of whole-diet interventions, one study to date has examined the interaction of **FADS** genotype and the Mediterranean diet on serum and colonic fatty acid profiles. In a 6-month intervention (n 108) and genotyping for four **FADS** SNP, a significant diet by genotype interaction for AA concentrations in the colon was observed; subjects with **FADS** major alleles following the Mediterranean diet had 18 % lower AA concentrations than subjects on the control diet (healthy eating diet) There were no significant diets by genotype interactions for other colonic or serum fatty acids. Overall, it is clear that further research is necessary to determine the potential of the diet, particularly dietary fatty acids, to modify the relationship between the **FADS** genotype and fatty acid status. An investigation of diet composition × **FADS** genotype × fatty acid status represents a secondary objective of the recently completed NU-AGE intervention.

**NU-AGE: a focus on older adults**

The NU-AGE (New dietary strategies addressing the specific needs of the elderly population for healthy ageing in Europe) study investigated the impact of a whole-diet intervention on markers of chronic inflammation in older adults (aged 65–79 years). The NU-AGE recommendations for the consumption of oily fish, as well as the provision of an aLNA-rich spread, aimed to increase total n-3 PUFA intakes and the dietary n-6 : n-3 PUFA ratio of study participants. As previously discussed, although a small number of dietary interventions have been shown to modify the relationship between the **FADS** genotype and PUFA status, none have examined the impact of a 1-year whole-diet (including significant fatty acid manipulation) intervention in older adults, a group who are likely to be in a higher state of chronic inflammation and CVD risk relative to healthy general adult population. Therefore, we aim to examine whether the NU-AGE diet could influence the relationship between the **FADS** genotype and plasma PUFA status in our study population. Specifically, we wish to establish if the NU-AGE diet can overcome any identified negative impacts of **FADS** minor alleles on EPA and DHA status, as well as the potential negative effect that the major allele has on AA status. We will also examine the interactive impact of diet and **FADS** genotype on CVD risk biomarkers, including inflammatory and plasma lipid status and measures of vascular function and arterial stiffness.

**Conclusion**

Current estimates indicate that for most countries, average population intakes of EPA and DHA are 0·2 g/d, and <0·05 g/d in non-fish consumers. In this latter large population subgroup, the efficacy of endogenous synthesis from aLNA determines the tissue EPA and DHA status. A comprehensive understanding of the determinants of the regulation of the desaturation and elongation pathway is lacking. Although common **FADS** variants have been consistently associated with LC-PUFA status, the exact size of the effect is relatively unquantified and the **FADS** functional gene variant(s) has not been identified. A recent study by Li et al. (described in Table 1) reported a difference of 8·3 % in plasma EPA and DHA combined between those homozygous for the major allele and those homozygous for the minor allele of the rs174537 **FADS** genotype. This is clinically significant as previous research, which showed that EPA and DHA status was associated with sudden cardiac death in US males, reported 90 % lower blood EPA and DHA concentrations in the sudden death group compared with controls. Modest dietary intakes of EPA and DHA could overcome this genotype effect; supplementation of 300 mg EPA and DHA or 90 g salmon per week has been shown to increase combined plasma EPA plus DHA by about 30 %. The mechanistic basis of the relationship between the **FADS** genotype and LC n-3 PUFA interactions are also poorly understood. The impact of **FADS** genotype on PUFA status should be carefully considered when using plasma and tissue EPA and DHA concentrations as biomarkers of dietary EPA and DHA exposure in randomised controlled trials and epidemiological studies, with a greater contribution of endogenously synthesised EPA, and to a lesser extent DHA, to the total pool likely in **FADS** major allele carriers. Furthermore, **FADS** genotype could contribute to future stratification and targeting of dietary advice with additional EPA and DHA intakes recommended for those carrying the **FADS** minor allele.
Acknowledgement

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Conflict of Interest

None.

Authorship

C. M. O. N. drafted the outline of the manuscript, conducted the literature search and drafted the manuscript. A. M. M. was responsible for critically reviewing the manuscript. All authors read and approved the final manuscript before submission.

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56. Horiguchi S, Nakayama K, Iwamoto S et al. (2016) Associations between a fatty acid desaturase gene polymorphism and blood arachidonic acid compositions in


