Original Article

Relationship between the estimates of desaturase activities and cardiometabolic phenotypes in Koreans

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(Received 6 December, 2010; Accepted 1 February, 2011; Published online 16 July, 2011)

In the present study, we evaluated the relationships of estimated desaturase activities with cardiometabolic risk factors including abdominal obesity, atherogenic lipoprotein phenotype and inflammation in Koreans. Ninety-three healthy volunteers participated in this cross-sectional study. LDL particle size was determined using gradient gel electrophoresis and inflammatory markers including C-reactive protein, soluble intercellular adhesion molecule-1, and adiponectin were measured. Stearoyl–coA desaturase, delta-6 desaturase and delta-5 desaturase were estimated as precursor to fatty acid ratios. The results showed that stearoyl–coA desaturase was correlated with body mass index ($r = 0.235$, $p<0.05$), triglyceride ($r = 0.261$, $p<0.001$), and HDL-cholesterol ($r = -0.226$, $p<0.05$). Stearoyl–coA desaturase was associated with only triglyceride ($r = 0.283$, $p<0.01$). Delta-6 desaturase was correlated with body mass index ($r = 0.236$, $p<0.05$), waist circumference ($r = 0.218$, $p<0.05$), triglyceride ($r = 0.399$, $p<0.001$), C-reactive protein ($r = 0.333$, $p<0.001$), soluble intercellular adhesion molecule-1 ($r = 0.229$, $p<0.05$), HDL-cholesterol ($r = -0.325$, $p<0.01$), LDL particle size ($r = -0.297$, $p<0.01$) and adiponectin ($r = -0.233$, $p<0.05$). In contrast, delta-5 desaturase was correlated with body mass index ($r = -0.324$, $p<0.01$), waist circumference ($r = -0.276$, $p<0.01$), triglyceride ($r = -0.329$, $p<0.01$), C-reactive protein ($r = -0.215$, $p<0.05$), HDL-cholesterol ($r = 0.262$, $p<0.05$) and LDL particle size ($r = 0.278$, $p<0.01$). Stepwise multiple regression analysis revealed that delta-6 desaturase ($p<0.01$) together with waist circumference ($p<0.001$) were found to be independent factors for determining plasma levels of C-reactive protein ($R^2 = 0.230$). Estimated desaturase activities are closely associated with the features of cardiometabolic risk in Koreans.

***Key Words*: desaturase, fatty acid composition, cardiometabolic risk factor, inflammation, atherogenic dyslipidemia**

The concept of cardiometabolic risk factors is a cluster of conventional cardiovascular risk factors and metabolic syndrome factors including central obesity, hypertension, insulin resistance, dyslipidemia, and inflammatory responses,[1] which are known to increase cardiovascular morbidity. It has been demonstrated that early detection and control of cardiometabolic risk factors effectively reduce cardiovascular disease (CVD).[2–3] Therefore, clinical settings require identifying potential biomarkers to serve as noninvasive and sensitive predictors for the early stage CVD and new markers for the cardiometabolic phenotype clusters.

Accumulating data have demonstrated that estimates of fatty acid desaturases along with individual serum fatty acids are related to CVD and predict risks and mortality of CVD.[4] Fatty acid desaturase is the enzyme that catalyzes an endogenous fatty acid synthesis. Desaturase activity is estimated indirectly as a product/precursor fatty acid ratio in serum phospholipid or cholesterol esters which reflects both dietary fatty acids intake and endogenous metabolism of fatty acids.[5] Evidence from observational, case-control and prospective studies has shown that desaturase avtivities are associated with CVD, obesity, insulin resistance and metabolic syndrome.[6–8]

Based on the above information, evaluating the relationships between estimated desaturase activities and comprehensive cardiometabolic risk factors that are emerging risk factors for CVD is clinically relevant, but it has not been extensively studied. In the present study, we examined the associations between estimated desaturase activities and individual fatty acid profiles with cardiometabolic risk factors including abdominal obesity, atherogenic lipoprotein phenotype and inflammation in Koreans. For the measurements of cardiometabolic risks, we determined body mass index (BMI) and waist circumference as surrogate measures for abdominal obesity. Also, serum levels of triglyceride (TG), HDL-cholesterol and LDL particle size were measured to evaluate atherogenic dyslipidemia. And finally, plasma levels of adiponectin, C-reactive protein (CRP) and soluble intercellular adhesion molecule-1 (sICAM-1) were determined as markers for inflammation.

Methods

Study subjects. Ninety-three volunteers participated in the present study. The subjects were all healthy and those who were taking hypolipidemic medication, antioxidative vitamins, or had been diagnosed with uncontrolled hypertension or type 2 diabetes mellitus were excluded. The purpose of the study was carefully explained to all participants and their informed consent was obtained prior to their participation. The study protocol was approved by the Institutional Review Board of Yonsei University College of Medicine and carried out in accordance with the Helsinki Declaration.

Body weight and height were measured and BMI was calculated. Waist circumference was measured twice to the nearest 0.1 cm with a flexible tape measure at the level of the minimum circumference, usually at the level of the navel. Venous blood samples were collected from the forearm in EDTA-treated and plain tubes after a fasting period. The tubes were immediately covered with aluminum foil and placed on ice until they arrived at the analytical laboratory, where they were stored at −70°C until analysis.

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doi: 10.3164/jcbn.10-147

Serum lipid profiles and LDL particle size. Fasting blood samples were taken and serum cholesterol, LDL-cholesterol and HDL-cholesterol were measured with commercially available kits (Choongwae, Seoul, Korea) by enzymatic methods. Serum triglyceride levels were analyzed using a total glycerol test kit (Roche, Basel, Switzerland). All determinations were performed on a Hitachi 747 auto-analyzer (Hitachi Ltd. Tokyo, Japan). Non-denaturing polyacrylamide gradient gel electrophoresis with lipid staining of the plasma was performed to determine peak LDL particle diameter, as described previously.[9] Within this procedure, a smaller LDL peak diameter indicates a relative abundance of small, dense LDL particles.

Plasma CRP, sICAM-1 and adiponectin concentrations. Plasma CRP was measured by an Express Plus autoanalyzer (Chiron Diagnostics Co., MA) using a commercially available high-sensitivity kit, CRP-Latex (II) X2 (Seiken Laboratories Ltd., Tokyo, Japan). Plasma levels of sICAM-1 were measured by enzyme immunoassay (ELISA Kit, R&D Systems, Minneapolis, MN). The resultant color reaction was read at 450 nm using a Victor^2 reader. Plasma adiponectin concentration was measured using an enzyme immunoassay (Human Adiponectin ELISA kit, B-Bridge International Inc., CA). The assay was read using a Victor^2 (Perkin Elmer Life Sciences, Turku, Finland) at 450 nm and the wavelength correction was set to 540 nm.

Serum phospholipid fatty acid composition and estimation of desaturase activity. Total lipids were extracted according to the method of Folch, and the phospholipid fraction was isolated by using thin-layer chromatography with hexane:diethyl ether:acetic acid (80:20:2) development solvent. The phospholipid fractions were then directly transesterified to prepare fatty acid methyl esters (FAMEs) by the method of Lepage and Roy.[10] The FAME of individual fatty acids of phospholipids were separated on a gas chromatograph (model 6890, Agilent Technologies Inc., Palo Alto, CA) equipped with a capillary column (Omegawax™ 250; 30 m, Supelco, Bellefonte, PA) as previously described.[11] Peak retention times were identified by comparison with known standards (37 component FAME mix and PUFA-2, Supelco, Bellefonte, PA; GLC37, NuCheck Prep, Elysian, MN) and analyzed with ChemStation software (Agilent Technologies). Serum phospholipid fatty acids were expressed as the percentage of total fatty acids. The desaturase activities were calculated as product/precursor ratios of individual fatty acids in serum phopholipids. In this study, desaturase activities were estimated as follows: stearoyl–coA desaturase (SCD) 16 = 16:1n-7/16:0, SCD18 = 18:1n-9/18:0, delta-6 desaturase (D6D) = 20:3n-6/18:2n-6, delta-5 desaturase (D5D) = 20:4n-6/20:3n-6.[4,8,12–13]

Statistical analysis. The SPSS 12.0 software package was used for statistical analysis. Data are presented as the means ± SD Each variable was examined for normal distribution, and abnormally distributed variables were log-transformed. Pearson correlation coefficients were used to evaluate correlations between variables. Stepwise multiple regression analysis was performed to determine the contributing factors to plasma levels of CRP. p values less than 0.05 were considered statistically significant.

Results

Age, gender, anthropometrics and biochemical measurements of total subjects were presented in Table 1. This study consisted of 93 subjects with a mean age of 54.4 ± 12.6 years (36 males and 57 females). All were healthy and their mean BMI was 23.3 ± 2.7 kg/m^2.

Serum phospholipid fatty acid composition in total subjects. Table 2 shows the relative contents (%) of several individual fatty acids in serum phospholipids. Desaturase activities estimated by fatty acid product-to-precursor ratios are also shown in Table 2.

Table 1. Age, gender, anthropometrics and biochemical measurements in total subjects

	Total subjects (n = 93)
Age (years)	54.4 ± 13.4
Gender (M:F)	36:57
BMI (kg/m^2)	23.3 ± 2.7
Waist circumferences (cm)	78.5 ± 7.5
Triglyceride (mg/dL)	161.0 ± 134.1
Total cholesterol (mg/dL)	194.2 ± 38.9
LDL-cholesterol (mg/dL)	126.8 ± 35.7
HDL-cholesterol (mg/dL)	51.5 ± 12.9
LDL particle size (nm)	26.2 ± 1.9
C-reactive protein (mg/dL)	0.94 ± 1.63
Adiponectin (μg/dL)	7.4 ± 3.5
sICAM-1(ng/dL)	628.3 ± 152.2

mean ± SD.

Table 2. Proportions of fatty acid composition in serum phospholipids and estimated desaurase activities in total subjects

	Total subjects (n = 93)
12:0 lauric acid	0.15 ± 0.1
14:0 myristic acid	0.68 ± 0.16
16:0 palmitic acid	27.9 ± 2.41
16:1 palmitoleic acid	0.77 ± 0.23
18:0 stearic acid	14.99 ± 1.52
18:1 ω9 oleic acid	7.87 ± 1.16
18:1t ω9 elaidic acid	2.3 ± 0.47
18:2 ω6 linoleic acid	14.7 ± 2.22
18:2 tt linolelaidic acid	0.76 ± 1.94
18:3 ω6 γ-linolenic acid	0.2 ± 0.14
18:3 ω3 α-linolenic acid	0.55 ± 0.32
20:0 arachidic acid	0.99 ± 0.37
20:1 ω9 gondoic acid (cis-11-eicosenoic acid)	0.4 ± 0.23
20:2 cis-11,14-eicosadienoic acid	1.32 ± 0.42
20:3 ω6 dihimo-r-linolenic acid	2.64 ± 0.66
20:3 ω3 5-8-11-eicosatrienoic acid	0.51 ± 0.33
20:4 ω6 arachidonic acid	6.52 ± 1.37
20:5 ω3 EPA	2.68 ± 0.9
22:0 behenic acid	1.89 ± 0.43
22:1 erucic acid	0.52 ± 0.23
22:2 docosadienoic acid	0.25 ± 0.22
24:0 lignoceric acid	1.91 ± 0.5
22:6 ω3 DHA	8.2 ± 1.71
SCD16 (16:1n-7/16:0)	0.028 ± 0.008
SCD18 (18:1n-9/18:0)	0.529 ± 0.084
D6D (20:3n-6/18:2n-6)	0.185 ± 0.059
D5D (20:4n-6/20:3n-6)	2.58 ± 0.7

mean ± SD. Expressed as percentage of total fatty acids.

Correlation analysis between fatty acids/estimated desaturase activities and cardiometabolic risks. As shown in Table 3, palmitoleic acid was positively correlated with BMI (r = 0.250, p<0.05) and serum levels of TG (r = 0.310, p<0.01) and negatively correlated with serum levels of HDL-cholesterol (r = –0.222, p<0.05) and LDL particle size (r = –0.245, p<0.05), while oleic acid was positively correlated with serum levels of TG (r = 0.318, p<0.01). Also, the proportion of linoleic acid (LA) was negatively related to waist circumference (r = –0.280, p<0.01), serum levels of TG (r = –0.238, p<0.05), and CRP (r = –0.230, p<0.05) and positively related to LDL particle size (r = 0.305,

doi: 10.3164/jcbn.10-147

Table 3. Correlation analysis between serum phospholipid fatty acids and cardiometabolic risks

	BMI	waist	TG	HDL-c	LDL particle size	CRP	Adiponectin	sICAM-1
12:0	–0.026	–0.071	–0.14	–0.06	–0.064	–0.084	0.045	0.057
14:0	–0.202	–0.136	–0.152	–0.048	–0.033	–0.028	0.2	–0.085
16:0	0.079	0.104	0.193	0.001	–0.202	–0.044	0.013	–0.016
16:1	0.250*	0.159	0.310**	–0.222*	–0.245*	0.072	–0.066	0.125
18:0	0.015	0.069	0.04	–0.041	–0.07	0.005	0.067	0.058
18:1 ω9	–0.048	–0.037	0.318**	0.067	–0.197	–0.128	–0.022	–0.062
18:1t ω9	–0.017	–0.014	–0.311**	0.053	0.116	0.031	0.187	0.169
18:2	–0.174	–0.280**	–0.238*	0.163	0.305**	–0.230*	0.262*	–0.221
18:2 tt	0.036	0.099	0.078	–0.149	–0.102	0.039	0.081	0.029
18:3 ω6	0.081	–0.02	0.074	–0.02	0.115	0.073	–0.023	0.007
18:3 ω3	–0.032	–0.136	–0.017	0.038	0.155	0.112	–0.028	–0.104
20:0	0.055	0.093	–0.189	0.04	0.146	0.148	0.106	0.109
20:1 ω9	–0.091	0.131	0.054	0.008	–0.071	0.038	–0.104	0.186
20:2	0.137	0.076	–0.179	–0.024	0.038	0.02	0.084	0.056
20:3 ω6	0.192	0.136	0.383***	–0.335***	–0.218*	0.278**	–0.179	0.135
20:3 ω3	0.109	0.133	0.121	0.005	–0.008	0.178	–0.165	0.145
20:4 ω6	–0.194	–0.204	–0.016	0.02	0.14	0.051	–0.154	–0.066
20:5 ω3	0.189	0.168	0.116	–0.02	–0.167	0.206	–0.332**	0.018
22:0	0.012	0.127	–0.288**	0.026	0.067	0.026	0.103	0.187
22:1	–0.049	–0.004	–0.104	0.017	0.006	0.249*	–0.076	0.034
22:2	–0.086	–0.107	–0.185	0.161	0.278**	0.036	0.087	–0.045
24:0	0.033	0.096	–0.321**	0.048	0.148	0.051	0.154	0.205
22:6 ω3	–0.001	0.02	–0.06	–0.021	0.051	0.011	–0.173	–0.046

*p<0.05, **<0.01, ***<0.001.

Table 4. Correlates between estimated desaturase activity and cardiometabolic risks in total subjects

	BMI	Waist	TG	HDL-c	LDL particle size	CRP	Adiponectin	sICAM-1
SCD16	0.235*	0.125	0.261**	–0.226*	–0.189	0.087	–0.07	0.127
SCD18	–0.05	–0.07	0.283**	0.087	–0.16	–0.115	–0.061	–0.087
D6D	0.236*	0.218*	0.399***	–0.325**	–0.297**	0.333***	–0.233*	0.229*
D5D	–0.324**	–0.276**	–0.329**	0.262*	0.278**	–0.215*	0.045	–0.187

*p<0.05, **<0.01, ***<0.001. D5D: delta-5 desaturase. D6D: delta-6 desaturase. SCD: stearoyl–CoA desaturase.

p<0.01) and plasma levels of adiponectin (r = 0.262, p<0.05). Furthermore, the proportion of dihomo-r-linolenic acid (DHLA) was significantly associated with serum levels of TG (r = 0.383, p<0.001), HDL-cholesterol (r = –0.335, p<0.001), CRP (r = 0.278, p<0.01) and LDL particle size (r = –0.218, p<0.05). On the other hand, eicosapentaenoic acid (EPA) was negatively associated with plasma levels of adiponectin (r = –0.322, p<0.01).

Table 4 presents the correlates between estimated desaturase activities and cardiometabolic risks in total subjects. Specifically, SCD16 was positively correlated with BMI (r = 0.235, p<0.05), and serum levels of TG (r = 0.261, p<0.001), and negatively correlated with serum levels of HDL-cholesterol (r = –0.226, p<0.05). Also, a high degree of SCD16 tended to show reduced LDL particle size, which did not reach statistical significance (r = –0.189, p = 0.07). On the other hand, SCD18 was positively associated with only serum levels of TG (r = 0.283, p<0.01). D6D was positively correlated with BMI (r = 0.236, p<0.05), waist circumference (r = 0.218, p<0.05), serum levels of TG (r = 0.399, p<0.001), CRP (r = 0.333, p<0.001), and sICAM-1 (r = 0.229, p<0.05) and negatively correlated with serum levels of HDL-cholesterol (r = –0.325, p<0.01), LDL particle size (r = –0.297, p<0.01) and plasma levels of adiponectin (r = –0.233, p<0.05). In contrast, D5D was negatively correlated with BMI (r = –0.324, p<0.01), waist circumference (r = –0.276, p<0.01), serum levels of TG (r = –0.329, p<0.01) and CRP (r = –0.215, p<0.05) and positively correlated with serum levels of HDL-cholesterol (r = 0.262, p<0.05) and LDL particle size (r = 0.278, p<0.01).

Stepwise multiple regression analysis to identify factors affecting plasma CRP levels. Stepwise multiple regression analysis was performed to identify factors influencing CRP, a surrogate marker for systemic inflammation. The independent variables include baseline characteristics such as age, gender, BMI, waist circumference, alcohol intake, smoking and exercise, serum levels of TG and HDL-cholesterol and estimated desaturase index. The results show that D6D (p<0.01) together with waist circumference (p<0.001) were found to be independent factors for determining plasma levels of CRP (R^2 = 0.230, Table 5).

Discussion

In the present study, we comprehensively examined the relationships of estimated desaturase activities and individual serum fatty acids with cardiometabolic risk factors in Koreans. This cross-sectional study showed that not only palmitoleic acid, LA and DHLA but also desaturases such as SCD16, SCD18, D6D and D5D were closely related to cardiometabolic risk factors. In addition, D6D was found to be an independent factor for determining CRP which is a surrogate marker for low grade chronic inflammation.

A number of clinical studies have reported that individual

Table 5. Stepwise multiple regression analysis to identify factors influencing C-reactive protein levels

Dependent variable	Independent variable	Adjusted β-coefficients	*p* value	R^2	*p* value
CRP	Waist circumference	0.355	<0.001	0.23	<0.001
	D6D	0.255	<0.01		

Independent variables include: baseline characteristics (age, gender, BMI, waist circumference, alcohol intake, smoking and exercise), TG, HDL-cholesterol and desaturases.

serum fatty acids were related to CVD and predicted risk and mortality of CVD. Specifically, proportions of LA[14] and palmitic acid[4,15] were related to CVD, and low serum proportions of LA could predict myocardial infarction over 19 years and were correlated with a high rate of CVD mortality.[4,16] The mechanism by which serum fatty acids are associated with CVD has not been fully elucidated, but is possibly mediated by their involvement in blood cholesterol concentrations, insulin resistance, inflammation and endothelial function.[17–20] Indeed, it was reported in a Spanish study[21] that LA and n-3 fatty acid were inversely related to CRP levels and α-linolenic acid and EPA were inversely associated with CRP in a French study.[22] There is also evidence that DHLA is related to insulin resistance and obesity[23–24] through the increased activity of D6D in response to lower intake of 18:2 n-6, which can further contribute to CVD. Similar to previous studies, our results show that palmitoleic acid was positively correlated with BMI and serum levels of TG and negatively correlated with serum levels of HDL-cholesterol and LDL particle size, while oleic acid was positively correlated with serum levels of TG. In addition, the proportion of LA was negatively related to waist circumference, serum levels of TG, and CRP and positively related to LDL particle size and plasma levels of adiponectin. Furthermore, the proportion of DHLA was significantly associated with serum levels of TG, HDL-cholesterol, CRP and LDL particle size. These data support that fatty acid profiles as reflected by dietary intakes may affect the cardiometabolic risks, which may be a potential mechanism explaining the residual cardiovascular risks beyond LDL-cholesterol levels.

Of interest is the observation that the proportions of EPA were negatively associated with plasma levels of adiponectin. Adiponectin is an important mediator linking obesity and cardiovascular disease through various mechanisms including anti-atherogenic and anti-inflammatory effects.[25] Regarding the stimulating effect of EPA on adipoectin secretion in adipocytes, previous experimental studies have shown conflicting data. It was reported that EPA and docosahexaenoic acid (DHA) may upregulate adiponectin by acting as ligands of peroxisome proliferator-activated receptor-γ (PPARγ),[26] the transcriptional regulator interacting directly with adiponectin promoters. In contrast, others have reported that EPA significantly decreased adiponectin gene expression and protein secretion and reduced PPARγ mRNA levels in adipocytes, suggesting that this impairment in PPARγ could explain, at least in part, the decrease in adiponectin gene expression and protein secretion induced by EPA treatment.[27] Further studies to elucidate the underlying mechanism for the stimulation of adiponectin by fatty acids are warranted.

With respect to the associations of desaturase activities and CVD, high SCD and D6D are generally known to have adverse effects on metabolic and CVD risk factors, while high D5D acts favorably.[4,6,13,28] For example, SCD18 was positively associated with BMI, blood pressure, total and LDL-cholesterol and negatively associated with HDL-cholesterol.[13] Cross-sectional research in adolescents demonstrated that D6D was positively correlated with most of the CVD risk factors but D5D was inversely correlated with TG and insulin.[8] There is also evidence that that low D5D can be related to the development of coronary heart disease and it may predict metabolic syndrome and cardiovascular mortality.[4,16,29] In the present study, consistent with the earlier results, SCD16 was associated with abdominal obesity as measured by BMI and atherogenic lipoprotein phenotype such as TG and HDL-cholesterol, while SCD18 was positively associated with only serum levels of TG. In addition, D6D was favorably associated with a constellation of cardiometabolic risk factors. In contrast, D5D was unfavorably associated with a cluster of cardiometabolic risk factors. Moreover, D6D along with waist circumference were found to be independent factors for CRP, suggesting that D6D among desaturase activities may be the most useful predictor for cardiometabolic risks. CRP is a marker of systemic low-grade inflammation with high sensitivity and is an independent factor for coronary vascular disease.[30] Therefore, it is possible that D6D can contribute to chronic diseases by involving inflammatory responses. This study also provides additional information on their relationships to LDL particle size, which is known to be a predictor of CVD development.[31–32]

Remarkably, an important finding in our study is that D6D showed a positive association with sICAM-1, an endothelium derived proinflammatory cytokine and a negative association with adiponectin which has an anti-inflammatory property. The potential mechanism linking D6D to inflammation is that the long chain polyunsaturated fatty acids (PUFAs) synthesized by D6D may affect the permeability and function of cell membranes,[33] and furthermore, they can be used as ligands for transcriptional factors[34–35] that are responsible for inflammatory pathways. Alternatively, PUFAs synthesized by D6D participate in synthesizing eicosanoids[36] which act as inflammatory mediators. Considering that average dietary fat intake is relatively low in the background diet of Koreans, the quantity and quality of endogenously synthesized fat by desaturases can be important in modulating inflammatory pathways.

Taken together, the metabolic effects mediated by desaturases are so profound that they can influence obesity, atherogenic lipoprotein phenotype and proinflammatory responses, a cardiometabolic phenotype cluster. There are some limitations of this study as follows. We demonstrated that D6D had close associations with cardiometabolic risk factors but could not prove the cause or result, since this is a cross-sectional study and a small sample size makes it difficult to generalize the results. Thus, a prospective study with a large sample size is needed to confirm our data. Finally, there is no data on dietary fatty acids, so we cannot identify relationships between dietary fatty acids and serum fatty acids. Despite these limitations, this is the first study to evaluate associations between various desaturase activities along with serum individual fatty acids and overall cardiometabolic risks in Koreans. In conclusion, estimated desaturase activities are closely associated with the features of cardiometabolic risks in Koreans, raising the possibility that such activities might be effective biomarkers for the prediction of cardiovascular and metabolic diseases.

Acknowledgment

This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0013603). There is no potential conflict of interest.

doi: 10.3164/jcbn.10-147

Abbreviations

BMI	body mass index
CRP	C-reactive protein
CVD	cardiovascular disease
DHLA	dihomo-γ-linolenic acid
DHA	docosahexaenoic acid
D5D	delta 5 desaturase
D6D	delta 6 desaturase
EPA	eicosapentaenoic acid
FAME	fatty acid methyl ester
LA	linoleic acid
PPAR	peroxisome proliferator-activated receptor
PUFAs	polyunsaturated fatty acids
SCD	stearoyl–CoA desaturase
sICAM-1	soluble intercellular adhesion molecule-1
TG	triglyceride

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