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Association between *FADS1* rs174547 and levels of long-chain PUFA: a meta-analysis

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Abstract

In the present study, we analysed the effects of SNP rs174547 (T/C) in the fatty acid desaturase 1 (*FADS1*) gene on long-chain PUFA levels. Four databases were searched to retrieve related literature with keywords such as fatty acid (FA), SNP, *FADS1* and rs174547. A meta-analysis of the data was performed using Stata12.0 software, including summary statistics, test for heterogeneity, evaluation of publication bias, subgroup analysis and sensitivity analysis. The associations between rs174547 in *FADS1* and seven types of FA, and Δ-5 (D5D) and Δ-6 fatty acid desaturase (D6D) activity were assessed based on the pooled results from eleven papers. A total of 3713 individuals (1529 TT and 2184 TC + CC) were included. The results demonstrated that minor C allele carriers of rs174547 had higher linoleic acid (LA; $P < 0{\cdot}001$) and α-linolenic acid ($P = 0{\cdot}020$) levels, lower γ-linolenic acid (GLA; $P = 0{\cdot}001$) and arachidonic acid ($P = 0{\cdot}024$) levels, and lower D5D ($P = 0{\cdot}005$) and D6D ($P = 0{\cdot}004$) activities than the TT genotype group. Stratification analysis showed that minor C allele carriers of rs174547 had higher LA and lower GLA levels and lower D6D activities in plasma (LA, $P < 0{\cdot}001$; GLA, $P < 0{\cdot}001$; D6D activity, $P < 0{\cdot}001$) samples and in Asian populations (LA, $P < 0{\cdot}001$; GLA, $P = 0{\cdot}001$; D6D activity, $P = 0{\cdot}001$) than the TT genotype group. In conclusion, minor C allele carriers of the SNP rs174547 were associated with decreased activity of D5D and D6D.

Key words: *FADS1* gene: Long-chain PUFA: SNP: Meta-analyses

PUFA are a group of critical nutrients that modulate brain development, cognition and several diseases, including CVD, cancers and diabetes[1–4]. PUFA are classified as *n*-3 and *n*-6 fatty acids (FA).

Humans derive long-chain (LC) PUFA directly from their diet and can synthesise them endogenously from their essential *n*-6 and *n*-3 precursors, linoleic acid (LA) and α-linolenic acid (ALA), respectively[5]. This process requires a consecutive series of desaturation involving Δ-5 (D5D) and Δ-6 fatty acid desaturases (D6D) encoded by the fatty acid desaturase 1 (*FADS1*) and fatty acid desaturase 2 (*FADS2*) genes, respectively, and elongation reactions. Human desaturase complementary DNA was first cloned by Cho *et al.*[6,7] and later identified in a cluster on chromosome 11 (11q12–13.1)[8]. D5D and D6D are expressed across several tissues but predominantly expressed in the liver[6,7]. LA and ALA are metabolised by the same series of enzymes, and EPA and DHA are produced at limited conversion rates of 0·2–6 % and less than 0·05 %, respectively, in men[9]. The synthesis efficiency of endogenous EPA and DHA is thought to be affected by gene polymorphisms. A 5-locus haplotype explains 1·4, 5·2 and 27·7 % of the variability in DHA, EPA and arachidonic acid (AA) levels, respectively[10].

As described, genetic variation in *FADS* appears to be important for modulating the LC-PUFA status. SNP in *FADS1* may affect LC-PUFA production and consequently alter FA levels[11]. The rs174547 SNP is located in intron 9 of *FADS1*[12]. Over the past two decades, several genome-wide association studies have reported the associations of rs174547 with FA[13–15]. Previously, we demonstrated that SNP of the rs174547 (T/C) genotype in *FADS1* were associated with the FA composition in Chinese populations[16]. rs174547 is a functional variant associated with decreased *FADS1* expression in the human liver[17]. Several studies[12,16,18–26] have focused on this variant and its association with PUFA levels. Among the tag SNP of *FADS1* gene, rs174547 tags up to seven other SNP in an 11-kb genomic region of *FADS1* with a linkage disequilibrium threshold of $R^2 > 0{\cdot}8$[16].

In the present study, we performed a meta-analysis to determine the effects of rs174547 in *FADS1* on PUFA levels.

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; DGLA, dihomo-γ-linolenic acid; D5D, Δ-5 fatty acid desaturase; D6D, Δ-6 fatty acid desaturase; FA, fatty acid; FADS1, fatty acid desaturase 1; FADS2, fatty acid desaturase 2; GLA, γ-linolenic acid; LA, linoleic acid; LC, long chain; SMD, standardised mean difference.

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Methods

Literature retrieval

Four databases (Pubmed, Web of Science, China National Knowledge Infrastructure (CNKI) and Wanfang databases) were searched to retrieve related literature with key words such as fatty acid, SNP, *FADS1* gene and rs174547 published in English and Chinese Language before 5 October 2020. The detailed search strategy is presented in Supplementary Table 1.

Assessment of eligibility

Studies were suggested to be eligible if they meet the following inclusion criteria: (1) studies reported in Chinese or English; and (2) full-text applicable, with access to required materials and data from the authors and (3) studies with good design quality were selected for analysis. Studies were excluded if they were (1) duplicated publications, (2) abstracts, case reports/series, comments, editorial articles, summary, animal/plant/cell studies, reviews or meta-analysis, (3) data expressed as medians (25–75th percentiles) and (4) missing data that were not presented in the literature and we did not get reply from the authors who published those studies.

Data extraction and quality assessment

Author, publication year, country, age, sample size, genotypes, measurement method, tissues and FA content were extracted from the included studies. Two investigators independently extracted data from included literature, and any disagreement was resolved by discussion. The Newcastle–Ottawa Scale[27] was used to assess the quality of included study, and quality assessment results were presented in Supplementary Table 2. A study that scored ≥6 points (total is 8 points) was defined as high quality. The three genotypes (TT, TC and CC) of subjects were divided into major homozygotes carriers and minor allele carriers groups (TT and TC + CC) using the method of weighing according to retrieved studies[28].

Statistical analysis

The meta-analysis of data was performed using Stata12.0 software. Heterogeneity of the included studies was performed by Q test and I^2 test. When P values was >0·1 and I^2 values was ≤50 %, a fixed effects model was used; otherwise, a random effects model was used. The random effect model was selected and effect indexes of each study were calculated as standardised mean difference (SMD) and 95 % CI. Heterogeneity of studies was assessed by subgroup analysis and sensitivity analysis. Subgroup analysis was performed by region, tissue and score of quality of studies group. Metafunnel and Egger's or Begger's test were used to assess publication bias. $P < 0·05$ was considered to be statistically significant.

Results

Included literature

Total of 1967 relevant publications were searched. Based on the inclusion and exclusion criteria, eleven high-quality publications were finally included in the meta-analysis; the flow diagram of retrieval process was shown in Fig. 1. A Population; Exposure; Comparision and Outcomes (PECO) table for included papers is presented in Supplementary Table 3.

Study characteristics

Data from seventeen trials were extracted from eleven literature (since one literature focused on the study of PUFA in plasma and erythrocytes at the same time, one focused on the study of PUFA in mothers and fetuses, one has two cohorts study in normal-weight and overweight population at two different times, and another one has two cohorts study in normal-weight and overweight population). A total of 3713 individuals (1529 TT and 2184 TC + CC) were included. Subjects of these studies were from Asia, Europe and Oceania. These studies detected the FA composition of plasma, erythrocyte and breast milk. The Newcastle–Ottawa Scale scores of the studies varied from 6 to 7 points, indicating the good quality of the included studies. More information or characteristics of the included studies are summarised in Table 1.

Results of meta-analysis

Effects of rs174547 in FADS1 on linoleic acid levels

The effects of rs174547 on LA levels are shown in Fig. 2(a). The LA level in minor C allele carriers was significantly higher than in the TT genotype group (SMD: 1·16, 95 % CI 0·65, 1·68, $P < 0·001$), and significant heterogeneity ($I^2 = 96·5$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the LA level in minor C allele carriers was significantly higher than that in the TT genotype group across Asian populations, Oceanian populations, plasma samples, erythrocyte samples and study quality groups (score = 7 and score = 6), respectively (Table 2).

Effects of rs174547 in FADS1 on γ-linolenic acid level

The effects of rs174547 on γ-linolenic acid (GLA) level are shown in Fig. 2(c). The GLA level in minor C allele carriers was significantly lower than that in the TT genotype group (SMD: −3·18, 95 % CI −5·02, −1·34, $P = 0·001$), and significant heterogeneity ($I^2 = 99·4$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the GLA level in minor C allele carriers was significantly lower than that in the TT genotype group across Asian populations, plasma samples, breast milk samples and study quality groups (score = 7 and score = 6), respectively (Table 2).

Effects of rs174547 in FADS1 on dihomo-γ-linolenic acid level

The effects of rs174547 on dihomo-γ-linolenic acid (DGLA) level are shown in Fig. 2(e). The difference of DGLA level was not significant between minor C allele carriers and the TT genotype group (SMD: 0·42, 95 % CI −0·05, 0·89, $P = 0·079$), and significant heterogeneity ($I^2 = 96·0$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the DGLA level in minor C allele carriers was significantly higher than that in the TT genotype group in European populations and erythrocyte samples group (Table 2).

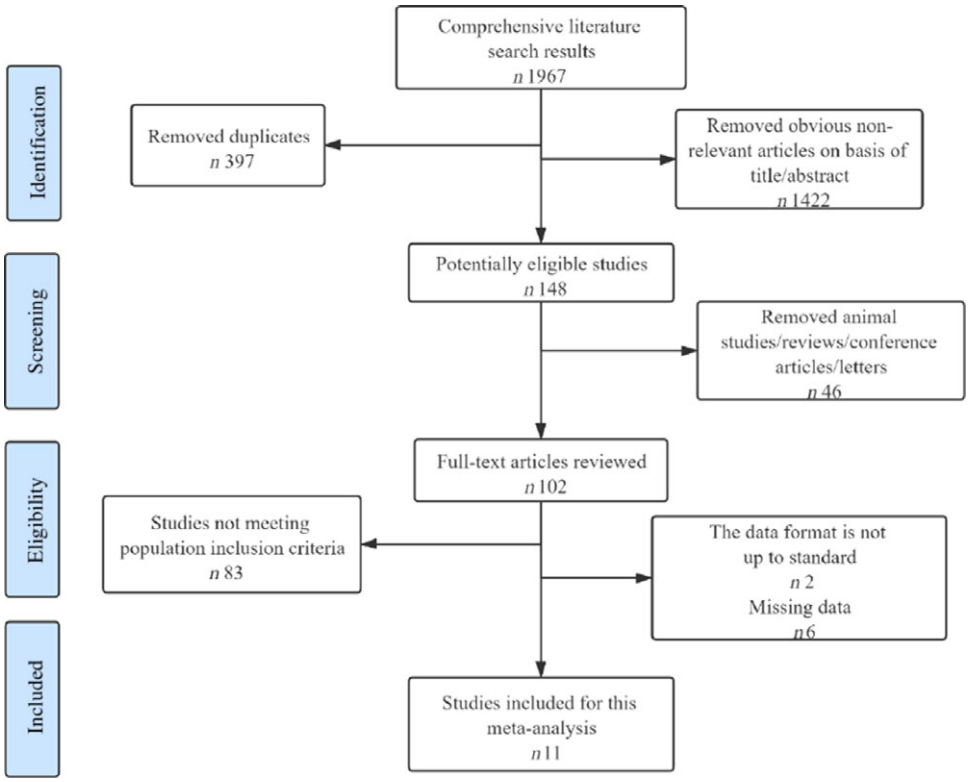

Fig. 1. Flow diagram of the selection process of the literature search.

Effects of rs174547 in FADS1 *on arachidonic acid level*

The effects of rs174547 on AA level are shown in Fig. 2(g). The AA level in minor C allele carriers was significantly lower than that in the TT genotype group (SMD: −1·19, 95 % CI −2·23, −0·16, $P = 0·024$), and significant heterogeneity ($I^2 = 99·1$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the AA level in minor C allele carriers was significantly higher than that in the TT genotype group across Asian populations, all tissue groups and all study quality groups, respectively (Table 2).

Effects of rs174547 in FADS1 *on α-linolenic acid level*

The effects of rs174547 on ALA level are shown in Fig. 2(b). The ALA level in minor C allele carriers was significantly higher than that in the TT genotype group (SMD: 0·77, 95 % CI 0·12, 1·42, $P = 0·020$), and significant heterogeneity ($I^2 = 97·9$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the ALA level in minor C allele carriers was significantly higher than that in the TT genotype group in Oceanian populations, plasma samples and study quality group (score = 7) (Table 2).

Effects of rs174547 in FADS1 *on EPA level*

The effects of rs174547 on EPA level are shown in Fig. 2(d). The difference of EPA level was not significant between minor C allele carriers and the TT genotype group (SMD: −0·75, 95 % CI −1·85, 0·34, $P = 0·177$), and significant heterogeneity ($I^2 = 99·2$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the EPA level in minor C allele carriers was significantly lower than that in the TT genotype group in Asian populations group (Table 2).

Effects of rs174547 in FADS1 *on DHA level*

The effects of rs174547 on DHA level are shown in Fig. 2(f). The difference of DHA level was not significant between minor C allele carriers and the TT genotype group (SMD: −0·41, 95 % CI −1·35, 0·52, $P = 0·388$), and significant heterogeneity ($I^2 = 99·2$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the DHA level in minor C allele carriers was significantly lower than that in the TT genotype group in study quality group (score = 6) (Table 2).

Effects of rs174547 in FADS1 *on Δ-5 fatty acid desaturase activity*

The effects of rs174547 on D5D activity (the ratio of AA to DGLA) are shown in Fig. 2(h). The D5D activity in minor C allele carriers was significantly lower than that in the TT genotype group (SMD: −1·55, 95 % CI −2·62, −0·48, $P = 0·005$), and significant heterogeneity ($I^2 = 98·7$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the D5D activity in minor C allele carriers was significantly lower than that in the TT genotype group across Asia populations, European populations, plasma samples, erythrocyte samples and quality of studies (score = 6) group (Table 2).

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Table 1. Characteristics of studies included in the meta-analysis
(Mean values and standard deviations)

Author	Year	Country	Score	Subject		PUFA detection methods	Age (years)		Sex (male/female)		Tissues	Genotyping method
				TT	TC+CC		TT	TC+CC	TT	TC+CC		
							Mean	SD				
Merino *et al.*[18]	2011	Caucasians	6	30	48	GC	22·9	0·30	23/55		Plasma	Sequenom MassARRAY platform
Lu *et al.*[19]	2012	The Netherlands	7	545	701	GLC	45·2	8·5	573/673		Plasma	Sequenom MassARRAY
Horiguchi *et al.* a[20]	2016	Japan	6	47	77	GC	83·2 8·40	84·7 8·37	13/34	24/53	Plasma	TaqMan genotyping assay systems
Horiguchi *et al.* b[20]	2016	Japan	6	47	77	GC	83·2 8·40	84·7 8·37	13/34	24/53	Erythrocytes	TaqMan genotyping assay systems
Ding *et al.*[16]	2016	China	6	103	97	GC	30·00	4·00	0/200		Breast milk	Sequenom MassARRAY system
Cribb *et al.*[21]	2017	Australia	6	59	82	GC	44·4	14·9	67/175		Erythrocyte	Sequenom MassARRAY
de la Garza Puentes *et al.* a[22]	2017	Spain	7	15	23	GC	30·91	4·09	0/88		Plasma	TaqMan OpenArray Genotyping technology
de la Garza Puentes *et al.* b[22]	2017	Spain	7	12	20	GC	30·64	4·20	0/92		Plasma	TaqMan OpenArray Genotyping technology
Huang *et al.*[23]	2017	China	7	23	153	GC	58·3	8·9	54/99		Plasma	GenomeLabTM SNPstream® genotyping platform
Kim *et al.* a/b[12]	2018	Korea	7	91	112	GC-MS	44·9 0·98	44·2 0·82	32/59	42/70	Plasma	SNaPShot assay kit
Kim *et al.* c/d[12]	2018	Korea	7	47	37	GC-MS	44·5 1·40	45·1 1·56	18/29	15/22	Plasma	SNaPShot assay kit
Muzsik *et al.*[24]	2018	Poland	6	72	54	GC	60·7	5·1	0/126		Erythrocytes	Probe on a LightCycler 480 instrument
Sasaki *et al.*[25]	2019	Japan	7	19	36	GLC	45·0 4·50	46·5 4·60	8/11	13/23	Plasma	TaqMan genotyping assay system
Nita *et al.* a[26]	2020	Japan	6	150	266	GLC	32·1 4·6	31·3 4·96	0/150	0/266	Erythrocytes	TaqMan genotyping assay system
Nita *et al.* b[26]	2020	Japan	6	131	252	GLC	–		–		Erythrocytes	TaqMan genotyping assay system

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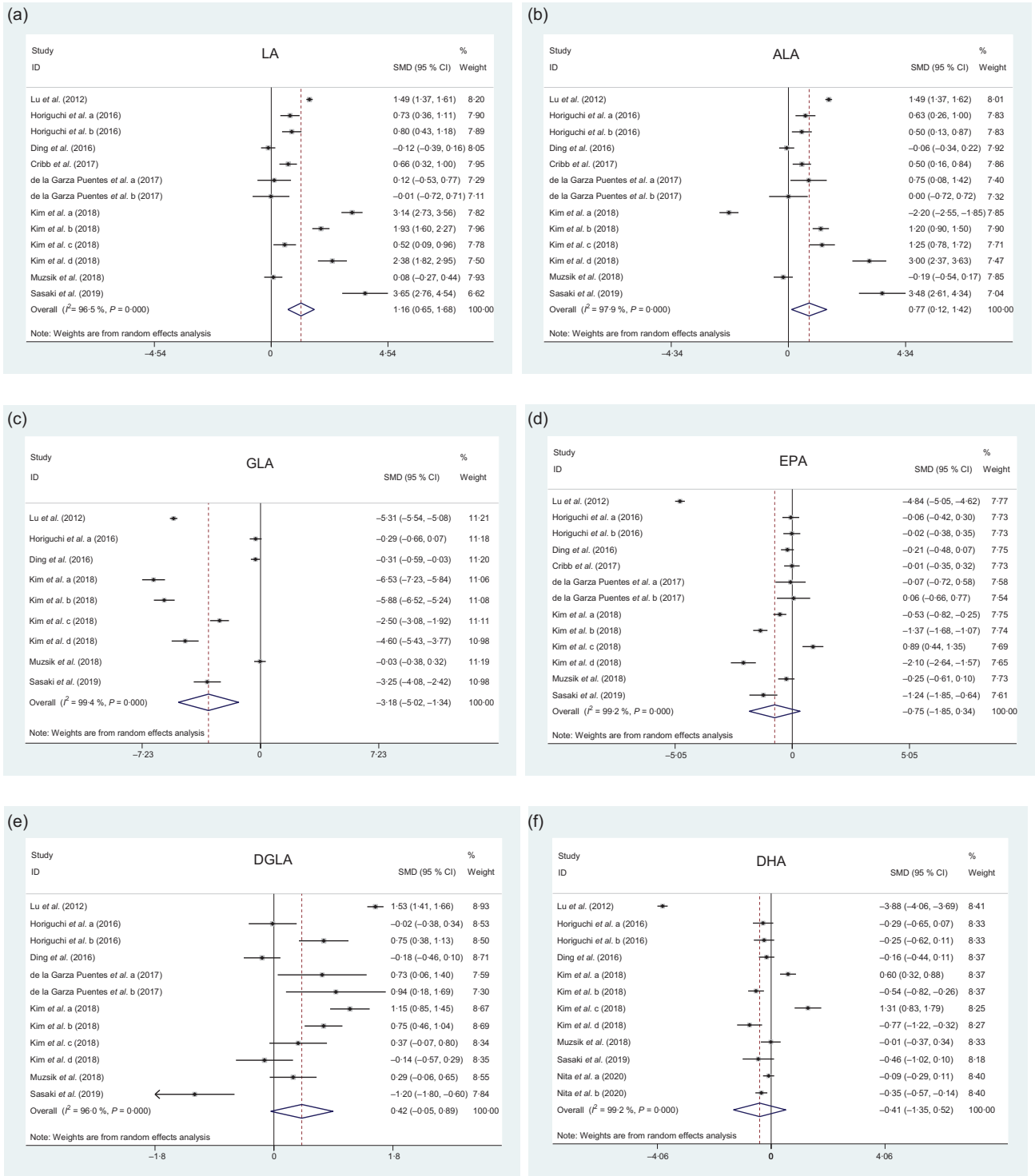

Fig. 2. Forest plots showing PUFA levels difference between minor C allele carriers and TT genotype of rs174547 in *FADS1*. (a) Forest plot of linoleic acid (LA); (b) forest plot of α-linolenic acid (ALA); (c) forest plot of γ-linolenic acid (GLA); (d) forest plot of EPA; (e) forest plot of dihomo-γ-linolenic acid (DGLA); (f) forest plot of DHA; (g) forest plot of arachidonic acid (AA); (h) forest plot of Δ-5 desaturase (D5D) activity; (i) forest plot of Δ-6 desaturase (D6D) activity. D5D and D6D activities were assessed by the ratio of AA to DGLA and GLA to LA, respectively.

Effects of rs174547 in FADS1 on Δ-6 fatty acid desaturase activity

The effects of rs174547 on D6D activity (the ratio of GLA to LA) are shown in Fig. 2(i). The D6D activity in minor C allele carriers was significantly lower than that in the TT genotype group (SMD: −2·84, 95 % CI −4·78, −0·90, $P = 0·004$), and significant heterogeneity ($I^2 = 99·2$ %, $P < 0·001$) was observed. Subgroup analysis demonstrated that the D6D activity in minor C allele carriers was

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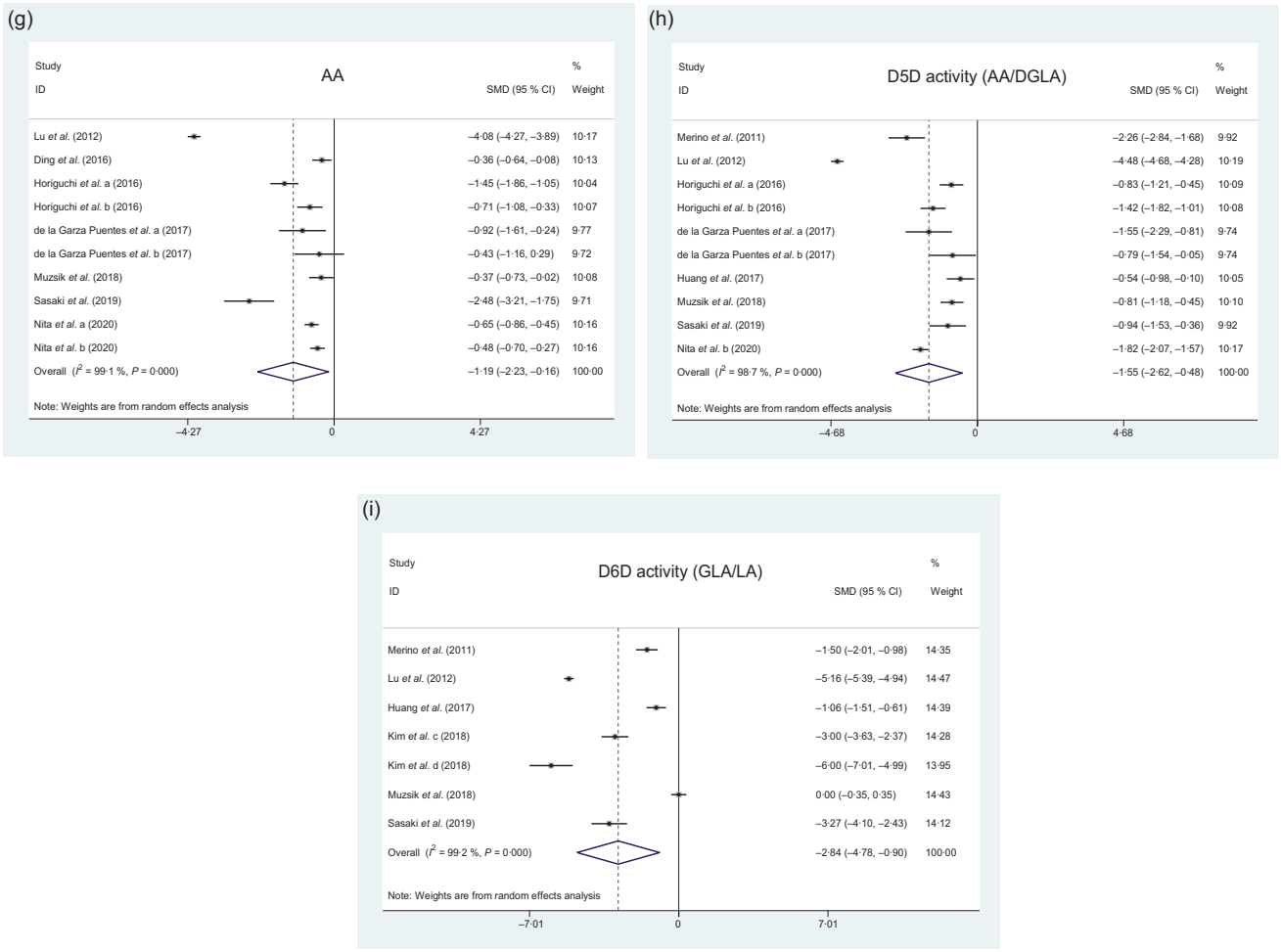

Fig. 2. Continued

significantly lower than that in the TT genotype group across Asian populations, plasma populations and study quality group (score = 7) (Table 2).

Sensitivity analysis

Sensitivity analysis was performed by removing studies one by one to evaluate the stability of the results. As shown in Supplementary Fig. 1, although each study was successively removed, the results did not alter obviously in LA, GLA, D5D and D6D activities, indicating the high stability of the meta-analysis results. When the study from Sasaki *et al.*[25] was excluded, the difference of ALA (SMD: 0·57, 95 % CI −0·09, 1·22, P = 0·092) between minor C allele carriers and the TT genotype group and AA (SMD: −1·06, 95 % CI −2·16, 0·05, P = 0·060) levels was not statistically significant, and DGLA (SMD: 0·56, 95 % CI 0·10, 1·01, P = 0·016) level in minor C allele carriers was significantly higher than that in the TT genotype group. When the study from Lu *et al.*[19] was excluded, the EPA (SMD: −0·41, 95 % CI −0·80, −0·01, P = 0·043) level in minor C allele carriers was significantly lower than that in the TT genotype group.

Publication bias

The funnel plots of the SNP rs174547 on LC-PUFA level did not reveal substantial publication bias (Supplementary Fig. 2), indicating no significant publication bias of results. Egger's or Begger's test was carried out to analyse the publication bias. The analysis results showed the presence of publication bias in DGLA (Egger's test P = 0·006) and D5D activity (Egger's test P = 0·041) (Supplementary Table 4).

Discussion

In the present study, the associations between rs174547 in *FADS1* and seven types of FA, D5D activity and D6D activity were assessed based on the pooled results from eleven papers[12,16,18–26]. The results demonstrated that minor C allele carriers of rs174547 had higher LA and ALA levels, lower GLA and AA levels, and lower D5D and D6D activities than the TT genotype group. Desaturation of LC-PUFA, derived from ALA and LA through elongation and desaturation, is regulated by D5D and D6D[29]. We observed a weaker association between

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Table 2. Subgroup meta-analysis of the SNP rs174547 in *FADS1* on the level of long-chain-PUFA (Numbers, standardised mean differences (SMD) and 95 % confidence intervals)

	Region			Tissue			Quality of studies	
	Asia	Europe	Oceania	Plasma	Erythrocytes	Breast milk	Score = 7	Score = 6
LA								
Trials (*n*)	8	4	1	9	3	1	8	5
SMD	1·60	0·45	0·66	1·54	0·51	−0·12	1·64	0·42
95 % CI	0·74, 2·46	−0·53, 1·42	0·32, 1·00	0·95, 2·12	0·08, 0·94	−0·39, 0·16	1·00, 2·29	0·04, 0·81
P	<0·001	0·370	<0·001	<0·001	0·019	0·413	<0·001	0·033
GLA								
Trials (*n*)	7	2		7	1	1	6	3
SMD	−3·32	−2·67		−4·05	−0·03	−0·31	−4·69	−0·23
95 % CI	−5·22, −1·43	−7·85, 2·50		−5·96, −2·14	−0·38, 0·32	−0·59, −0·03	−5·81, −3·56	−0·41, −0·04
P	0·001	0·312		<0·001	0·875	0·030	<0·001	0·019
DGLA								
Trials (*n*)	8	4		9	2	1	8	4
SMD	0·21	0·88		0·47	0·52	−0·18	0·53	0·20
95 % CI	−0·24, 0·66	0·12, 1·65		−0·08, 1·02	0·06, 0·97	−0·46, 0·10	−0·03, 1·10	−0·20, 0·60
P	0·359	0·024		0·095	0·025	0·205	0·063	0·328
AA								
Trials (*n*)	6	4		7	2	1	4	6
SMD	−0·92	−1·46		−1·50	−0·53	−0·36	−1·99	−0·65
95 % CI	−1·30, −0·54	−3·84, 0·92		−2·89, −0·11	−0·86, −0·21	−0·64, −0·08	−3·99, 0·00	−0·90, −0·39
P	<0·001	0·229		0·034	0·001	0·013	0·050	<0·001
ALA								
Trials (*n*)	8	4	1	9	3	1	8	5
SMD	0·94	0·53	0·50	1·05	0·27	−0·06	1·10	0·27
95 % CI	−0·07, 1·96	−0·53, 1·58	0·16, 0·84	0·12, 1·97	−0·18, 0·72	−0·34, 0·22	0·04, 2·17	−0·06, 0·60
P	0·069	0·326	0·004	0·027	0·239	0·660	0·043	0·108
EPA								
Trials (*n*)	8	4	1	9	3	1	6	7
SMD	−0·57	−1·28	−0·01	−1·04	−0·09	−0·21	−1·16	−0·12
95 % CI	−1·11, −0·02	−4·32, 1·75	−0·35, 0·32	−2·55, 0·48	−0·29, 0·11	−0·48, 0·07	−2·80, 0·49	−0·27, 0·03
P	0·042	0·406	0·940	0·180	0·368	0·145	0·168	0·114
DHA								
Trials (*n*)	10	2		9	2	1	6	6
SMD	−0·11	−1·95		−0·50	−0·13	−0·16	−0·63	−0·20
95 % CI	−0·40, 0·19	−5·73, 1·84		−1·70, 0·69	−0·38, 0·12	−0·44, 0·11	−2·52, 1·27	−0·31, −0·09
P	0·491	0·313		0·412	0·314	0·250	0·518	<0·01
D5D activity*								
Trials (*n*)	5	5		8	2		5	5
SMD	−1·13	−1·99		−1·66	−1·11		−1·67	−1·41
95 % CI	−1·65, −0·61	−3·90, −0·07		−2·93, −0·39	−1·70, −0·52		−3·78, 0·44	−1·92, −0·90
P	<0·001	0·042		0·011	<0·001		0·121	<0·001
D6D activity*								
Trials (*n*)	4	3		6	1		5	2
SMD	−3·29	−2·22		−3·32	0·00		−3·68	−0·74
95 % CI	−5·17, −1·42	−5·81, 1·37		−5·10, −1·53	−0·35, 0·35		−5·63, −1·73	−2·20, 0·73
P	0·001	0·225		<0·001	1·000		<0·001	0·325

LA, linoleic acid; GLA, γ-linolenic acid; DGLA, dihomo-γ-linolenic acid; AA, arachidonic acid; ALA, α-linolenic acid; D5D, Δ-5 desaturase; D6D, Δ-6 desaturase.
* D5D and D6D activities were assessed by the ratio of AA to DGLA and GLA to LA, respectively.

LA and GLA among carriers of the minor C allele of a representative SNP in *FADS1* (rs174547), suggesting a lower rate of LA-to-GLA conversion in these individuals. The increased proportions of substrates (LA) and decreased products (GLA) demonstrated lower D6D activity in the *n*-6 LC-PUFA synthetic pathway. Additionally, minor C allele carriers of the SNP rs174547 (*FADS1*) were associated with decreased D5D and D6D activities. This suggests that *FADS1* variants influence the rate of conversion of LA into other *n*-6 PUFA, indicating an associated loss-of-function effect. GLA is generated from LA catalysed by D6D. However, the GLA level and D6D activity are thought to be associated with genetic polymorphisms in *FADS1*[12], consistent with our findings. The SNP rs174547 is linked with the SNP rs174570 in *FADS2*, which is related to *D6D*, as they are in the same linkage disequilibrium block[30] ($r^2 = -1$; HapMap JPT + CHB panel (Japanese and Han Chinese individuals)). Thus, the rs174547 genotype may reflect the entire metabolic process of *n*-6 PUFA conversion from LA to AA, including desaturation by D5D and D6D. Variants in *FADS1* play important roles in regulating *n*-6 PUFA. Moreover, the SNP rs174547 was previously recognised for its association with *n*-6 PUFA and desaturase activities in the genome-wide association studies [14].

A meta-analysis of genome-wide association studies[31] that reported the association of minor alleles of SNP in *FADS1* with higher levels of ALA and lower levels of EPA and DPA. Although these results were not completely consistent with

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our findings, they indicate that the precursor and product FA compositions differed when there was a mutation in the *FADS1* SNP. To date, there are few and conflicting studies on the effects of dietary PUFA and *FADS1* interactions. The associations of *FADS1* with the PUFA levels did not vary depending on the frequency of fatty fish consumption, suggesting that the genetic effects are independent of dietary intake consumption in the studied populations[29]. Other studies suggested that the associated effects of SNP in *FADS1* on FA concentrations can be modified by dietary PUFA intake[17].

We performed subgroup analysis because of the marked heterogeneity observed in our analysis. We found that different ethnicities and tissue types may contribute to the observed heterogeneity. In stratification analysis, we found that minor C allele carriers of rs174547 had higher LA and lower GLA levels and lower D6D activities in the plasma samples and in Asian populations than the TT genotype group. This suggests that the rs174547 polymorphism is a crucial genetic factor in Asian populations. It may also be possible to predict plasma *n*-6 FA LA and GLA levels in Asian populations based on genotype. However, the number of other ethnic group studies in our meta-analysis was small; only one study in Oceania was included[21]. Moreover, they focused on PUFA in the plasma and erythrocytes, with a single study focusing on breast milk.

Growing evidence has suggested that PUFA play important roles in disease. The *n*-3 and *n*-6 PUFA metabolic pathways participate in several inflammatory processes[32]. However, the interactions of *n*-3 and *n*-6 PUFA in inflammation are complex and poorly understood. A previous study[32] proposed that increasing dietary intake of the *n*-6 PUFA AA or its precursor LA can increase inflammation. However, studies in healthy human adults have demonstrated that increased intake of AA or LA does not increase concentrations of inflammatory factors. Moreover, epidemiological studies suggested that AA and LA are associated with reduced inflammation[33]. *n*-3 LC-PUFA have also been observed in a variety of inflammatory diseases, including asthma[34], rheumatoid arthritis[35] and cancer[36]. Regular dietary intake of *n*-6 FA may help prevent and treat hypertension in a healthy population. In contrast, studies have also shown that regular intake of *n*-6 FA in people with diabetes may increase the risk of hypertension[37]. Recently, a negative correlation between *n*-3 FA and CVD was demonstrated[38]. The reciprocal associations support the important role of genetic variation in the pathway for circulating levels of PUFA in diseases.

Our meta-analysis had some limitations. First, our pooled results were based on raw data, with no adjustments made to accommodate for influencing factors. This was because of missing and incomplete information. Second, we did not investigate the interactions between gene and diet or gene and gene because of the limited access to raw data from eligible studies. To comprehensively analyse the effects of rs174547 on PUFA levels, we did not exclude observational studies[25] or clinical trials[19], potentially creating selection bias. Thus, an increased number of original studies with comprehensive raw data are required to confirm the associations between *FADS1* polymorphisms and PUFA levels. We focused on only one rs174547 variant within the *FADS* gene cluster and its association with PUFA levels. Some additional studies may have been missed because they used a different SNP marker to investigate comparable associations. Broader studies are needed to summarise the evidence of the genetic contribution of the *FADS* gene cluster to the PUFA level.

In conclusion, minor C allele carriers of the SNP rs174547 in *FADS1* were associated with decreased activity of D5D and D6D. Stratification analysis revealed that minor C allele carriers of rs174547 were associated with decreased activity of D6D in plasma and Asian populations and decreased activity of D5D in the plasma and erythrocytes samples, as well as Asian and European populations.

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L. X. conceived the study design; Y. J. and W. X. searched and selected the trials, N. U., H. Y. and Y. Wu extracted, analysed and interpreted the data; Y. Wang and Y. T. drafted the manuscript.

The authors had no conflicts of interest relevant to this article to disclose.

Supplementary material

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