Inflammatory response to dietary linoleic acid depends on *FADS1* genotype

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ABSTRACT

Background: The health benefits of substituting dietary polyunsaturated fatty acids (PUFAs) for saturated fatty acids are well known. However, limited information exists on how the response to dietary intake of linoleic acid (LA; 18:2n–6) is modified by polymorphisms in the fatty acid desaturase (FADS) gene cluster.

Objectives: The aim of the current study was to test the hypothesis that the *FADS1* rs174550 genotype modifies the effect of dietary LA intake on the fatty acid composition of plasma lipids, fasting glucose, and high-sensitivity C-reactive protein (hsCRP).

Methods: Associations were investigated between genotype, plasma PUFAs, fasting glucose, and hsCRP concentrations in the cross-sectional, population-based Metabolic Syndrome in Men cohort ($n = 1337$). In addition, 62 healthy men from the cohort who were homozygotes for the TT or CC genotype of the *FADS1* rs174550 were recruited to a 4-wk intervention (FADSDIET) with an LA-enriched diet. The fatty acid composition of plasma PUFAs and concentrations of plasma fasting glucose, serum hsCRP, and plasma lipid mediators (eicosanoids and related analogs) were measured at the beginning and end of the 4-wk intervention period.

Results: In the FADSDIET trial, the plasma LA proportion increased in both genotype groups in response to an LA-enriched diet. Responses in concentrations of serum hsCRP and plasma fasting glucose and the proportion of arachidonic acid (20:4n–6) in plasma phospholipids and cholesteryl esters differed between genotype groups (interaction of diet × genotype, $P < 0.05$). In TT homozygous subjects, plasma eicosanoid concentrations correlated with the arachidonic acid proportion in plasma and with hsCRP ($r = 0.4$–0.7, $P < 0.05$), whereas in the CC genotype there were no correlations.

Conclusions: Our findings show that the *FADS1* genotype modifies metabolic responses to dietary LA. The emerging concept that personalized dietary counseling should be modified by the *FADS1* genotype needs to be tested in larger randomized trials. The study was registered at clinicaltrials.gov as NCT02543216. *Am J Clin Nutr* 2019;108:1–11.

Keywords: human, diet, dietary intervention, *FADS1*, fatty acid, linoleic acid, genotype, lipid, oxylipin, gene–diet interaction

Introduction

The fatty acid composition of tissues and blood lipids is predominantly determined by dietary intake and endogenous metabolism, which is strongly genetically regulated (1–6). The Δ5 (D5D) and Δ6 (D6D) desaturases are encoded by the fatty acid desaturase (FADS) *FADS1* and *FADS2* genes, respectively. Both of these genes are located on chromosome 11 (11q12–13.1) and are the key enzymes in the synthesis pathway of long-chain PUFAs (**Figure 1**). Regulating fatty acid metabolism (2–5), polymorphisms in the *FADS* gene cluster also have an important impact on lipid profiles and glucose homeostasis (6–8). The health benefits of substituting dietary long-chain PUFAs for SFAs are well known (9), and many studies also support metabolic benefits of n–6 PUFAs, especially linoleic acid (LA; 18:2n–6) (9–13). Conversely, there are concerns related to endogenous conversion of LA to arachidonic acid (AA; 20:4n–6), which may lead to increased production of downstream proinflammatory and prothrombotic metabolites of AA (e.g., eicosanoids) (14). Although it is important to study the effects of individual PUFAs on inflammation and metabolic diseases, there is also a need to better understand how the enzymes regulating fatty acid metabolism, and the genes coding them, influence this effect.

Many of the downstream products of PUFAs are lipid mediators with prominent roles in pro- and anti-inflammatory processes. This class of lipids arises from metabolism of n–6 and n–3 PUFAs by 1 of 3 major enzymatic pathways, cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP), or by nonenzymatic auto-oxidation (Figure 1) (15). Few studies have investigated how PUFA intake affects the overall lipid mediator profile, and studies conducted in humans are rare (16–19).

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Genetic variation in *FADS1* impacts not only the synthesis of AA but also the synthesis of 5-LOX products (20). However, there are no data related to interactions between dietary intake of PUFAs and genetic variants related to long-chain PUFA metabolism and their possible link to low-grade inflammation.

The aim of this study was to investigate how the interaction of *FADS1* rs174550 genotypes and LA proportions in plasma lipids associate with fasting glucose and low high-sensitivity C-reactive protein (hsCRP). In addition, we investigated how increased consumption of LA affects the fatty acid composition of plasma lipids (primary outcome), lipid mediator profiles, hsCRP, and fasting glucose in individuals with different genotypes (TT or CC) of *FADS1* rs174550 polymorphism in a clinical trial. A common intron variant, rs174550, was selected as a marker for variation in the FADS1/2 locus, because it has been strongly associated with both serum fatty acids and fasting plasma glucose (8, 21).

Methods

Subjects and study design

Metabolic Syndrome in Men cohort.

The Metabolic Syndrome in Men (METSIM) Study includes 10,197 Finnish men, aged 45–73 y at baseline, randomly selected from the population register of the town of Kuopio, Eastern Finland, and examined in 2005–2010 (22). The principal aim of the METSIM study is to investigate genetic and nongenetic factors associated with the risk of type 2 diabetes, cardiovascular disease, and cardiovascular disease risk factors in cross-sectional and longitudinal settings. This study includes a random sample of 1352 men with plasma fatty acids measured at baseline (23), variant rs174550 genotyped, and hsCRP <15 mg/L.

FADSDIET intervention.

Altogether, 225 men from the METSIM study population were invited to participate in the FADSDIET intervention study conducted during spring 2015 at the Department of Clinical Nutrition, University of Eastern Finland [Consolidated Standards of Reporting Trials (CONSORT) flow diagram; **Figure 2**]. Invited men were homozygotes for the *FADS1* rs174550 single nucleotide polymorphism (SNP), nondiabetic, and living in the Kuopio area and had BMIs (kg/m^2) of <30. Homozygote participants were invited in order to obtain the maximum difference in D5D activity between the genotype groups. Exclusion criteria were the use of anticoagulant treatment and severe chronic diseases. Altogether, 62 healthy men were allocated to the intervention, and 59 of them completed the study (Figure 2). During the 4-wk run-in period, the diet was unchanged, but the participants discontinued consumption of fish oil or other oil supplements or lipid-lowering products (plant stanol or plant sterol–containing products), which were not allowed during the study. They completed a 4-d food record representing their baseline diet. Food records were completed in consecutive predefined days including 1 weekend day, and a clinical nutritionist checked the records upon return. Portion sizes were weighed or estimated using household measures and portion-size pictures. During the 4-wk intervention period, participants

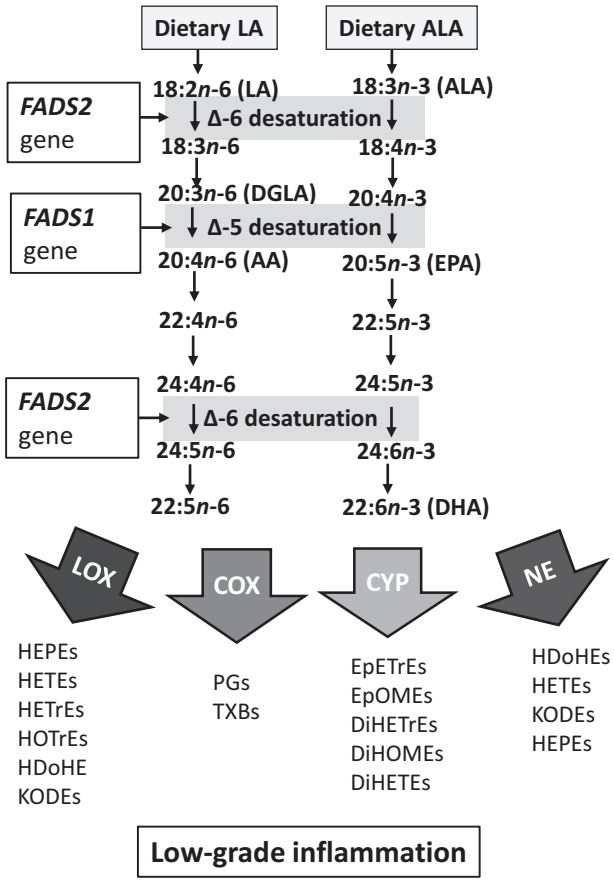

FIGURE 1 Simplified schematic overview of endogenous synthesis of long-chain PUFAs and synthesis of their downstream products via COX, LOX, CYP, and NE. In the absence of stereochemistry, it is not possible to discern the synthetic route of the mono-hydroxy fatty acids, and these compounds are accordingly listed in multiple pathways. AA, arachidonic acid; ALA, α-linolenic acid; COX, cyclooxygenase; CYP, cytochrome P450; DGLA, dihomo-γ-linolenic acid; DiHETE, dihydroxyeicosatetraenoic acid; DiHETrE, dihydroxyeicosatrienoic acid; DiHOME, dihydroxyoctadecenoic acid; EpETrE, epoxyeicosatrienoic acid; EpOME, epoxyoctadecenoic acid; *FADS*, fatty acid desaturase; HDoHE, hydroxydocosahexaenoic acid, HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxytetraenoic acid; HETrE, hydroxyeicosatrienoic acid; HOTrE, hydroxyoctadecatrienoic acid; KODE, oxo-octadecadienoic acid; LA, linoleic acid; LOX, lipoxygenase; NE, nonenzymatic auto-oxidation; PG, prostaglandin; TXB, thromboxane.

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Supplemental Tables 1–4 and Supplemental Figures 1–4 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn.

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Abbreviations used: AA, arachidonic acid; COX, cyclooxygenase; CYP, cytochrome P450; D5D, Δ5 desaturase; D6D, Δ6 desaturase; E%, percentage of total energy; *FADS*, fatty acid desaturase; hsCRP, high-sensitivity C-reactive protein; LA, linoleic acid; LOX, lipoxygenase; SNP, single nucleotide polymorphism.

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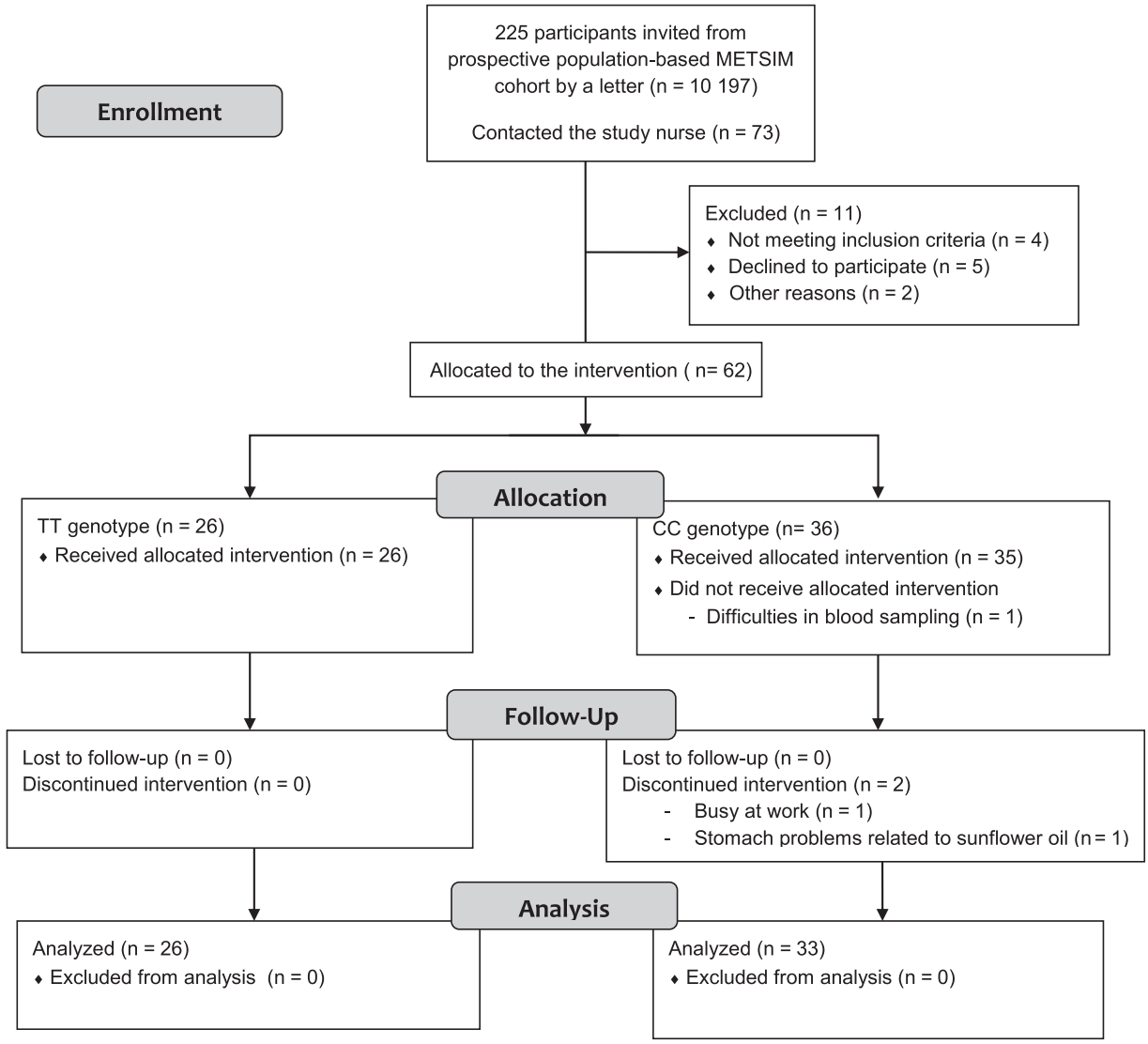

FIGURE 2 CONSORT 2010 flowchart of the FADSDIET study. CONSORT, Consolidated Standards of Reporting Trials; METSIM, Metabolic Syndrome in Men.

consumed their habitual diet with a supplement of 30, 40, or 50 mL (27–45 g) sunflower oil (62% of LA) daily depending on BMI. This supplement provided 17–28 g [6% of total energy (E%)] of LA daily on top of the mean intake of ∼10–12 g (4.5 E%). A 7-d food record (predefined consecutive days) was kept during the intervention period. Participants also recorded their daily consumption of sunflower oil throughout the study. The food records were analyzed by AivoDiet nutrient calculation software (version 2.0.2.1; Aivo Finland) based on national and international analyses and international food-composition tables. The study plan was approved by the Ethical Committee of the Hospital District of Northern Savo. The subjects received both oral and written information.

The *FADS1* rs174550 variant has a high effect size on fatty acids. Therefore, it is possible to observe differences between genotypes with a relatively small sample size: for example, with 10 homozygotes participants/group, there is 95% power to observe significant differences between homozygote genotypes (TT compared with CC, $\alpha = 0.05$) in AA (30% difference) based on cross-sectional data in the METSIM study. However, there were no earlier data on the genotype-specific responses to LA in intervention studies. Based on these assumptions, we estimated that a sample size of 30/group would provide sufficient statistical power.

Measurements

Genotyping.

The variant rs174550 (*FADS1*) was genotyped using the TaqMan SNP Genotyping Assay (Applied Biosystems) according to their protocol.

Biochemical analyses (lipids, glucose, insulin, hsCRP, fatty acids, and lipid mediator profiling).

Concentrations of serum total, LDL, and HDL cholesterol and total triglycerides were analyzed using commercial kits

(981813, 981656, 981823, and 981786, respectively; Thermo Fisher Scientific) and the Konelab 20XTi Clinical Chemistry Analyzer (Thermo Fisher Scientific). The within-run variations (CV%) were 1.9–3.9% and the between-run CV% values were 1.8–3.6 for the lipids. Plasma glucose was analyzed using the Konelab 20XTi Clinical Chemistry Analyzer and Enzymatic photometric (glucose hexokinase) method (kit 981304; Thermo Fisher Scientific). Plasma insulin concentration was analyzed using a chemiluminometric immunoassay method (DiaSorin Liaison Analyzer; DiaSorin GmbH). The within-run variations for glucose and insulin were 2.7% and 3.7%, respectively, and the between-run variations were between 1.8–4.1% and 3.8–5.1%.

hsCRP was analyzed by enhanced immunoturbimetric assay using the Cobas 6000 automated analyzer (Hitachi High Technology Co.) and C-reactive Protein High Sensitive Assay reagent (Roche Diagnostics GmbH). The fatty acid composition of plasma lipid fractions was measured by gas chromatography, as previously described (24). In brief, lipids were extracted from plasma samples using chloroform–methanol (2:1), and lipid fractions were separated with an aminopropyl column. Fatty acids in lipid fractions were transmethylated with 14% borontrifluoride in methanol. Finally, fatty acid methyl esters were analyzed by a 7890A gas chromatograph (Agilent Technologies, Inc.) equipped with a 25-m free fatty acid phase column (Agilent Technologies, Inc.). Cholesteryl nonadecanoate (Nu Chek Prep, Inc.), trinonadecanoin, and phosphatidylcholine dinonadecanoyl (Larodan Fine Chemicals) served as internal standards.

The within-run variation for AA in phospholipids was 0.85%, and the between-run variation was 1.17%. The corresponding CV% values in cholesteryl esters were 0.6% and 1.73%. D5D and D6D activities were estimated by the ratios of 20:4n–6 to 20:3n–6 and 18:3n–6 to 18:2n–6, respectively. Lipid mediator profiling was performed by liquid chromatography–mass spectrometry, as previously described (25).

Statistical methods

Statistical analyses were performed using the IBM SPSS statistics software (version 23; IBM Corp.). Biochemical and statistical analyses were performed only for those individuals who had samples at baseline and after the intervention ($n = 59$; not intention to treat). The normality of the distributions of the variables was tested using a Kolmogorov–Smirnov normality test with Lilliefors significance correction. Variables with skewed distribution were transformed to base-10 logarithmic scale to achieve normal distribution. Nonparametric tests were used when a normal distribution was not achieved. Differences according to the LA tertiles within the genotypes were tested using 1-factor ANOVA. Interaction between genotypes (additive model) and LA proportion were tested using ANCOVA adjusted for LA, genotype, and their interaction. Differences in clinical characteristics and fatty acid distribution between the 3 genotypes were tested using ANOVA for normally distributed variables and a Kruskal–Wallis test for skewed variables. Within-genotype comparisons (0 wk compared with 4 wk) were performed using a paired-samples *t* test for normally distributed variables and a Wilcoxon signed rank test for skewed variables. The diet × genotype interaction was tested with a repeated-measures general linear model. Comparisons between the genotypes were performed using an independent-samples *t* test for normally distributed variables and a Mann–Whitney *U* test for skewed variables. The Pearson chi-square test was used to test differences by statin use between the genotypes. Fold changes were calculated by dividing endpoint values by baseline values. Correlation analyses were performed using Spearman's rank correlation. The Benjamini–Hochberg false-discovery rate was used to adjust general lipid mediator profiling results for multiple comparisons (24). A false-discovery rate *P* value of <0.05 was considered significant among lipid mediators. False-discovery rate *P* values were calculated using R Project for Statistical Computing version 3.4.0 (R Foundation for Statistical Computing).

Results

Clinical characteristics and n–6 PUFAs according to *FADS1* rs174550 genotype in the METSIM study

The clinical characteristics of the METSIM participants according to the genotypes of rs174550 of the *FADS1* gene are shown in **Table 1**. Clinical characteristics did not differ according to genotype, except for participants with the rs174550-TT genotype, who had a lower diastolic blood pressure ($P = 0.034$; Table 1). The proportions of n–6 PUFAs differed across the genotypes in all plasma lipid fractions (**Table 2**), as expected.

Interaction between proportion of plasma LA and rs174550 genotype in the METSIM study

A higher content of LA in plasma phospholipids was associated with favorable clinical characteristics in the METSIM study, including lower fasting glucose and hsCRP (**Supplemental Table 1**). In participants with the rs174550-TT genotype, the concentration of fasting glucose was lower in the second and third LA tertiles, whereas in those with the CC genotype, there were no significant differences between the LA tertiles (genotype × LA interaction, $P = 0.05$; **Figure 3**).

Clinical characteristics, dietary intake, and compliance with the diet in the FADSDIET trial

In order to study the effect of increased consumption of LA in individuals with rs174550-CC or rs174550-TT genotypes of the *FADS1* gene, we conducted a genotype-based trial (FADSDIET) with 59 participants recruited from the METSIM study. The clinical characteristics of the FADSDIET participants are shown in **Table 3**. There were no significant differences in the clinical characteristics at baseline, except for participants in the CC genotype group who were older than those in the TT group ($P < 0.001$). Fasting glucose decreased significantly in participants with the CC genotype ($P = 0.001$) but did not change in participants with the TT genotype (diet × genotype interaction, $P = 0.008$; Table 3).

Based on daily records, the adherence to the consumption of sunflower oil was excellent. The mean consumption of sunflower oil was 30 mL/d (range: 27–30 mL/d) in those who aimed to consume 30 mL/d, 39 mL/d (range: 34–41 mL/d) in those who aimed to consume 40 mL/d, and 49 mL/d (range: 39–50 mL/d) in those who aimed to consume 50 mL/d. Mean consumption was similar with both genotypes ($P = 0.4$). The intakes of energy, total fat (grams and E%), MUFAs (grams and E%), and PUFAs (grams

TABLE 1
Clinical characteristics of METSIM participants according to genotype for *FADS1* rs174550[1]

Clinical characteristics	Genotype TT ($n = 444$)	TC ($n = 648$)	CC ($n = 245$)	*P*
Age, y	54.6 ± 5.6	55.1 ± 5.7	55.4 ± 5.5	0.142
BMI, kg/m[2]	26.4 ± 3.4	26.5 ± 3.7	26.6 ± 3.4	0.636
Waist circumference, cm	96.2 ± 9.6	96.3 ± 10.3	96.1 ± 9.3	0.962
Serum fasting total cholesterol, mmol/L	5.52 ± 0.93	5.51 ± 0.87	5.45 ± 0.89	0.594[2]
Serum fasting LDL cholesterol, mmol/L	3.47 ± 0.81	3.50 ± 0.77	3.41 ± 0.82	0.239[2]
Serum fasting HDL cholesterol, mmol/L	1.50 ± 0.41	1.46 ± 0.39	1.50 ± 0.40	0.211[2]
Serum fasting triglycerides, mmol/L	1.36 ± 0.79	1.41 ± 0.92	1.39 ± 1.02	0.401
Systolic blood pressure, mm Hg	133. ± 16	135 ± 15	135 ± 14	0.134
Diastolic blood pressure, mm Hg	86 ± 9	87 ± 9	87 ± 8	0.034
Plasma fasting glucose, mmol/L	5.8 ± 0.7	5.8 ± 0.6	5.8 ± 0.5	0.434
Plasma fasting insulin, mU/L	7.5 ± 5.2	7.7 ± 5.4	7.4 ± 4.8	0.714
hsCRP, mg/L	1.52 ± 1.81	1.56 ± 1.76	1.57 ± 1.61	0.853

[1]Values are means ± SDs. *P* values were derived by Kruskal–Wallis test unless otherwise indicated. *FADS1*, fatty acid desaturase 1; hsCRP, high-sensitivity C-reactive protein; METSIM, Metabolic Syndrome in Men.
[2]One-factor ANOVA.

and E%) increased during the intervention period (**Table 4**). There were no differences in dietary intake between genotypes. The mean intake of LA increased from a mean of 10 g to 31 g, similarly in both genotype groups (Table 4).

n–6 PUFA composition of plasma lipids in the FADSDIET trial

The percentage changes in n–6 PUFA proportions and estimated D5D and D6D activities in plasma lipid fractions are shown in **Figure 4**. There was a significant increase in the LA proportion in all lipid fractions in both genotype groups. A significant interaction between intervention and genotype was observed in AA, the proportion of which decreased in participants with the CC genotype, but remained unchanged (in phospholipids) or decreased only slightly (in cholesteryl esters) in participants with the TT genotype. The results were similar with absolute concentrations (results not shown).

D5D and D6D activities

The estimated activities of both D5D and D6D were elevated in individuals with the TT genotype compared with individuals with the CC genotype at baseline and after the intervention in

TABLE 2
Proportions of n–6 PUFAs in the METSIM study according to *FADS1* rs174550 genotypes[1]

PUFAs	Genotype TT ($n = 444$)	TC ($n = 648$)	CC ($n = 245$)	*P*
Phospholipids, mol%				
18:2n–6	17.64 ± 2.37	18.75 ± 2.56	20.07 ± 2.68	<0.001
20:3n–6	2.68 ± 0.50	2.81 ± 0.61	2.86 ± 0.81	0.009
20:4n–6	10.01 ± 1.58	8.86 ± 1.30	7.69 ± 1.23	<0.001
20:4n–6 to 20:3n–6 (D5D)	3.85 ± 0.91	3.29 ± 0.77	2.89 ± 0.90	<0.001
Cholesteryl esters, mol%				
18:2n–6	46.97 ± 4.80	48.63 ± 4.89	50.62 ± 4.88	<0.001
18:3n–6	1.11 ± 0.42	0.87 ± 0.35	0.66 ± 0.33	<0.001
20:3n–6	0.76 ± 0.14	0.78 ± 0.17	0.77 ± 0.22	0.280
20:4n–6	7.33 ± 1.36	6.27 ± 1.12	5.20 ± 1.01	<0.001
18:3n–6 to 18:2n–6 (D6D)	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	<0.001
20:4n–6 to 20:3n–6 (D5D)	9.90 ± 2.24	8.34 ± 1.97	7.15 ± 2.08	<0.001
Triglycerides, mol%				
18:2n–6	13.15 ± 3.13	13.33 ± 3.32	13.44 ± 3.35	0.629
18:3n–6	0.43 ± 0.18	0.29 ± 0.14	0.20 ± 0.11	<0.001
20:3n–6	0.33 ± 0.08	0.31 ± 0.08	0.30 ± 0.10	<0.001
20:4n–6	1.50 ± 0.41	1.26 ± 0.34	1.05 ± 0.32	<0.001
18:3n–6 to 18:2n–6 (D6D)	0.03 ± 0.02	0.02 ± 0.01	0.02 ± 0.01	<0.001
20:4n–6 to 20:3n–6 (D5D)	4.73 ± 1.34	4.21 ± 1.30	3.80 ± 1.51	<0.001

[1]Values are means ± SDs. *P* values were derived by using ANOVA, calculated from logarithmic values. D5D, Δ5 desaturase; D6D, Δ6 desaturase; *FADS1*, fatty acid desaturase 1; METSIM, Metabolic Syndrome in Men; mol%, mole percent.

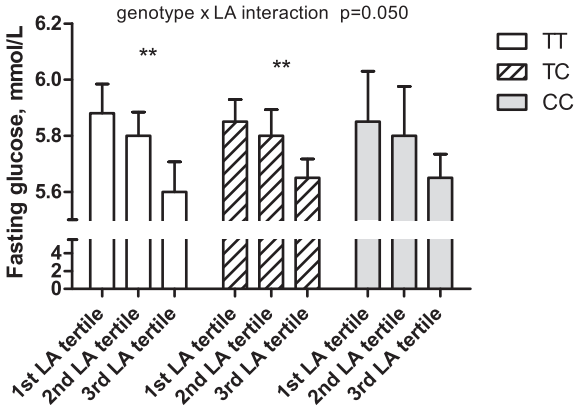

FIGURE 3 Fasting glucose concentration according to *FADS1* rs174550 genotypes and tertiles of LA proportions in phospholipids in the METSIM population ($n = 444$ in TT, $n = 648$ in TC, and $n = 245$ in CC genotypes). Values are means (95% CIs). Differences according to LA tertiles within genotypes have been tested using 1-factor ANOVA. Interactions between genotypes (additive model) and LA proportions were tested using ANCOVA adjusted for LA, genotype, and their interaction. $^{**}P < 0.01$. *FADS1*, fatty acid desaturase 1; LA, linoleic acid; METSIM, Metabolic Syndrome in Men.

the FADSDIET study (**Supplemental Figure 1**), as detailed in a previous publication (26). The same findings were observed in the METSIM study (Table 2).

Low-grade inflammation

In the METSIM population, participants with rs174550-TT or rs174550-TC genotypes had a lower hsCRP concentration in the tertile with the highest proportion of LA in phospholipids compared with the other LA tertiles, whereas this was not observed in carriers of the CC genotype (**Supplemental Figure 2**A). However, there were no significant genotype × LA interactions. In the FADSDIET intervention, the response to higher LA intake in hsCRP was different between the genotypes. Following the high-LA diet, individuals with the rs174550-TT genotype had a trend toward decreased ($P = 0.088$) hsCRP, whereas individuals with the rs174550-CC genotype had a trend toward increased ($P = 0.084$) hsCRP (diet × genotype interaction, $P < 0.05$; **Figure 5**).

Lipid mediator concentrations

The distributions of lipid mediator concentrations according to their parent PUFAs are shown in **Supplemental Figure 3**. The genotype affected concentrations of AA-derived lipid mediators (eicosanoids) belonging to various pathways, including LOX, COX, and CYP450 (**Supplemental Table 2**). Eicosanoid concentrations were higher in individuals with the TT genotype than in participants with the CC genotype, both at baseline and at the end of the intervention; however, only a few lipids changed during the intervention (Supplemental Figure 3, Supplemental Table 2). As expected, increased consumption of LA in the FADSDIET intervention increased the concentrations of most of the LA-derived lipid mediators in both genotype groups (Supplemental Table 2). After correction for multiple comparisons, there were no significant diet × genotype interactions. The results for the individual stereoisomers are shown in **Supplemental Table 3**.

Lipid mediators to the PUFA ratios

Because results for absolute concentrations of lipid mediators were different from our hsCRP findings, we looked at the lipid mediator to phospholipid PUFA ratios in plasma to examine the relative levels of lipid mediators compared with their precursors PUFAs. Conversely, with the absolute levels, the relative levels of many eicosanoids were lower in the TT genotype group than in the CC genotype group at baseline and after

TABLE 3
Clinical characteristics of the FADSDIET participants according to *FADS1* rs174550 genotypes at baseline and after the 4-wk high-LA diet[1]

	0 wk		4 wk		0 wk vs. 4 wk		
						P[3]	
Clinical characteristics	TT ($n = 26$)	CC ($n = 33$)	TT ($n = 26$)	CC ($n = 33$)	P (diet × genotype)[2]	TT	CC
Age, y	55.2 ± 2.3	58.6 ± 3.1					
Weight, kg	80.8 ± 10.3	79.1 ± 8.9	80.8 ± 10.3	79.2 ± 9.0	0.799		
BMI, kg/m^2	25.6 ± 2.4	24.7 ± 2.2	25.6 ± 2.4	24.7 ± 2.2	0.997		
Waist circumference, cm	94.4 ± 8.4	93.4 ± 6.6	94.3 ± 8.3	93.3 ± 6.6	0.952		
Systolic blood pressure, mm Hg	128 ± 11	127 ± 13	126 ± 9	125 ± 13	0.99		
Diastolic blood pressure, mm Hg	82 ± 7	82 ± 8	82 ± 6	81 ± 8	0.166		
Plasma glucose,[4] mmol/L	5.6 ± 0.4	5.7 ± 0.4	5.6 ± 0.5	5.6 ± 0.4	0.008	0.483	0.001
Plasma insulin,[4] mU/L	7.5 ± 3.2	7.8 ± 3.6	7.7 ± 3.1	7.8 ± 4.3	0.703		
Serum total cholesterol,[4] mmol/L	5.2 ± 0.8	5.5 ± 1.2	5.1 ± 0.6	5.2 ± 1.0	0.371		
Serum HDL cholesterol,[4] mmol/L	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.3	1.4 ± 0.4	0.612		
Serum LDL cholesterol,[4] mmol/L	3.2 ± 0.6	3.4 ± 0.9	3.0 ± 0.5	3.1 ± 0.8	0.732		
Serum triglycerides,[4] mmol/L	1.2 ± 0.6	1.4 ± 0.8	1.2 ± 0.7	1.5 ± 1.0	0.625		
Use of statins, *n* (%)	2 (8)	2 (6)					

[1] Values are means ± SDs unless otherwise indicated. *FADS1*, fatty acid desaturase 1; LA, linoleic acid.
[2] Repeated-measures general linear model.
[3] Paired-samples *t* test.
[4] Fasting.

TABLE 4
Dietary intake during the FADSDIET intervention based on 4-d (baseline) and 7-d (intervention) food records[1]

	Baseline		Intervention		
	TT ($n = 26$)	CC ($n = 33$)	TT ($n = 26$)	CC ($n = 33$)	*P*-intervention
Energy, kcal	2262 ± 391	2340 ± 456	2503 ± 416	2592 ± 429	<0.001
Carbohydrates					
E%	41.1 ± 7.3	41.1 ± 5.8	37.1 ± 7.0	36.7 ± 5.6	<0.001
g	230.0 ± 50.4	238.5 ± 47.7	230.7 ± 52.6	239.1 ± 59.0	0.899
Fiber, g	25.1 ± 9.0	27.8 ± 8.0	25.0 ± 7.2	27.3 ± 7.9	0.881
Sucrose					
E%	7.6 ± 2.9	8.0 ± 2.6	6.0 ± 2.2	7.6 ± 2.9	0.001
g	43.5 ± 19.0	47.3 ± 20.4	38.4 ± 16.2	51.1 ± 26.6	0.579
Protein					
E%	18.3 ± 4.1	17.3 ± 2.9	15.1 ± 2.9	15.0 ± 2.1	<0.001
g	102.5 ± 28.6	100.6 ± 23.0	94.6 ± 26.3	97.1 ± 19.8	0.018
Fat					
E%	34.8 ± 7.1	34.1 ± 5.3	43.2 ± 4.6	42.3 ± 4.7	<0.001
g	88.6 ± 27.6	89.9 ± 26.6	119.7 ± 22.3	120.8 ± 18.1	<0.001
SFAs					
E%	12.5 ± 3.8	12.1 ± 2.4	12.3 ± 2.1	11.8 ± 2.5	0.506
g	31.7 ± 12.0	32.0 ± 10.9	34.6 ± 9.5	34.0 ± 8.9	0.001
g/total fat	0.36 ± 0.05	0.35 ± 0.04	0.29 ± 0.04	0.28 ± 0.04	<0.001
MUFAs					
E%	11.9 ± 2.5	12.1 ± 2.3	13.3 ± 1.5	13.2 ± 1.6	<0.001
g	30.4 ± 10.0	31.8 ± 9.9	36.9 ± 7.5	37.7 ± 6.3	<0.001
g/total fat	0.34 ± 0.03	0.35 ± 0.03	0.31 ± 0.01	0.31 ± 0.02	<0.001
PUFAs					
E%	6.2 ± 1.8	6.1 ± 1.6	13.5 ± 2.5	13.3 ± 2.2	<0.001
g	15.8 ± 6.3	15.9 ± 5.1	37.0 ± 7.6	37.7 ± 4.8	<0.001
g/total fat	0.18 ± 0.05	0.18 ± 0.04	0.31 ± 0.05	0.32 ± 0.05	<0.001
Linoleic acid					
g	9.8 ± 4.4	9.8 ± 3.8	31.4 ± 7.4	31.1 ± 4.9	<0.001
E%	3.8 ± 1.3	3.8 ± 1.3	11.4 ± 2.5	11.0 ± 2.1	<0.001
α-Linolenic acid, g	2.6 ± 1.3	2.4 ± 1.2	2.5 ± 8.3	2.5 ± 8.0	0.289
Cholesterol, mg	339 ± 176	302 ± 130	315 ± 142	274 ± 71	0.049

[1]Values are mean ± SDs. *P* values were derived by using a repeated-measures general linear model. E%, percentage of total energy.

the intervention (**Supplemental Table 4**). After correction for multiple comparisons, there were no significant diet × genotype interactions.

Correlations between lipid mediators, fatty acids, and hsCRP

The correlations between proportions of substrate PUFAs in plasma phospholipids and concentrations of plasma lipid mediators are shown in **Figure 6** and **Supplemental Figure 4**. As expected, LA-derived lipid mediators correlated positively with LA, and AA-derived lipid mediators correlated positively with AA. However, correlations between the AA proportion in the plasma phospholipids and eicosanoids in plasma were much stronger and only reached significance in the TT genotype. Correlations between lipid mediators and hsCRP were also strongly dependent on genotype. At baseline, many eicosanoids correlated positively with hsCRP in the TT genotype but not in participants with the CC genotype. Correlations between eicosanoids and hsCRP were lost at the end of the intervention. There were no direct correlations between AA proportion in phospholipids and hsCRP concentration in either genotype.

Discussion

Low-grade inflammation is an important factor in the progression of many chronic diseases such as type 2 diabetes and cardiovascular diseases (27, 28). Low-grade inflammation could be affected by diet (29), but the effect of the amount or quality of dietary fat has remained controversial (10, 30). Based on our data, the discrepant findings could be partly related to a genetic variation in the *FADS1* locus. We showed that besides regulation of proportions of PUFAs in plasma lipids, the *FADS1* rs174550 genotype modified concentrations of inflammation-related lipid mediators. Furthermore, responses in concentrations of serum hsCRP and plasma fasting glucose differed between the genotype groups. In addition, correlations between lipid mediators and their substrate fatty acids as well as correlations between lipid mediators and plasma hsCRP concentrations in healthy men were modified by genotype.

As expected, increased intake of LA significantly elevated the plasma concentrations of many LA-derived lipid mediators in both genotypes. However, there were few observed changes in eicosanoid concentrations following the LA intervention. Recently, Leng et al. (19) showed in rats that increased dietary LA resulted in higher concentrations of AA and other n–6–derived lipid mediators in tissues such as kidney and liver. However, in

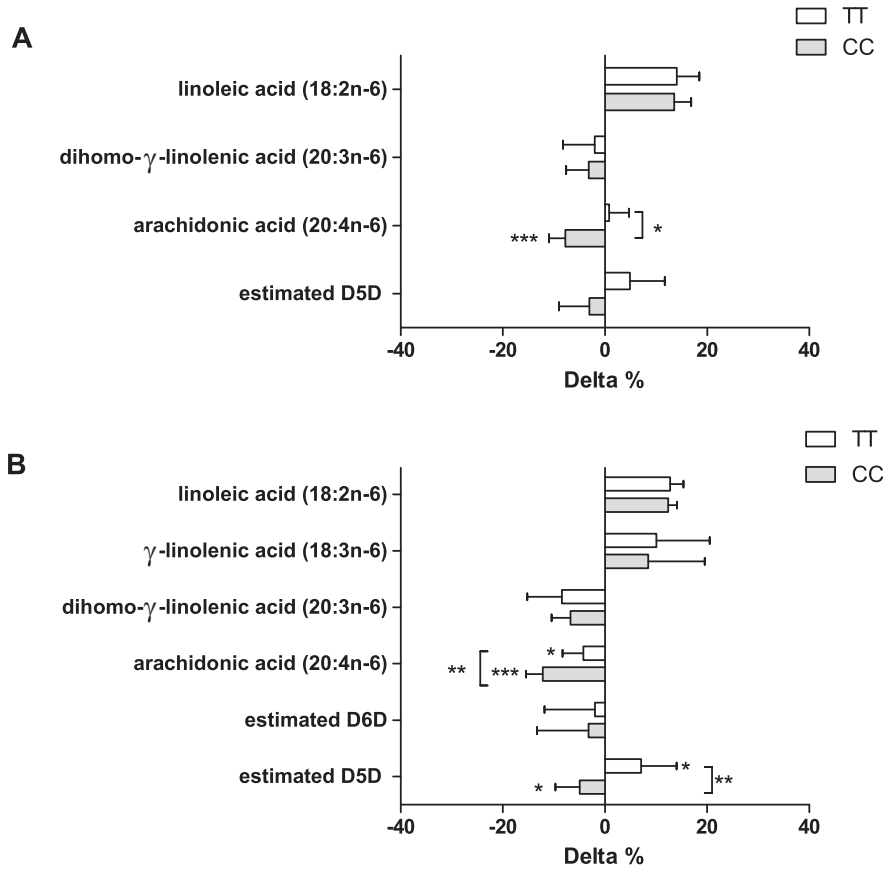

FIGURE 4 Changes in proportions of n–6 PUFAs in plasma phospholipids (A) and cholesteryl esters (B) according to *FADS1* rs174550 genotypes in the FADSDIET intervention. Values are mean (95% CI) percentages. The diet × genotype interaction was tested using a repeated-measures general linear model. There were significant diet × genotype interactions for arachidonic acid in phospholipids ($P = 0.014$) and arachidonic acid in cholesteryl esters ($P = 0.003$) and for estimated D5D activity in cholesteryl esters ($P = 0.004$). Within-genotype comparisons (0 wk compared with 4 wk) were performed using a paired-samples *t* test . $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. TT, $n = 26$; CC, $n = 33$. D5D, Δ5 desaturase; D6D, Δ6 desaturase; *FADS1*, fatty acid desaturase 1.

agreement with our findings, only LA-derived lipid mediators were increased in serum. The effect of the *FADS1* genotype upon fatty acid and lipid mediator profiles in other tissues in humans remains to be elucidated.

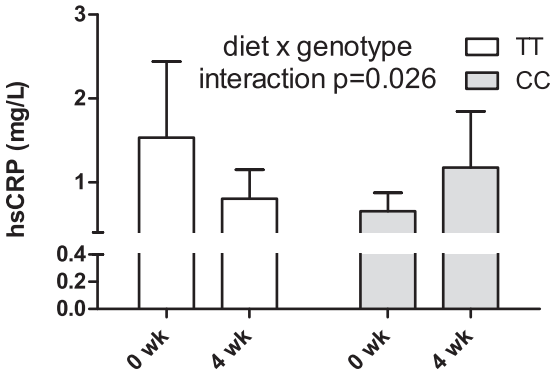

FIGURE 5 Mean (95% CI) concentrations of hsCRP ($n = 26$ in TT, $n = 33$ in CC) at baseline and after the 4-wk high-LA diet according to rs174550 genotypes in the FADSDIET intervention. The diet × genotype interaction was tested using a repeated-measures general linear model. There was a significant diet × genotype interaction ($P = 0.026$). hsCRP, high-sensitivity C-reactive protein.

Recent findings in *Fads1* knockdown mice showed promotion of hepatic inflammation, especially following supplementation of substrate fatty acids for long-chain PUFA biosynthesis (31). In those mice for which n–3 substrate fatty acids were provided, the findings were in line with our observation of increased hsCRP in the participants with decreased D5D and D6D activities (individuals with the CC allele) during the high-LA intervention. It is noteworthy that inflammation seems not to be mediated by increased AA concentration, because AA concentration was decreased during the intervention both in *Fads1* knockdown mice and in participants of the present intervention with a genotype related to decreased D5D activity. Furthermore, despite increased hepatic inflammation, *FADS1* knockdown mice had improvements in glucose tolerance (31), similar to our findings of significantly decreased fasting glucose concentration in the CC genotype compared with the TT genotype. The *FADS1* rs174550 genotype has previously been linked to fasting glucose, but there are no previous studies in humans showing diet × genotype interactions regarding this SNP and glucose metabolism.

It has been suggested that the association between PUFAs and inflammation is mediated by anti- and proinflammatory lipid mediators such as eicosanoids (5). In our study, lipid mediator profiling did not reveal a simple explanation for the genotype-specific response in hsCRP. However, we found that the

			Linoleic acid						Arachidonic acid						hs-CRP					
			Baseline		4 week		FOLD		Baseline		4 week		FOLD		Baseline		4 week		FOLD	
Lipid mediator	**PUFA**	**Pathway**	**TT**	**CC**	**TT**	**CC**	**TT**	**CC**	**TT**	**CC**	**TT**	**CC**	**TT**	**CC**	**TT**	**CC**	**TT**	**CC**	**TT**	**CC**
13-HODE	LA	LOX/NE	0.2	-0.1	0.2	0.0	0.1	-0.1	-0.2	0.1	0.1	-0.2	0.2	0.0	0.4	0.0	0.2	-0.1	0.1	0.1
13-KODE	LA	LOX/NE	-0.2	-0.2	0.1	0.1	0.0	-0.5	0.1	0.0	0.1	-0.2	0.0	-0.1	0.3	0.1	-0.1	-0.1	0.0	0.1
12(13)-EpOME	LA	CYP450	0.3	0.3	0.4	0.3	0.2	0.0	-0.3	-0.3	-0.2	-0.3	-0.1	-0.2	0.1	0.1	0.3	0.0	0.2	0.2
9(10)-EpOME	LA	CYP450	0.1	0.1	0.3	0.2	0.2	0.0	0.0	-0.2	-0.1	-0.2	0.0	-0.1	0.2	0.2	0.4	0.1	0.2	0.0
12,13-DiHOME	LA	CYP450/sEH	0.2	0.2	0.5	0.3	0.3	0.0	-0.4	-0.2	-0.4	-0.3	0.0	-0.1	0.1	0.0	0.1	-0.2	0.1	0.1
9,10-DiHOME	LA	CYP450/sEH	0.4	-0.1	0.6	0.2	0.4	0.3	-0.5	-0.1	-0.3	-0.2	-0.1	-0.3	-0.1	0.2	0.2	0.0	-0.1	-0.1
9-HODE	LA	LOX/NE	0.0	0.0	0.0	0.0	0.0	-0.2	0.0	-0.1	0.2	-0.2	0.1	0.1	0.4	0.1	0.3	-0.1	0.2	-0.1
9,10,13-TriHOME	LA	LOX	0.1	0.1	0.0	0.3	0.1	0.1	0.2	0.1	0.1	-0.2	-0.3	0.0	0.0	0.0	0.2	0.1	0.3	0.1
9,12,13-TriHOME	LA	LOX	0.1	0.2	0.1	0.3	0.1	0.3	-0.2	-0.1	0.1	-0.1	-0.2	-0.2	-0.2	-0.1	0.3	0.1	0.0	0.0
9-KODE	LA	LOX/NE	-0.1	0.2	-0.1	0.1	0.2	0.0	0.3	-0.3	0.2	-0.3	0.0	-0.1	0.3	0.1	0.3	-0.1	0.0	-0.1
EKODE	LA	NE	0.3	0.2	-0.1	0.3	0.0	0.4	-0.4	-0.2	0.0	-0.1	0.1	-0.1	-0.2	-0.3	0.2	-0.3	-0.1	0.0
12(13)-EpODE	LA	CYP450	0.0	0.2	0.3	0.0	-0.1	-0.2	-0.2	-0.1	-0.4	0.1	-0.2	0.1	0.0	0.0	0.1	0.1	0.1	-0.1
12-HETE	AA	LOX/CYP/NE	-0.4	-0.3	-0.4	-0.5	-0.2	-0.3	0.4	0.3	0.6	0.5	0.2	0.3	0.6	-0.1	0.3	0.0	0.1	-0.1
12-KETE	AA	LOX/NE	-0.4	-0.5	-0.2	-0.2	-0.1	-0.4	0.3	0.4	0.3	0.1	-0.1	0.1	0.5	-0.1	-0.3	-0.3	0.1	0.0
15-HETE	AA	LOX/CYP/NE	-0.3	-0.2	-0.3	-0.3	0.0	-0.3	0.4	0.2	0.5	0.1	0.1	0.2	0.4	-0.2	0.2	0.1	-0.1	-0.1
15-KETE	AA	LOX/NE	-0.3	-0.2	-0.2	-0.1	0.1	-0.5	0.2	0.0	0.2	-0.1	0.0	0.0	0.2	0.0	-0.2	0.0	-0.1	0.0
5-HETE	AA	LOX/NE	-0.6	-0.4	-0.1	-0.5	-0.3	-0.4	0.5	0.1	0.4	0.4	0.2	0.3	0.2	0.1	0.1	-0.2	0.2	-0.2
5-KETE	AA	LOX/NE	0.1	-0.2	-0.3	-0.1	-0.1	0.2	0.0	0.2	0.4	0.2	0.0	-0.1	0.1	-0.2	0.2	-0.2	0.5	0.2
TXB2	AA	COX	-0.3	-0.1	-0.2	-0.1	-0.2	-0.2	0.4	0.1	0.3	-0.1	0.2	0.2	0.5	-0.1	0.2	0.0	0.0	0.0
PGE2	AA	COX	-0.3	-0.1	-0.2	0.0	-0.1	-0.2	0.4	0.0	0.3	-0.1	0.2	0.1	0.4	-0.1	0.2	0.1	0.1	0.2
PGF2a	AA	COX	-0.1	-0.2	-0.5	-0.2	0.1	-0.2	0.3	0.0	0.7	0.0	0.1	0.3	0.3	0.2	0.3	-0.1	0.0	0.1
12-HHTrE	AA	COX	-0.2	-0.2	-0.2	-0.1	0.0	-0.3	0.4	0.1	0.4	0.0	0.0	0.3	0.6	-0.1	0.2	0.0	0.0	0.0
11(12)-EpETrE	AA	CYP450	0.2	-0.1	0.1	-0.3	0.1	0.0	0.1	0.0	0.0	0.2	-0.1	0.1	0.4	0.1	0.1	-0.1	0.2	0.0
8(9)-EpETrE	AA	CYP450	-0.4	-0.4	-0.3	-0.5	-0.2	-0.5	0.4	0.3	0.5	0.3	0.1	0.2	0.6	-0.1	-0.1	-0.2	0.1	-0.1
14(15)-EpETrE	AA	CYP450	0.2	0.0	0.0	-0.2	0.1	-0.4	-0.2	0.0	0.0	0.1	0.0	0.3	0.2	-0.2	-0.1	0.1	-0.1	0.1
5,6-DiHETrE	AA	CYP450-sEH	-0.3	-0.1	0.0	-0.2	-0.6	-0.4	0.3	0.1	0.2	0.1	0.4	0.5	0.2	0.1	0.3	0.3	0.3	-0.1
11,12-DiHETrE	AA	CYP450-sEH	-0.2	0.1	0.0	-0.1	-0.4	-0.1	0.3	0.1	0.2	0.3	0.4	0.2	-0.2	-0.1	0.1	-0.1	0.1	-0.2
14,15-DiHETrE	AA	CYP450-sEH	-0.2	0.1	-0.1	-0.2	-0.2	-0.3	0.4	0.1	0.3	0.3	0.5	0.3	-0.1	-0.1	0.2	-0.1	0.0	-0.2
8,9-DiHETrE	AA	CYP450-sEH	-0.2	-0.2	0.0	-0.2	-0.3	-0.3	0.4	0.2	0.3	0.3	0.3	0.2	0.1	0.2	0.3	0.1	0.0	-0.3
19-HETE	AA	CYP450	-0.2	-0.4	-0.2	0.0	-0.2	-0.1	0.3	0.4	0.4	0.1	0.4	-0.3	0.2	0.0	0.1	0.1	0.1	0.0
8-HETE	AA	CYP/NE	-0.5	-0.3	-0.4	-0.4	0.0	0.0	0.3	0.2	0.6	0.4	0.2	0.1	0.1	-0.1	0.1	-0.3	0.0	-0.2
11-HETE	AA	CYP450/NE	-0.4	-0.2	-0.3	-0.3	-0.2	-0.3	0.5	0.1	0.5	0.2	0.2	0.2	0.6	-0.1	0.2	-0.1	0.1	-0.1
5-iPF2α-VI	AA	NE	0.1	0.1	-0.2	0.2	0.3	0.3	0.0	0.1	0.1	0.0	-0.4	0.0	0.2	-0.1	0.0	-0.2	-0.3	-0.2

Color scale for r	-1.0	-0.8	-0.6	-0.4	-0.2	0.0	0.2	0.4	0.6	0.8	1

FIGURE 6 Spearman rank correlations between the fatty acid substrates and lipid mediators and hsCRP at baseline and at the end of the intervention in the FADSDIET study ($P < 0.05$). AA, arachidonic acid; COX, cyclooxygenase; CYP450/CYP, cytochrome P450; DiHETrE, dihydroxyeicosatrienoic acid; DiHOME, dihydroxyoctadecenoic acid; EpETrE, epoxyeicosatrienoic acid; EpOME, epoxyoctadecenoic acid; EKODE, epoxyketo-octadecenoic acid; EpODE, Epoxyoctadecadienoic acid; HETE, hydroxytetraenoic acid; hsCRP, high-sensitivity C-reactive protein; HODE, hydroxyoctadecadienoic acid; HHTrE, hydroxy-heptadecatrienoic acid; iPF2a-VI, Isoprostane F2a-VI; KETE, ketoeicosatetraenoic acid; KODE, oxo-octadecadienoic acid; LA, linoleic acid; LOX, lipoxygenase; NE, nonenzymatic auto-oxidation; PGE, prostaglandin E; PGF2a, prostaglandin F2a; sEH, soluble epoxide hydrolase; TriHOME, trihydroxyoctadecenoic acid; TXB, thromboxane.

correlation between eicosanoids and hsCRP is modified by the *FADS1* genotype, further strengthening the conclusion that the genotype modifies the interaction between diet and inflammation. In future studies, it would be important to also investigate *FADS1* genotype–specific effects on n–3 fatty acid interventions, because in real life, the diet is always a combination of both n–3 and n–6 fatty acids, and there is competition with the same enzymes both in long-chain PUFAs (32) and in lipid mediator synthesis pathways (33–35). The regulation of lipid mediator biosynthesis is known to be complex. In in vitro analyses, the selectivity for formation of CYP products of n–3 over n–6 PUFAs has been shown (35), whereas the opposite selectivity has been shown in other studies of LOX and COX enzymes (33, 34). It was recently shown in mice that *Fads1* is an important regulator of inflammation initiation and resolution, and endogenous and exogenous (dietary) n–3 and n–6 fatty acids are key determinants of inflammatory disease progression (31). The *FADS1* rs174550 genotype has not been previously linked to hsCRP, although few other *FADS* variants have been associated with CRP (5, 36). Interestingly, hsCRP concentration did not differ among the genotypes in our cross-sectional data, but the response to a high-LA diet was genotype specific.

The relatively small sample size could be considered a limitation in our clinical intervention. However, the study design is unique and powerful due to the genotype-based recruitment of individuals matched for sex and BMI. Furthermore, the *FADS1* rs174550 variant has a high effect size on fatty acid concentrations, and so it was possible to observe differences between genotypes with this sample size exceeding power calculations. In this study, a common variant, rs174550, associated with PUFA concentrations and fasting glucose was selected as a marker for variation in the *FADS1/2* locus (8, 21). In this type of candidate gene–based intervention, only a single SNP could be considered. A more complex approach that takes into consideration an additive model of *FADS* SNPs or *FADS* haplotypes could have shown stronger effects (36). However, from a practical point of view, the selection of participants from a population based on a longer haplotype would be extremely challenging.

Another limitation of the study is that we were able to determine changes only in plasma. We were not able to measure tissue concentrations of PUFAs in this study, and it is possible that changes in tissue concentrations could explain the missing link between the proportions of fatty acids and the concentration of hsCRP. Our earlier findings suggest that there seems to be a complex interaction, partly regulated by the *FADS* genotype, regulating the interactions between fatty acids in adipose tissue and inflammation in the liver (37). Based on food records, energy intake was significantly increased during the intervention period, which could be considered a third limitation. However, there were no changes in body weight or BMI, and an increase in energy intake was similar in both genotype groups. It is likely that the increased energy intake was at least partly related to the fact that oil consumption was carefully recorded during the intervention period. Energy intake should in any case be considered, especially in longer interventions. A major strength of this study is that we were able to combine data from both cross-sectional and intervention studies. However, because both studies were performed in middle-aged and older men, these results cannot be generalized to women or the younger population, for example.

In conclusion, the *FADS1* genotype modifies the lipid mediator profile and inflammatory responses to an LA-rich diet. This is a new concept warranting further randomized trials in individuals with specific genotypes to demonstrate potentially divergent effects of diets with modified fatty acid content. It remains to be elucidated if it would be beneficial to have genotype-based modifications in recommendations for the intake of LA and possibly also for n–3 fatty acids.

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The authors' responsibilities were as follows—JP, ML, and US: designed the research; US and MAL: planned and conducted the clinical dietary intervention; CEW: provided essential reagents and equipment for lipid mediator profiling analyses; AF, BS, and MAL: performed lipid mediator profiling analyses; MAL: performed statistical analyses, wrote the manuscript, and had primary responsibility for final content; JÅ: responsible for fatty acid analyses and all authors: approved the final draft of the manuscript and read and approved the final manuscript. The authors reported no conflicts of interest.

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