British Journal of Nutrition (2024), 132, 1423–1432 doi:10.1017/S0007114524001624

Effects of the rs174575 single nucleotide polymorphism in FADS2 on levels of long-chain PUFA: a meta-analysis

Motong Liu, Yanyan Wu, Song Ni, Jiayu Gong, Yifei Chen, Yuan He, Shutong Chen, Haitao Yu and Lin Xie*

Department of Nutrition and Food Hygiene, School of Public Health, Jilin University, Changchun 130021, Jilin Province, People's Republic of China

(Submitted 2 January 2024 – Final revision received 26 July 2024 – Accepted 3 August 2024 – First published online 11 November 2024)

Abstract

The influence of the SNP rs174575 (C/G) within the fatty acid desaturase 2 gene on the levels of long-chain PUFA was determined through statistical meta-analysis. Six databases were searched to retrieve the relevant literature. Original data were analysed using Stata 17·0, encompassing summary statistics, tests for heterogeneity, assessment of publication bias, subgroup analysis and sensitivity analysis. A total of ten studies were identified and grouped into twelve trials. Our results showed that individuals who carried the minor G allele of rs174575 had significantly higher dihomo-γ-linolenic acid levels ($P = 0·005$) and lower arachidonic acid levels ($P = 0·033$) than individuals who were homozygous for the major allele. The subgroup analysis revealed that the G-allele carriers of rs174575 were significantly positively correlated with linoleic acid ($P = 0·002$) and dihomo-γ-linolenic acid ($P < 0·001$) and negatively correlated with arachidonic acid ($P = 0·004$) in the European populations group. This particular SNP showed a potential association with higher concentrations of dihomo-γ-linolenic acid ($P = 0·050$) and lower concentrations of arachidonic acid ($P = 0·030$) within the breast milk group. This meta-analysis has been registered in the PROSPERO database (ID: CRD42023470562).

Keywords: **LC-PUFA: FADS2 gene: SNP: Meta-analysis**

Long-chain PUFA (LC-PUFA) are essential nutrients for human brain development and neurotransmitter functions. These fatty acids (FA) are involved in various physiological processes, including the formation and maintenance of cell membranes, neuronal signalling, and regulation of inflammation. Notably, LC-PUFA such as docosahexaenoic acid (DHA) and arachidonic acid (ARA) are particularly important during critical periods of brain growth and development, including fetal development and early childhood[1,2]. The LC-PUFA content in the blood and other tissues is closely associated with a number of health conditions, including cardiovascular diseases and psychiatric disorders[3–5]. An adequate intake and balanced levels of LC-PUFA are crucial for promoting optimal cognitive function and maintaining overall brain health throughout life.

Notably, PUFA are mainly classified as *n*-3 and *n*-6 FAs, and α-linolenic acid (ALA) and linoleic acid (LA) have been identified as their precursors; therefore, LA and ALA are considered essential FAs (EFA)[6]. The EFA are obtained from the diet because they cannot be manufactured by cells (double bonds can be introduced into all positions of the fatty acid chain, except at the *n*-3 and *n*-6 positions). Notably, ALA is an *n*-3 fatty acid that is converted to EPA, EPA is converted to docosapentaenoic acid (DPA) and then to DHA. Whereas, LA is the parent fatty acid of the *n*-6 FA class. Notably, LA is converted to γ-linoleic acid (GLA), which is further converted to arachidonic acid (AA), a precursor of several classes of eicosanoids. In the nervous system, cell membranes contain relatively high concentrations of PUFA, such as DHA[7].

Furthermore, the same enzyme desaturates and elongates both the *n*-3 and *n*-6 pathways[8]. The synthesis process involves a series of elongation and desaturation steps catalysed by fatty acid desaturases (FADS) and requires a sequential series of desaturations with FADS[8–10]. Notably, FADS family members (FADS) play key roles in the conservation of the dynamic balance of FAs[11]. Mammalian FADS include FADS1, FADS2, FADS3, FADS4, FADS5, FADS6, FADS7 (DEGS1) and FADS8 (DEGS2)[12]. The human body can synthesis various LC-PUFA using FADS1 known as Δ5-fatty acid desaturases (D5D), FADS2

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; D5D, Δ5-fatty acid desaturases; D6D, Δ6-fatty acid desaturases; DGLA, dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; DTA, docosatetraenoic acid; EDA, eicosadienoic acid; EFA, essential fatty acids; FA, fatty acids; FADS, fatty acid desaturase; GLA, γ-linoleic acid; LA, linoleic acid; LC-PUFA, long-chain PUFA.

* **Corresponding author**: Lin Xie, email xielin@jlu.edu.cn

known as Δ6-fatty acid desaturases (D6D) and elongase[13]. Therefore, genetic variation in FADS appears to be important for modulating LC-PUFA status.

Evidence from epidemiological and observational studies supports the association between LC-PUFA synthesis and genetic variations in the FADS cluster located on chromosome 11 (11q12-q13·1)[14–19]. For instance, FADS2 expression is determined by the FADS2 gene, which is located on chromosome 11q12-q13·1. SNP in FADS2 can affect PUFA production, which can subsequently affect LC-PUFA levels[20]. Cribb found that LA and ALA are associated with major depressive disorder and are potentially modulated by genetic variations in the FADS gene cluster[17]. Observations indicate that the FADS genotypes of both mothers and children were associated with LC-PUFA concentrations in the cord[19]. In addition, rs174575 is situated in the promoter region of the FADS2 gene. These studies specifically focused on the effect of the rs174575 SNP in FADS2 on LC-PUFA levels. In this study, we conducted a comprehensive meta-analysis to investigate the effects of the rs174575 SNP in FADS2 on LC-PUFA levels.

This meta-analysis has been registered on PROSPERO (ID: CRD42023470562).

Methods

Literature retrieval

Keywords such as PUFA, SNP, FADS2 and rs174575 were used to search six databases (China National Knowledge Infrastructure, PubMed, Web of Science, Science Direct, EMBASE and Scopus) published in English and Chinese before 15 July 2024. In total, 3570 articles were retrieved from the searches.

Assessment of eligibility

Studies were suggested to be eligible if they meet the following inclusion criteria:

(1) Reported in Chinese or English

(2) Available in full text with access to the necessary materials and data from the authors and

(3) Had good design quality.

Studies were excluded if they were

(1) Duplicate releases

(2) Reviews, meta-analysis, animal/plant/cell studies, abstracts, commentaries, case reports or editorials; and

(3) Contained missing data that had not been presented in the literature and could not be obtained from the authors of the published studies.

Data extraction and quality assessment

Literature quality was assessed using the Newcastle-Ottawa scale[21], which was developed to assess the quality of non-randomised studies based on three broad perspectives: selection of the study group (four items), comparability of groups (two items) and ascertainment of either exposure or outcome (two items). The total Newcastle-Ottawa scale score ranges from zero to eight, based on the assessment items. Studies with a score of six were considered to have high methodological quality.

The author, year of publication, measurement method, genotypes, tissue type, country, age, sample size and LC-PUFA content were extracted from the included studies. Two groups (CC and CG + GG) were formed from the three genotypes (CC, CG and GG). Two reviewers independently extracted data from the included studies, and any disagreements were discussed and resolved.

Statistical analysis

Meta-analysis was performed using Stata 17.0. Effect indices of each study were calculated as standardised mean difference (SMD) and 95 % CI. The heterogeneity of the included studies was assessed using the I^2 test. If I^2 was ≤ 50 %, a fixed effects model was used, otherwise a random effects model was used. Publication bias was assessed using funnel plots and Egger's and Begg's tests, and statistical significance was set at $P < 0{\cdot}05$. In addition, sensitivity analysis was performed by excluding one study at a time (online Supplementary Figure 1). A subgroup analysis was used to assess the heterogeneity of the studies. Subgroup analyses were performed according to the regions, tissues, and quality scores of the studies.

Result

Literature description

Literature search. Figure 1 illustrates the selection process implemented according to our literature search strategy. Finally, ten articles[7,14,16,17,19,22–26] were selected for the meta-analysis.

Study characteristics. The characteristics of the included studies are presented in Table 1. Twelve studies were extracted from the ten articles (one article simultaneously focused on plasma and breast milk and another had two cohorts of normal weight and overweight). A total of 3048 participants, representing different ethnic populations from ten countries, were included in the analysis.

Quality assessment. The methodological quality of the studies evaluated was based on the Newcastle-Ottawa scale, and all evaluated studies showed a high level of methodological quality.

Meta-analysis results

Effects of rs174575 gene variations on the n-6 *PUFA levels.* The effects of rs174575 on the AA levels are shown in Fig. 2(a). The AA levels were significantly lower in minor G allele carriers than in the CC genotype group (SMD: –0·7, 95 % CI (–1·3, –0·1), $P = 0{\cdot}033$), and significant heterogeneity ($I^2 = 98{\cdot}1$ %, 95 % CI (87·7 %, 99·3 %), $P < 0{\cdot}001$) was observed.

The effects of rs174575 on DGLA levels are shown in Fig. 2(b). The DGLA levels were significantly higher in minor G allele carriers than in the CC genotype group (SMD: 0·6, 95 % CI (0·2, 1·0), $P = 0{\cdot}005$), and significant heterogeneity ($I^2 = 93{\cdot}0$ %, 95 % CI (56·4 %, 97·3 %), $P < 0{\cdot}001$) was observed.

The effects of rs174575 on DTA levels are shown in Fig. 2(c). The DTA levels were not significantly different between minor G allele carriers and the CC genotype group (SMD: –0·2, 95 % CI

British Journal of Nutrition

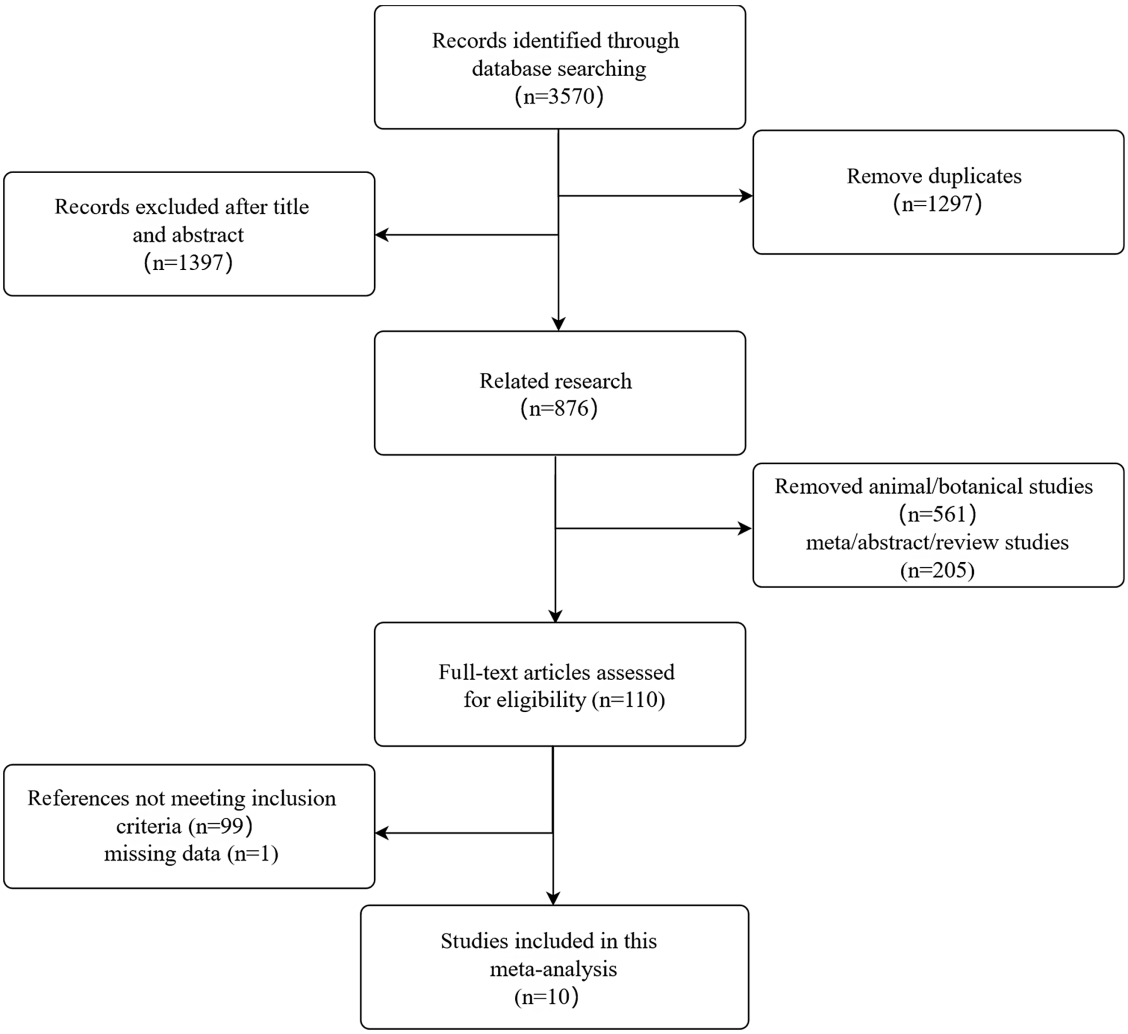

Fig. 1. Flow chart of the selection process of the literature search.

(–0·4, 0·0), $P = 0·050$), although heterogeneity ($I^2 = 68·2$ %, 95 % CI (0·0 %, 88·1 %), $P = 0·008$) was observed.

Effects of rs174575 gene variations on the n-3 PUFA levels. Figure 3 shows that the levels of ALA, DHA, DPA and EPA were not significantly different between minor G allele carriers and the CC genotype group, although significant heterogeneity was observed.

Effects of rs174575 in FADS2 on D5D levels. The effects of rs174575 on D5D levels are shown in Fig. 4. The D5D levels were not significantly different between minor G allele carriers and the CC genotype group (SMD: –1·6, 95 % CI (–3·6, 0·4), $P = 0·116$), although significant heterogeneity ($I^2 = 99·3$ %, 95 % CI (67·7 %, 99·8 %), $P < 0·001$) was observed.

Risk of bias evaluation

Online Supplementary Figure 2 shows funnel plots of the correlation between FADS2 rs174575 and PUFA levels. Judgements regarding the risk of bias for each included study are shown in Supplemental Table 4. There was no significant evidence that a publication bias affected the results.

Subgroup analysis

The results of the subgroup analyses are presented in Table 2. The LA levels in the minor G allele carriers were significantly higher than that in the CC genotype group in the European population ($I^2 = 41·4$ %, 95 % CI (0·0 %, 81·3 %), $P = 0·002$), erythrocyte ($I^2 = 0·0$ %, 95 % CI (0·0 %, 0·0 %), $P = 0·003$) and seven-score groups ($I^2 = 26·5$ %, 95 % CI (0·0 %, 71·6 %), $P = 0·001$). The DGLA levels in the minor G allele carriers were significantly higher than that in the CC genotype group in the European population ($I^2 = 65·0$ %, 95 % CI (0·0 %, 88·4 %), $P < 0·001$), plasma ($I^2 = 32·8$ %, 95 % CI (0·0 %, 81·9 %), $P = 0·001$), breast milk ($I^2 = 25·6$ %, 95 % CI (0·0 %, 79·9 %), $P = 0·050$) and the seven-score groups ($I^2 = 73·6$ %, 95 % CI (0·0 %, 90·1 %), $P = 0·001$). The DTA levels in the minor G allele carriers were significantly lower than that in the CC genotype group in the European population ($I^2 = 56·3$ %, 95 % CI (0·0 %, 88·2 %), $P = 0·001$) and seven-score groups ($I^2 = 63·5$ %, 95 % CI

Table 1. Characteristics of studies included in the meta-analysis

Year	Author	Genotyping methods	Genotype	PUFA detection methods	Tissues	Country	Number
2008	Xie et.al[22]	TaqMan SNP	C/G	GLC	Breast milk	Canada	54
2010	Moltó-Puigmartí Carolina et.al a[14]	TaqMan SNP	C/G	GC	Plasma	Netherlands	309
2010	Moltó-Puigmartí Carolina et.al b[14]	TaqMan SNP	C/G	GC	Breast milk	Netherlands	309
2011	Oh Yoen Kim et.al[14]	TaqMan SNP	C/G	GC	Plasma	Korea	567
2013	Laurine BS Harsløf et.al[16]	Real-time polymerase chain reaction genotyping	C/G	GC	RBC	Danish	401
2015	S.A. Scholtz et.al[7]	TaqMan SNP	C/G	GC	RBC	Kansas	205
2016	Zhen Ding et.al[24]	Sequenom Mass Array system	C/G	GC	Breast milk	China	204
2017	Meng-Chuan Huang et.al[25]	GenomeLabTM SNP stream	C/G	GC	Plasma	America	176
2017	Lachlan Cribb et.al[17]	Single base extension assays	C/G	GC	RBC	Caucasia	141
2017	Andrea de la Garza Puentes et.al a[26]	PCR amplification	C/G	GC	Plasma	Spain	40
2017	Andrea de la Garza Puentes et.al b[26]	PCR amplification	C/G	GC	Plasma	Spain	35
2021	Marie C Conway et.al[19]	TaqMan realtime PCR	C/G	GC	Plasma	Republic of Seychelles	916

C, major allele; G, minor allele.

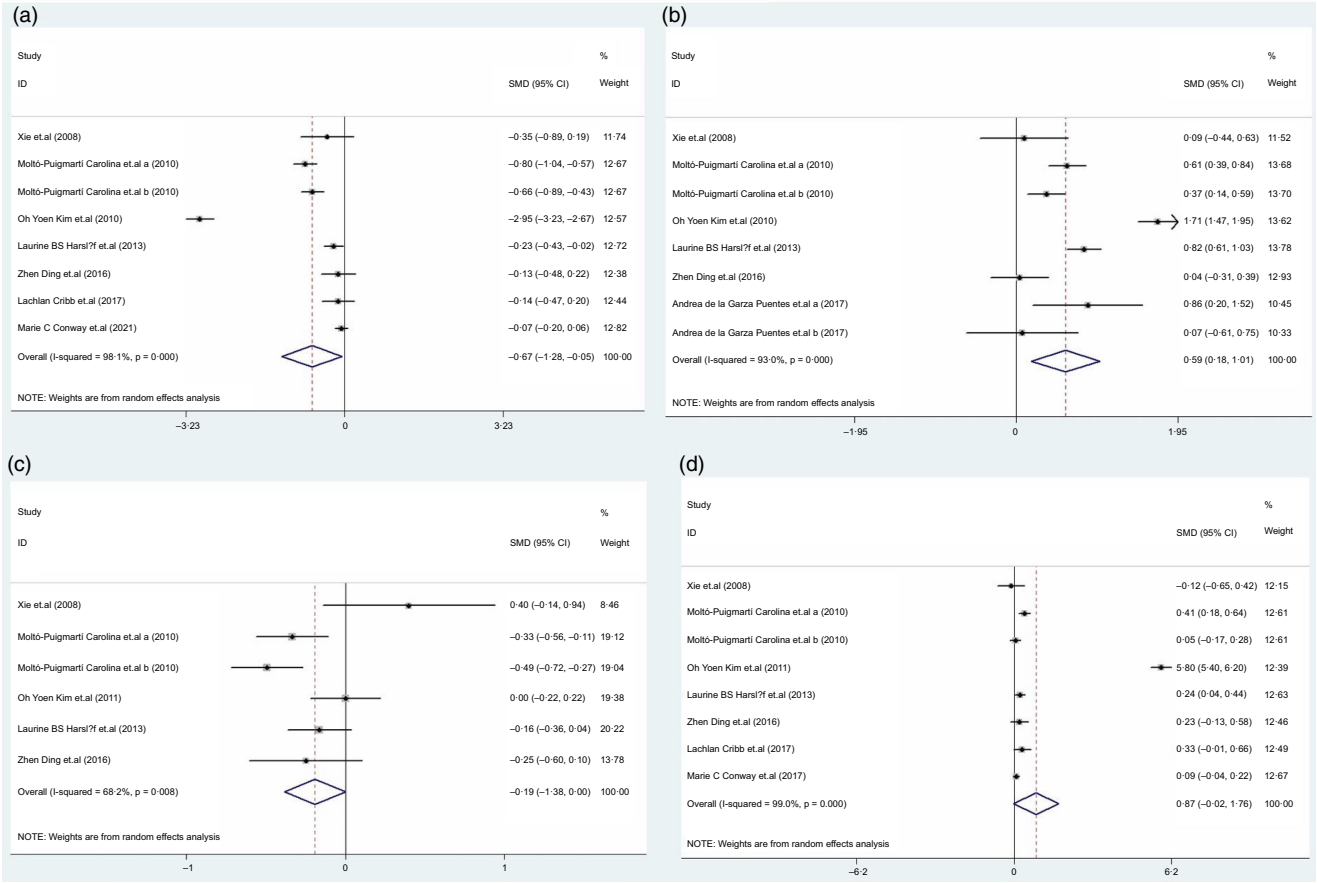

Fig. 2. Forest plots showing *n*-6 PUFA levels difference between minor G allele carriers and CC genotype of rs174575 in FADS2. (a) Forest plot of arachidonic acid (AA); (b) forest plot of dihomo-γ-linolenic acid (DGLA); (c) forest plot of docosatetraenoic acid (DTA); (d) forest plot of linoleic acid (LA).

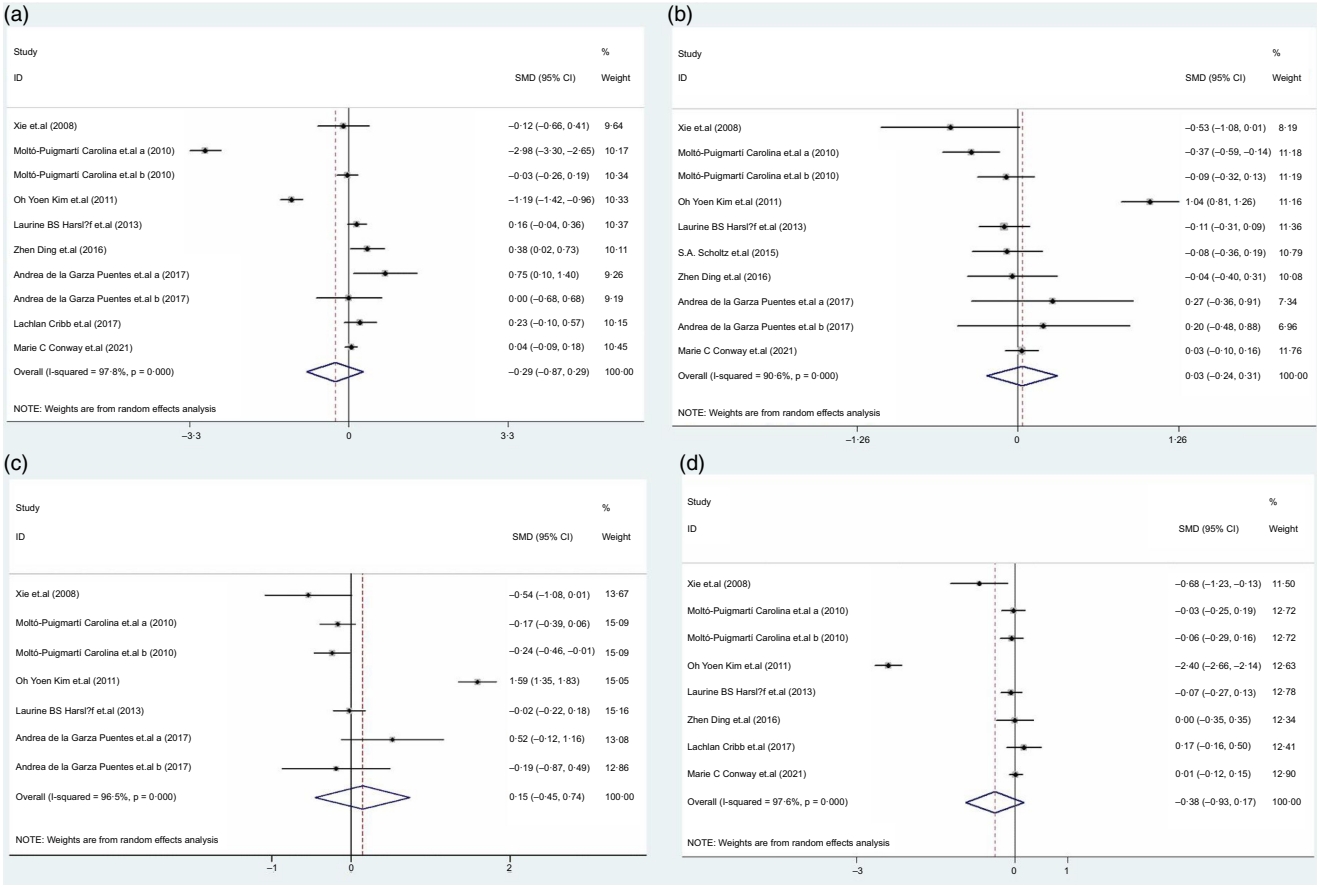

Fig. 3. Forest plots showing *n*-3 PUFA levels difference between minor G allele carriers and CC genotype of rs174575 in FADS2. (a) Forest plot of α-linolenic acid (ALA); (b) forest plot of docosahexaenoic acid (DHA); (c) forest plot of docosapentaenoic acid (DPA); (d) forest plot of eicosapentaenoic acid (EPA).

(0·0 %, 87·5 %), $P = 0·021$). The AA levels in the minor G allele carriers were significantly lower than that in the CC genotype group in the European population ($I^2 = 85·3$ %, 95 % CI (0·0 %, 95·3 %), $P = 0·004$), breast milk ($I^2 = 68·1$ %, 95 % CI (0·0 %, 91·7 %), $P = 0·030$), erythrocyte ($I^2 = 0·0$ %, 95 % CI (0·0 %, 5·9 %), $P = 0·022$) and seven-score groups ($I^2 = 78·8$ %, 95 % CI (0·0 %, 92·2 %), $P = 0·002$).

Discussion

In this meta-analysis, we evaluated the relationship between rs174575 in FADS2 and eight types of PUFA, as well as D5D activity. These assessments were conducted by pooling the results of ten studies.

The desaturation of LC-PUFA is derived from LA and ALA and is regulated by D5D and D6D[27]. We propose that SNP rs174575 affects the levels of DGLA and AA by altering the activity of certain desaturases in the pathway for the synthesis of LC-PUFA. In the common *n*-6 LC-PUFA pathway, D6D acts on LA, leading to GLA synthesis. This step is followed by elongation to DGLA and D5D conversion, resulting in AA production. We observed a lower rate of DGLA to AA conversion in these individuals, and the increased levels of DGLA and decreased levels of AA demonstrated lower D5D activity in the *n*-6 LC-PUFA synthesis pathway. The minor G allele of rs174575 has been associated with decreased D5D activity, leading to a decreased conversion rate of DGLA to AA and other *n*-6 PUFA. This effect is believed to be associated with loss of function. A meta-analysis of genome-wide association studies also provided new evidence for the genetic regulation of LC-PUFA by the FADS2 cluster, suggesting that the minor alleles of SNP rs174548 may reflect lower FADS1/2 activity, resulting in lower AA conversion[28]. Recent studies have shown that eicosadienoic acid (EDA) is associated with FADS2 and may modulate PUFA metabolism[29,30]. Furthermore, EDA is involved in the alternative AA synthesis pathways by the sequential action of a Δ8-fatty acid desaturases (D8D) and a D5D[31]. In addition to coding for D6D, FADS2 also influences D8D activity. Notably, D8D catalyses the conversion of EDA to DGLA, which is followed by a D5D conversion, resulting in AA production. Our results suggest that the rs174575 minor G allele is associated with increased D8D activity and improved DGLA conversion.

Our meta-analysis showed that minor G allele carriers of rs174575 had lower AA and higher DGLA levels than major CC allele homozygotes. In addition to a possible association with the minor G alleles of rs174575, which have been suggested to be associated with reduced D5D activity, this phenomenon may be explained by the fact that human tissues contain relatively high AA and DGLA (AA, 6·09 % and 0·44 % of total PUFA in

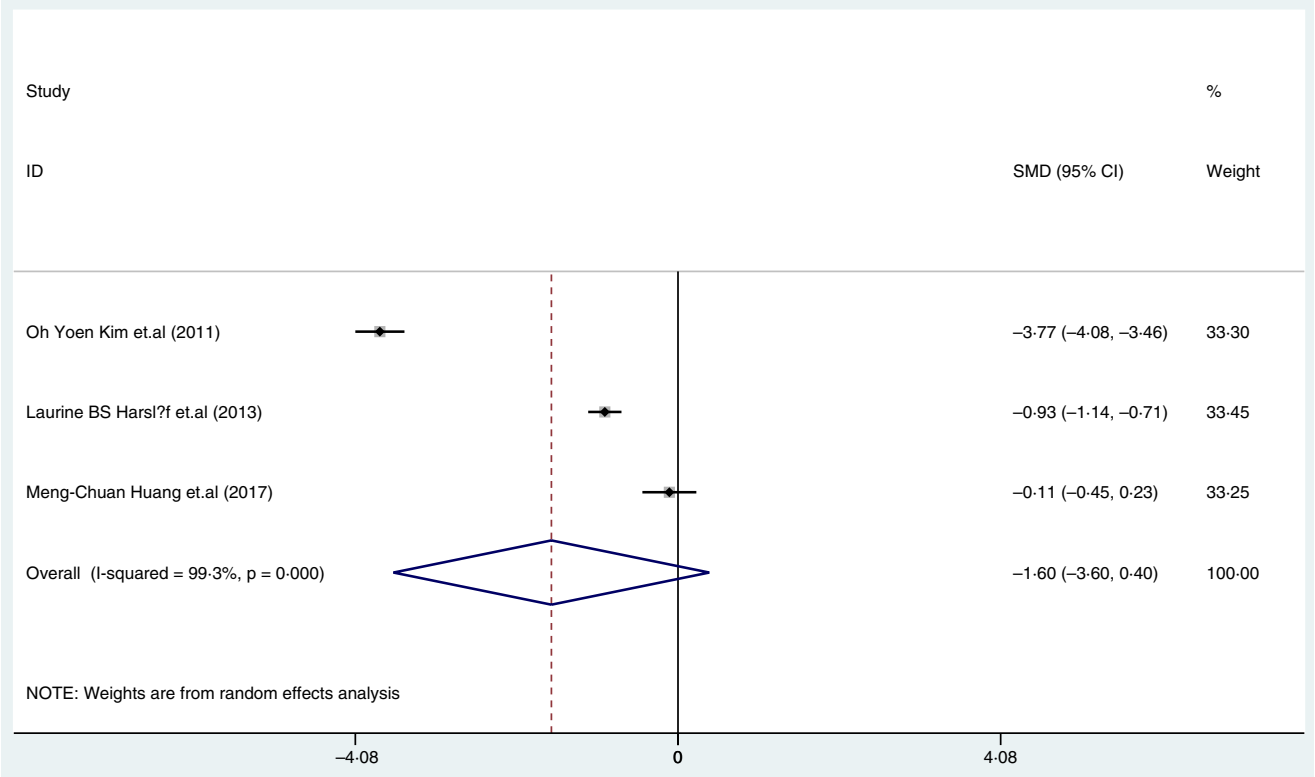

Fig. 4. Forest plot showing Δ5-desaturase (D5D) activity difference between minor G allele carriers and CC genotype of rs174575 in FADS.

erythrocytes and breast milk; DGLA, 1·38 % and 0·33 % of total PUFA in erythrocytes and breast milk)[32,33]. Because the normal AA and DGLA contents in blood and breast milk is high, the AA reduction and DGLA increase may be significant[34]. A single SNP in the FADS gene cluster has been suggested to have a greater tendency to affect *n*-6 PUFA than *n*-3 PUFA in breast milk, plasma and erythrocyte membranes across all age groups[1]. This may be explained by the fact that human tissues have a relatively higher *n*-6 PUFA content than *n*-3 PUFA. In contrast, some *n*-3 PUFA such as DHA and EPA originally existed in relatively low amounts in the tissues. Therefore, an accurate detection may be difficult. In addition, because of the wide range of *n*-3 PUFA levels among individuals, researchers often perform logarithmic transformations of *n*-3 PUFA levels. This may also have influenced the measurement of changes in *n*-3 PUFA levels.

A meta-analysis of genome-wide association studies found a significant positive direct effect of SNP rs174575 on weight during pregnancy. The rs174561 and rs174575 SNPs have direct adverse effects on plasma *n*-3 PUFA (EPA and ALA). Regarding the influence of SNPs on the plasma levels of PUFA, only rs174575 had positive direct effects on the plasma levels of ARA and the ARA/LA ratio of *n*-6 products. The rs3834458 SNP negatively affected the plasma concentrations of EPA[35]. Although these results were not entirely consistent with the results of our meta-analysis, they did indicate that in the presence of a mutation in the FADS2 SNP, the composition of the precursor and product FA were different. To date, few studies have explored the effects of dietary PUFA and FADS2 interactions, suggesting that the associated effects of SNP in FADS2 on LC-PUFA concentrations may be modified by dietary PUFA intake[36–38]. This suggests that LC-PUFA levels may also be influenced by dietary substrates. The balance between *n*-3 and *n*-6 PUFA is an important aspect of a healthy diet[39], with evidence suggesting that *n*-3 PUFA have anti-inflammatory properties and *n*-6 PUFA have pro-inflammatory properties[40–43]. However, another study suggested that a high intake of *n*-6 PUFA was not associated with an increase in inflammation in healthy men. Additionally, *n*-3 LC-PUFA are involved in inflammatory diseases[44]. Concomitant dietary patterns such as the Mediterranean diet, Nordic diet, Western diet, Chinese diet, or PUFA supplements may also change PUFA levels in different populations. Therefore, more research is needed to better understand the influence of dietary patterns on changes in PUFA levels in the minor G allele carriers of rs174575.

Due to the high heterogeneity observed, we performed a subgroup analysis by region, tissue, and study quality. We found that the level of heterogeneity has diminished in subgroup analyses and different regions, types of tissues and quality scores of the studies may contribute to the observed heterogeneity. In the region subgroup analysis, we found that carriers of the minor G allele had higher levels of LA and DGLA and lower AA levels in European populations than in the CC genotype group. Studies have shown ethnic discrepancies in the allele frequencies of FADS2[45,46]. Most of the studies included in the meta-analysis included European populations as the main participants, and fewer participants from other regions were included. This could have been a source of heterogeneity. We further divided the studies into subgroups based on plasma, erythrocyte, and breast

Table 2. Subgroup meta-analysis of the SNP rs174575 in FADS2 on the levels of LC-PUFA (Standardised mean difference, I^2 and 95 % confidence intervals)

		Region						Tissue						Quality of studies			
PUFAS		North America		Europe		Asia		Breast milk		Plasma		Erythrocytes		6		7	
LA	Trials	1		4		2		3		2		2		2		6	
	SMD (95 %CI)	−0·1	−0·7, 0·4	0·2	0·1, 0·4	3·0	−2·5, 8·5	0·1	−0·1, 0·3	0·2	−0·1, 0·5	0·3	0·1, 0·4	3·0	−2·7, 8·5	0·2	0·1, 0·4
	P	0·663		**0·002**		0·280		0·396		0·142		**0·003**		0·303		**0·001**	
	I^2 (95 %CI) (%)	0·0		41·4	0·0, 81·3	99·8	0·0, 100·0	0·0	0·0, 57·7	82·7	0·0, 96·6	0·0	0·0, 0·0	99·9	0·0, 100·0	26·5	0·0, 71·6
DGLA	Trials	1		5		2		3		3		1		1		7	
	SMD (95 %CI)	0·1	−0·4, 0·6	0·6	0·3, 0·8	0·9	0·2, 1·0	0·2	0·0, 0·4	0·6	0·2, 0·9	0·8	0·6, 1·0	1·7	1·5, 2·0	0·4	0·2, 0·7
	P	0·729		**<0·001**		0·292		**0·050**		**0·001**		<0·001		<0·001		**0·001**	
	I^2 (95 %CI) (%)	0·0		65·0	0·0, 88·4	98·3	0·0, 99·7	25·6	0·0, 79·9	32·8	0·0, 81·9	0·0		0·0		73·6	0·0, 90·1
DTA	Trials	1		3		2		3		1		1		1		5	
	SMD (95 %CI)	0·4	−0·1, 1·0	−0·3	−0·5, −0·1	−0·1	−0·3, 0·1	−0·2	−0·6, 0·3	−0·3	−0·6, −0·1	−0·2	−0·4, 0·0	0	−0·2, 0·2	−0·2	−0·4, −0·0
	P	0·149		**0·001**		0·474		0·440		0·004		0·111		1·000		**0·021**	
	I^2 (95 %CI) (%)	0·0		56·3	0·0, 88·2	27·1	0·0, 85·5	78·2	0·0, 94·4	0·0		0·0		0·0		63·5	0·0, 87·5
AA	Trials	1		4		2		3		2		2		2		6	
	SMD (95 %CI)	−0·4	−0·9, 0·2	−0·5	−0·8, −0·2	−1·5	−4·3, 1·2	−0·4	−0·8, −0·0	−0·4	−1·2, 0·3	−0·2	−0·4, −0·0	−1·5	−4·3, 1·3	−0·4	−0·7, −0·1
	P	0·198		**0·004**		0·274		**0·030**		0·238		**0·022**		0·295		**0·002**	
	I^2 (95 %CI) (%)	0·0		85·3	0·0, 95·3	99·3	93·3, 99·6	68·1	0·0, 91·7	96·5	0·0, 99·3	0·0	0·0, 5·9	99·7	0·0, 99·9	78·8	0·0, 92·2
EPA	Trials	1		4		2		3		2		2		2		6	
	SMD (95 %CI)	−0·7	−1·2, −0·1	−0·0	−0·1, 0·1	−1·2	−3·6, 1·2	−0·2	−0·5, 0·1	0·0	−0·1, 0·1	0·0	−0·2, 0·2	−1·2	−3·6, 1·2	−0·1	−0·1, 0·1
	P	0·015		0·635		0·316		0·284		0·965		0·917		0·324		0·428	
	I^2 (95 %CI) (%)	0·0		0·0	0·0, 42·8	99·1	0·0, 99·8	57·3	0·0, 88·8	0·0	0·0, 0·0	32·8	0·0, 86·6	99·6	0·0, 99·9	27·7	0·0, 72·1
DPA	Trials	1		5		1		2		3		1		1		6	
	SMD (95 %CI)	−0·5	−1·1, 0·0	−0·1	−0·3, 0·1	1·6	1·4, 1·8	−0·3	−0·5, −0·1	−0·0	−0·4, 0·4	−0·0	−0·2, 0·2	1·6	1·4, 1·9	−0·1	−0·3, 0·0
	P	0·053		0·211		<0·001		**0·008**		0·979		0·823		<0·001		0·122	
	I^2 (95 %CI) (%)	0·0		33·3	0·0, 76·6	0·0		0·0	0·0, 79·6	49·8	0·0, 86·7	0·0		0·0		39·2	0·0, 77·2
DHA	Trials	2		5		2		3		4		2		3		7	
	SMD (95 %CI)	−0·2	−0·7, 0·2	−0·1	−0·3, 0·0	0·5	−0·6, 1·6	−0·1	−0·3, 0·1	−0·0	−0·3, 0·2	−0·1	−0·3, 0·1	0·3	−0·3, 1·0	−0·2	−0·3, −0·0
	P	0·255		0·131		0·350		0·197		0·742		0·232		0·336		**0·049**	
	I^2 (95 %CI) (%)	51·6	0·0, 90·4	40·5	0·0, 79·4	96·1	0·0, 99·2	17·6	0·0, 77·7	71·3	0·0, 92·3	0·0	0·0, 0·0	96·8	0·0, 99·2	32·9	0·0, 72·8
ALA	Trials	1		6		2		3		4		2		2		8	
	SMD (95 %CI)	−0·1	−0·7, 0·4	−0·3	−1·3, 0·7	−0·4	−2·0, 1·1	0·1	−0·2, 0·4	−0·6	−2·3, 1·2	0·2	−1·4, −1·0	−0·6	−1·8, 0·6	−0·2	−1·0, 0·6
	P	0·658		0·536		0·598		0·575		0·538		**0·038**		0·356		0·608	
	I^2 (95 %CI) (%)	0·0		98·4	81·2, 99·5	98·1	0·0, 99·6	52·5	0·0, 87·4	99·0	33·2, 99·7	0·0	0·0, 0·0	98·8	0·0, 99·8	97·8	85·2, 99·2

LC-PUFA, long-chain PUFA; LA, linoleic acid; DGLA, dihomo-γ-linolenic acid; DTA, docosatetraenoic acid; AA, arachidonic acid; DPA, docosapentaenoic acid; ALA, α-linolenic acid. Boldface indicates significance in subgroups ($P \leq 0{\cdot}05$).

milk. The results indicated that the rs174575 variant had a greater effect on PUFA levels in the breast milk group. The G allele of rs174575 was significantly positively associated with breast milk DGLA and DPA concentrations and significantly negatively associated with AA. These findings are consistent with those of the overall analysis. A similar trend was observed in the groups of blood samples; a high level of DGLA was found in the plasma of the G allele group, and a low level of AA was found in the erythrocyte group. Notably, heterogeneity in each subgroup was reduced compared with overall heterogeneity, suggesting that different tissues may be the source of heterogeneity in this meta-analysis. It is important to acknowledge that both dietary intake and genetic predisposition play a role in determining the PUFA composition, so further investigation into the effects of rs174575 and its interaction with dietary patterns on fatty acid composition is required to elucidate this heterogeneity[15]. The results of our research may be less representative, primarily because of the low percentage of positive results observed in the plasma or erythrocyte group compared to the breast milk group included in the subgroup analysis. Furthermore, due to the limited number of relevant studies, we included articles with scores of six and seven. In the subgroup analyses, heterogeneity was reduced in studies with scores of seven, indicating that the quality of the included studies is also a source of heterogeneity.

Our meta-analysis had some limitations. First, we focused exclusively on the rs174575 variant within the FADS2 gene cluster and its association with LC-PUFA. This narrow focus may have resulted in the potential omission of studies that used different SNP markers, thereby introducing a selection bias. Second, our results were based on raw data without any adjustment for possible confounding factors owing to incomplete information. This lack of adjustment might have influenced the observed associations. Third, only a few studies have been conducted on this topic, indicating the need for more extensive and diverse research to establish stronger evidence of the relationship between variations in the FADS2 gene cluster and LC-PUFA levels.

To establish a relationship between genetic variations and LC-PUFA levels, further research, especially intervention studies, should focus on the effects of ethnic groups with different FADS2 variants and dietary habits on LC-PUFA levels[47].

Conclusion

Analysis of observational studies showed that the minor G allele of rs174575 in FADS2 was associated with higher DGLA levels and lower AA levels than those homozygous for the major allele.

Acknowledgments

None.

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

L. X., H. Y., J. G. and M. L. planned the research; J. G., Y. C. and S. N. searched the literatures; M. L., Y. W., Y. H. and S. C. extracted the data and assessed the quality; M. L., Y. W. and Y. C. analysed the data and wrote the paper; Y. H., M. L. and S. C. drew figures. All authors have read and agreed to the published version of the manuscript.

The author(s) declare none.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524001624

References

1. Lauritzen L, Brambilla P, Mazzocchi A, *et al.* (2016) DHA effects in brain development and function. *Nutrients* **8**, 6.
2. Lauritzen L, Sørensen LB, Harsløf LB, *et al.* (2017) Mendelian randomization shows sex-specific associations between long-chain PUFA-related genotypes and cognitive performance in Danish schoolchildren. *Am J Clin Nutr* **106**, 88–95.
3. Glaser C, Lattka E, Rzehak P, *et al.* (2011) Genetic variation in polyunsaturated fatty acid metabolism and its potential relevance for human development and health. *Matern Child Nutr* **7**, 27–40.
4. Bellino S, Bozzatello P, Badino C, *et al.* (2021) Efficacy of Polyunsaturated Fatty Acids (PUFAs) on impulsive behaviours and aggressiveness in psychiatric disorders. *Int J Mol Sci* **22**, 620.
5. Rangel-Huerta OD & Gil A (2018) *n*-3 fatty acids in cardiovascular disease risk factors: an updated systematic review of randomised clinical trials. *Clin Nutr* **37**, 72–77.
6. Anez-Bustillos L, Dao DT, Fell GL, *et al.* (2018) Redefining essential fatty acids in the era of novel intravenous lipid emulsions. *Clin Nutr* **37**, 784–789.
7. Scholtz SA, Kerling EH, Shaddy DJ, *et al.* (2015) Docosahexaenoic acid (DHA) supplementation in pregnancy differentially modulates arachidonic acid and DHA status across FADS genotypes in pregnancy. *Prostaglandins Leukot Essent Fatty Acids* **94**, 29–33.
8. Marquardt A, Stöhr H, White K, *et al.* (2000) CDNA cloning, genomic structure, and chromosomal localization of three members of the human fatty acid desaturase family. *Genomics* **66**, 175–183.
9. Cho HP, Nakamura M & Clarke SD (1999) Cloning, expression, and fatty acid regulation of the human Δ-5 desaturase. *J Biol Chem* **274**, 37335–37339.
10. Cho HP, Nakamura MT & Clarke SD (1999) Cloning, expression, and nutritional regulation of the mammalian Δ-6 desaturase. *J Biol Chem* **274**, 471–477.
11. Zhao T, Gao P, Li Y, *et al.* (2023) Investigating the role of FADS family members in breast cancer based on bioinformatic analysis and experimental validation. *Front Immunol* **14**, 1074242.
12. Mihelic R, Winter H, Powers JB, *et al.* (2020) Genes controlling polyunsaturated fatty acid synthesis are developmentally regulated in broiler chicks. *Br Poult Sci* **61**, 508–517.
13. Park WJ, Kothapalli KS, Reardon HT, *et al.* (2012) A novel FADS1 isoform potentiates FADS2-mediated production of eicosanoid precursor fatty acids. *J Lipid Res* **53**, 1502–1512.
14. Moltó-Puigmartí C, Plat J, Mensink RP, *et al.* (2010) FADS1 FADS2 gene variants modify the association between fish intake and the docosahexaenoic acid proportions in human milk. *Am J Clin Nutr* **91**, 1368–1376.

15. Rzehak P, Thijs C, Standl M, *et al.* (2010) Variants of the FADS1 FADS2 gene cluster, blood levels of polyunsaturated fatty acids and eczema in children within the first 2 years of life. *PLoS One* **5**, e13261.
16. Harsløf LB, Larsen LH, Ritz C, *et al.* (2013) FADS genotype and diet are important determinants of DHA status: a cross-sectional study in Danish infants. *Am J Clin Nutr* **97**, 1403–1410.
17. Cribb L, Murphy J, Froud A, *et al.* (2018) Erythrocyte polyunsaturated fatty acid composition is associated with depression and FADS genotype in Caucasians. *Nutr Neurosci* **21**, 589–601.
18. Carvalho GQ, Pereira-Santos M, Marcon LD, *et al.* (2019) Maternal polymorphisms in the FADS1 and FADS2 genes modify the association between PUFA ingestion and plasma concentrations of *n*-3 polyunsaturated fatty acids. *Prostaglandins Leukot Essent Fatty Acids* **150**, 38–46.
19. Conway MC, McSorley EM, Mulhern MS, *et al.* (2021) Maternal and child fatty acid desaturase genotype as determinants of cord blood long-chain PUFA (LCPUFA) concentrations in the Seychelles Child Development Study. *Br J Nutr* **126**, 1687–1697.
20. Reynolds LM, Howard TD, Ruczinski I, *et al.* (2018) Tissue-specific impact of FADS cluster variants on FADS1 and FADS2 gene expression. *PLoS One* **13**, e0194610.
21. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* **25**, 603–605.
22. Xie L & Innis SM (2008) Genetic variants of the FADS1 FADS2 gene cluster are associated with altered (*n*-6) and (*n*-3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. *J Nutr* **138**, 2222–2228.
23. Kim OY, Lim HH, Yang LI, *et al.* (2011) 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* **8**, 1–11.
24. Ding Z, Liu G-L, Li X, *et al.* (2016) Association of polyunsaturated fatty acids in breast milk with fatty acid desaturase gene polymorphisms among Chinese lactating mothers. *Prostaglandins Leukotrienes Essent Fatty Acids* **109**, 66–71.
25. Huang M-C, Chang W-T, Chang H-Y, *et al.* (2017) FADS gene polymorphisms, fatty acid desaturase activities, and HDL-C in type 2 diabetes. *Int J Environ Res Public Health* **14**, 572.
26. de la Garza Puentes A, Montes Goyanes R, Chisaguano Tonato AM, *et al.* (2017) Association of maternal weight with FADS and ELOVL genetic variants and fatty acid levels-The PREOBE follow-up. *Plos One* **12**, e0179135.
27. Juan J, Huang H, Jiang X, *et al.* (2018) Joint effects of fatty acid desaturase 1 polymorphisms and dietary polyunsaturated fatty acid intake on circulating fatty acid proportions. *Am J Clin Nutr* **107**, 826–833.
28. Mozaffarian D, Kabagambe EK, Johnson CO, *et al.* (2015) Genetic loci associated with circulating phospholipid trans fatty acids: a meta-analysis of genome-wide association studies from the CHARGE Consortium. *Am J Clin Nutr* **101**, 398–406.
29. Huang Y-S, Huang W-C, Li C-W, *et al.* (2011) Eicosadienoic acid differentially modulates production of pro-inflammatory modulators in murine macrophages. *Mol Cell Biochem* **358**, 85–94.
30. Tanaka T, Shen J, Abecasis GR, *et al.* (2009) Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. *PLoS Genet* **5**, e1000338.
31. Park WJ, Kothapalli KS, Lawrence P, *et al.* (2009) An alternate pathway to long-chain polyunsaturates: the FADS2 gene product Delta8-desaturates 20:2*n*-6 and 20:3*n*-3. *J Lipid Res* **50**, 1195–1202.
32. Koletzko B, Lattka E, Zeilinger S, *et al.* (2011) Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. *Am J Clin Nutr* **93**, 211–219.
33. Lattka E, Rzehak P, Szabó É, *et al.* (2011) Genetic variants in the FADS gene cluster are associated with arachidonic acid concentrations of human breast milk at 1·5 and 6 months postpartum and influence the course of milk dodecanoic, tetracosenoic, and trans-9-octadecenoic acid concentrations over the duration of lactation. *Am J Clin Nutr* **93**, 382–391.
34. Wu WC, Wu PY, Chan CY, *et al.* (2023) Effect of FADS1 rs174556 genotype on polyunsaturated fatty acid status: a systematic review and meta-analysis. *Adv Nutr* **14**, 352–362.
35. Santana JDM, Pereira M, Carvalho GQ, *et al.* (2022) FADS1 and FADS2 Gene polymorphisms modulate the relationship of *n*-3 and *n*-6 Fatty acid plasma concentrations in gestational weight gain: a NISAMI cohort study. *Nutrients* **14**, 1056.
36. Yeates AJ, Love TM, Engström K, *et al.* (2015) Genetic variation in FADS genes is associated with maternal long-chain PUFA status but not with cognitive development of infants in a high fish-eating observational study. *Prostaglandins Leukot Essent Fatty Acids* **102–103**, 13–20.
37. Muzsik A, Bajerska J, Jeleń HH, *et al.* (2019) FADS1 and FADS2 polymorphism are associated with changes in fatty acid concentrations after calorie-restricted Central European and Mediterranean diets. *Menopause* **26**, 1415–1424.
38. Porenta SR, Ko YA, Gruber SB, *et al.* (2013) Interaction of fatty acid genotype and diet on changes in colonic fatty acids in a Mediterranean diet intervention study. *Cancer Prev Res (Phila)* **6**, 1212–1221.
39. Virtanen JK, Mursu J, Voutilainen S, *et al.* (2018) The associations of serum *n*-6 polyunsaturated fatty acids with serum C-reactive protein in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Eur J Clin Nutr* **72**, 342–348.
40. Poggioli R, Hirani K, Jogani VG, *et al.* (2023) Modulation of inflammation and immunity by *n*-3 fatty acids: a possible role for prevention and to halt disease progression in autoimmune, viral, and age-related disorders. *Eur Rev Med Pharmacol Sci* **27**, 7380–7400.
41. Chang JP, Chang SS, Chen HT, *et al.* (2023) *n*-3 polyunsaturated fatty acids (*n*-3 PUFAs), somatic and fatigue symptoms in cardiovascular diseases comorbid major depressive disorder (MDD): a randomized controlled trial. *Brain Behav Immun* **112**, 125–131.
42. Pawelzik SC, Arnardottir H, Sarajlic P, *et al.* (2023) Decreased oxidative stress and altered urinary oxylipidome by intravenous *n*-3 fatty acid emulsion in a randomized controlled trial of older subjects hospitalized for COVID-19. *Free Radic Biol Med* **194**, 308–315.
43. Jerkic SP, Bächle L, Duecker RP, *et al.* (2023) Association between polyunsaturated fatty acid profile and bronchial inflammation in bronchiolitis obliterans. *Mediators Inflamm* **2023**, 3406399.
44. Best KP, Gold M, Kennedy D, *et al.* (2016) *n*-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Am J Clin Nutr* **103**, 128–143.

45. Sergeant S, Hugenschmidt CE, Rudock ME, *et al.* (2012) Differences in arachidonic acid levels and fatty acid desaturase (FADS) gene variants in African Americans and European Americans with diabetes or the metabolic syndrome. *Br J Nutr* **107**, 547–555.
46. Yang C, Veenstra J, Bartz TM, *et al.* (2023) Genome-wide association studies and fine-mapping identify genomic loci for *n*-3 and *n*-6 polyunsaturated fatty acids in Hispanic American and African American cohorts. *Commun Biol* **6**, 852.
47. Chen X, Wu Y, Zhang Z, *et al.* (2019) Effects of the rs3834458 single nucleotide polymorphism in FADS2 on levels of *n*-3 long-chain polyunsaturated fatty acids: a meta-analysis. *Prostaglandins Leukot Essent Fatty Acids* **150**, 1–6.