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Original article

Plasma fatty acid composition, estimated desaturase activities, and their relation with the metabolic syndrome in a population at high risk of cardiovascular disease

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SUMMARY

Background & aims: The metabolic syndrome (MetS) is a clustering of various metabolic abnormalities which is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus. Due to its increasing prevalence, it has become an important public health concern. Altered fatty acid (FA) composition and desaturase activities have been associated with several metabolic diseases, including MetS. The aim of the present study was to evaluate the relationship of the plasma FA profile and desaturase activities with the MetS in a Mediterranean population at high risk of CVD.
Methods: Baseline data from 427 participants aged 55–80 years who took part in the interventional PREDIMED study were obtained. Individual FA was determined in plasma and desaturase activities were estimated from product/precursor ratios. Odds ratios (OR) and partial correlation coefficients were used to examine these relations with MetS and its components, respectively.
Results: We found higher levels of C14:0, C16:0, C16:1*n*-7, estimated Δ^9- or stearoyl-CoA desaturase (SCD), and estimated Δ^6 desaturase (D6D), and lower levels of C18:2*n*-6 in people with MetS compared to those without it. After adjustment for several confounders, only higher quartiles of C14:0, C16:0, C16:1*n*-7, and D6D were found to be associated with an increasing prevalence of MetS, while higher quartiles of C18:2*n*-6 were inversely associated with MetS. High proportions of C14:0, C16:0, C16:1*n*-7, C20:3*n*-6, SCD, and D6D, and decreased proportions of C18:2*n*-6 and estimated Δ^5-desaturase (D5D) were associated with adverse profiles of several metabolic risk factors. Women showed more unhealthy FA pattern and lipid profiles than men, but only among those with MetS.

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; CVD, cardiovascular disease; D5D, Δ^5 desaturase; D6D, Δ^6 desaturase; DBP, diastolic blood pressure; DGLA, dihommo-γ-linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; GLA, γ-linolenic acid; HDL-C, high-density lipoprotein cholesterol; LA, linoleic acid; LDL-C, low-density lipoprotein cholesterol; MA, myristic acid; MetS, metabolic syndrome; MGA, margaric acid; OA, oleic acid; PA, palmitic acid; POA, palmitoleic acid; SA, stearic acid; SBP, systolic blood pressure; SCD, stearoyl coenzyme A desaturase; TC, total cholesterol; WC, waist circumference.

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Conclusion: A FA composition and estimated desaturase activities consisting in high levels of SFA, SCD and D6D, and low levels of PUFA and D5D are associated with increased MetS probability and are characteristic of people presenting MetS, especially women. These findings support those observed in non-Mediterranean populations in which an altered FA profile and estimated desaturase activities are associated with MetS.

1. Introduction

The metabolic syndrome (MetS) is a cluster of interrelated metabolic risk factors in one person[1,2] which increases the risk of developing both cardiovascular disease (CVD) and type 2 diabetes. The evidence available indicates that the prevalence of MetS is about 20–30% among adults from developed countries, increases with age, and is rising in relation to increasing obesity, diabetes and sedentary lifestyles.[2]

Since the predominant underlying risk factors for the pathogenesis of the MetS appear to be abdominal obesity and insulin resistance, environmental factors, such as diet and physical inactivity may play a role in the development of this syndrome.[1] In fact, total fat and type of dietary fat consumed have been associated with MetS and its components.[3]

The assessment of dietary fat composition from different food sources with the use of self-reporting methods is associated with substantial measurement error. Conversely, biomarkers of fatty acid (FA) intake, such as the plasma FA profile, are objective and potentially independent of these errors.[4] However, their ability to reflect dietary intake may be affected by non-dietary factors, such as endogenous metabolism, genetics, smoking, and physical activity.[4] Thus, several FA can be newly synthesized, elongated or desaturated by three desaturases: Δ^9 or stearoyl-CoA desaturase (SCD), Δ^6 desaturase (D6D), and Δ^5 desaturase (D5D), the activity of which may be estimated using FA product/precursor ratios.[5]

On the other hand, the FA profile can be used as an indicator of disease risk. The hallmarks for most pathological stages are the increased content of SFA and a lower content of PUFA. In fact, an altered FA profile and estimated activity of desaturases characterized mainly by high proportions of palmitic acid (PA, C16:0), palmitoleic acid (POA, C16:1*n*-7), dihommo-γ-linolenic acid (DGLA, C20:3*n*-6), SCD and D6D, and decreased levels of linoleic acid (LA, C18:2*n*-6) and D5D, have been associated with insulin resistance and increased risk to develop diabetes,[3] obesity,[6] hypertrygliceridemia,[7] cardiovascular disease,[8] and the development of the MetS.[9–15]

Nonetheless, few studies have investigated the relationship between plasma FA composition, estimated desaturase activities and the MetS. Moreover, to our knowledge, no studies have been conducted in a Mediterranean population. Therefore, the aim of the present study was to analyze for the first time the plasma FA and estimated desaturase activities in relation to MetS status, and to examine the cross-sectional associations between these patterns and the MetS and its components in a Spanish population.

2. Materials and methods

2.1. Study design

A cross-sectional study with baseline data from the PREDIMED (PREvención con DIeta MEDiterránea) study was performed. The PREDIMED study is a large, randomized, parallel-group, multicenter, controlled, 5-year clinical trial aimed at assessing the effects of the two Mediterranean diets supplemented with either virgin olive oil or mixed nuts compared with a low-fat diet on the primary prevention of CVD (http://www.predimed.org; ISRCTN35739639). The detailed protocol of this study has been previously described.[16] The institutional review boards of the participating recruitment centers approved the study protocol and participants provided signed informed consent. The current study was performed in a subset of participants recruited in 3 PREDIMED centers (Barcelona North, Reus, and Pamplona).

2.2. Participants

The population sample consisted of 427 asymptomatic subjects at high risk of CVD. Eligible participants were community-dwelling men, aged 55–80 years, and women, aged 60–80 years, who met at least one of the two following criteria: diagnosis of type 2 diabetes or the presence of ≥3 CVD risk factors (smoking, hypertension, dyslipidemia, overweight or obesity, and a family history of early CVD). Exclusion criteria were history of CVD, any severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, or a low predicted likelihood of changing dietary habits. Participant eligibility was based on a screening visit by the physician.

2.3. Measurements

At baseline, the following questionnaires were administered to the participants[16]: (a) a general 47-item questionnaire about education, lifestyle, medical conditions, and medication use; and (b) a previously validated 137-item FFQ. Moreover, participants underwent anthropometric and blood pressure measurements and collection of fasting blood samples.

2.3.1. Anthropometry

The anthropometric measures used in this study were height (m), weight (kg), BMI (calculated as weight in kg/height^2 in m^2) and waist circumference (WC). Height and weight (with light clothing and no shoes) were recorded using a calibrated balance beam scale and a wall-mounted calibrated stadiometer, respectively. WC was measured using an anthropometric measuring tape, at a horizontal plane midway between the lowest rib and the iliac crest. Blood pressure (BP) was measured in triplicate with a validated semi-automatic sphygmomanometer after a minimum of 5 min rest in the seated position.

2.3.2. Laboratory measurements

Blood samples were collected after an overnight fast, coded, shipped to a central laboratory, and stored at −80 °C until analyses. Laboratory technicians were blinded to the intervention. Plasma glucose level was analyzed by the glucose-oxidase method; total serum cholesterol (TC) and TG levels were measured by enzymatic procedures, and high-density lipoprotein cholesterol (HDL-C) levels were determined after precipitation with phosphotungstic acid and magnesium chloride. The plasma FA profile was determined by fast gas chromatography with a previous derivatization to their corresponding fatty acid methyl esters.[17] Results were expressed as relative percentages of total FA. The average of two measures was used for the analysis of laboratory variables.

2.3.3. Estimation of desaturase activities

Desaturase activity was estimated using FA product/precursor ratios.[5] Therefore, desaturase activities were estimated as the ratio of product to precursor of individual plasma FA according to the following: SCD-16 = C16:1*n*-7/C16:0, SCD-18 = C18:1*n*-9/C18:0, D6D = C18:3*n*-6/C18:2*n*-6, and D5D = C20:4*n*-6/C20:3*n*-6.

2.3.4. Definition of metabolic syndrome

The recent definition of the MetS proposed by six major organizations and societies (IDF, NHLBI, AHA, WHF, IAC, and IASO) was applied to the present work.[1] In this definition the presence of any 3 of 5 of the following risk factors constitutes a diagnosis of MetS: elevated TG (≥150 mg/dL or drug treatment for elevated triglycerides), reduced HDL-C (<40 mg/dL in men and <50 mg/dL in women), elevated BP (systolic ≥ 130 and/or diastolic ≥ 85 mmHg, or antihypertensive drug treatment), elevated fasting glucose (≥100 mg/dL or drug treatment of elevated glucose), and elevated WC. For this latter criterion the AHA/NHLBI (>102 cm for men and >88 cm for women) cut-off points were used in this study.

2.4. Statistical analysis

Since the statistical distribution of plasma FA concentrations was found to be skewed, geometric means were used to describe statistics. Moreover, FA concentrations were log-transformed for analysis. ANOVA and the χ^2 test were used to determine differences in baseline characteristics in individuals with and without the MetS for continuous and categorical variables, respectively. Differences in metabolic risk factors, FA concentrations and estimated desaturase activities were analyzed by general linear models, while differences in MetS components were assessed using a logistic regression model adjusting for gender, age, and energy intake in both cases. Logistic regression analysis was carried out to calculate the odds ratios (OR) and 95% confidence intervals (CI) to examine the associations between the prevalence of MetS across quartiles of plasma FA and estimated desaturase activities considering the lowest quartile as the reference and controlling for potential confounding factors (gender, age, energy intake, BMI, smoking status, occupation, and educational level). The relationship between plasma FA composition, estimated desaturase activities and metabolic risk factors was determined by partial correlation analysis controlling for medication for hypercholesterolemia, blood pressure, and diabetes, as well as the previously mentioned confounders. For all analyses, two-sided significance was determined at a $P < 0.05$. Analyses were performed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

3. Results

The baseline characteristics of the 427 participants (177 men and 250 women) based on MetS status are described in Table 1. By design, the participants were mostly overweight with an elevated number of CVD risk factors. Of the total population, 92.7%, 84.1%, 68.1%, and 45.9%, were overweight or obese, hypertensive, dyslipidemic, and had type II diabetes, respectively. As expected, most of the characteristics associated with the MetS were significantly higher among those with this syndrome. Gender differences were significant for several variables. Women were older than men (68.1 ± 5.3 vs. 66.8 ± 6.6, $P = 0.037$), had a higher prevalence of familial history of early CVD (26.4% vs. 11.9%, $P = 0.001$) and dyslipidemia (77.2% vs. 55.4%, $P < 0.001$), and had a lower education (72.4% vs. 62.7% for primary school, $P = 0.034$; 14.8% vs. 24.9% for secondary school, $P = 0.009$; and 4.8% vs. 10.7% for university, $P = 0.020$), weight (70.9 ± 9.8 vs. 79.0 ± 9.1, $P < 0.001$), and frequency of smoking (4.0% vs. 29.4%, $P < 0.001$).

Table 1
Baseline characteristics of participants according to the MetS status.

Characteristics	No MetS ($n = 112$)	MetS ($n = 315$)	P[a]
Age, *y*	67.8 ± 6.1	67.5 ± 5.9	0.67
Men, %	56.3	32.6	<0.001
Weight, kg	71.6 ± 9.8	75.6 ± 10.4	<0.001
Overweight or obese,[b] %	85.5	96.2	<0.001
Type 2 diabetes mellitus, %	34.1	51.6	0.001
Dyslipidemia,[c] %	47.3	75.6	<0.001
Hypertension,[d] %	84.8	83.8	0.80
Family history of CVD, %	18.8	21.0	0.85
Current smoker, %	19.6	12.7	0.07
Medications, %			
Aspirin or antiplatelet drugs	20.5	24.8	0.58
Antihypertensive agents	67.0	74.8	0.10
Lipid-lowering agents	0.9	40.0	<0.001
Insulin	7.1	6.0	0.77
Hypoglycemic agents	20.5	31.7	0.02
Occupation, %			
Worker	15.2	10.8	0.22
Unemployed or unfit	22.3	30.8	0.09
Retired	62.5	57.8	0.38
Education level, %			
None	2.7	4.1	0.49
Primary school	66.1	69.2	0.54
Secondary school	23.2	17.5	0.18
University	6.3	7.6	0.63

CVD, cardiovascular disease; MetS, metabolic syndrome.
Values are expressed as mean ± SD or percentage of participants.
[a] *P* value for comparison between-groups calculated by one-factor ANOVA for continuous variables or the χ^2 test for categorical variables.
[b] BMI ≥ 25 kg/m^2.
[c] Two or more of the following criteria: LDL cholesterol > 160 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides > 150 mg/dL, or previous diagnosis of dyslipidemia.
[d] Blood pressure ≥ 140/90 mmHg or treatment with antihypertensive drugs.

The metabolic risk factors between MetS and non MetS participants are detailed in Table 2. The prevalence of the MetS in the study population was 73.8%, whereas that of its components was 95.8%, 64.4%, 63.8%, 58.5%, and 55.7%, for elevated BP, WC, fasting

Table 2
Metabolic risk factors and MetS components according to MetS status.

	No MetS ($n = 112$)	MetS ($n = 315$)	P[c]
Metabolic risk factors[a]			
BMI, kg/m^2	28.0 ± 3.0	29.8 ± 3.2	<0.001
WC, cm	93.7 ± 9.2	100.6 ± 8.8	<0.001
TC, mg/dL	214.3 ± 38.6	208.4 ± 37.3	0.18
HDL-C, mg/dL	62.1 ± 15.0	52.2 ± 13.0	<0.001
LDL-C, mg/dL	132.8 ± 32.6	126.9 ± 32.9	0.13
TG, mg/dL	87.1 ± 33.4	127.9 ± 59.9	<0.001
SBP, mmHg	150.0 ± 22.4	151.9 ± 18.8	0.44
DBP, mmHg	81.8 ± 10.2	83.5 ± 9.9	0.17
Fasting glucose, mg/dL	108.7 ± 39.7	120.3 ± 36.5	0.002
MetS components[b]			
Elevated WC, %	35.7	74.6	<0.001
Elevated TG, %	2.7	78.4	<0.001
Reduced HDL-C, %	0.9	75.2	<0.001
Elevated BP, %	91.1	97.5	0.004
Elevated fasting glucose, %	43.8	71.0	<0.001

CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.
[a] Values are expressed as adjusted mean ± SD.
[b] Values are expressed as percentage of participants.
[c] *P* value for comparison between-groups calculated by general linear models and logistic regression model (both adjusted for gender, age, and energy intake) for metabolic risk factors and MetS components, respectively.

glucose, TG, and reduced HDL-C, respectively. As expected, all metabolic risk factors and components contributing to the MetS, as well as the BMI, were significantly different in participants with the MetS compared with those without. Women had a higher prevalence of elevated WC and reduced HDL-C than men (87.1% vs. 52.6%, $P < 0.001$; and 61.2% vs. 48.0%, $P = 0.007$; respectively), regardless of MetS status. Moreover, in women with the MetS the levels of TC were higher than the corresponding levels seen in men (211.7 ± 36.3 vs. 197.6 ± 38.3, $P = 0.001$).

Table 3 shows the comparison of the plasma FA profile, including estimated desaturase activities, between genders in participants with and without the MetS. The levels of myristic acid (MA, C14:0), PA, POA, SCD-16, and D6D were higher, and the level of LA was lower in subjects presenting the MetS. Strong differences were observed in the proportions of several FA and estimated desaturase activities between men and women in the MetS group. Hence, women with the MetS had higher values of MA, POA, γ-linolenic acid (GLA, C18:3*n*-6), DGLA, arachidonic acid (AA, C20:4*n*-6), SCD-16, and D6D, and lower values of SCD-18, and D5D than men with the MetS. Conversely, in the non MetS group, strong differences between men and women were only observed in OA, DGLA, and SCD-18.

The OR associated with having the MetS by quartiles of plasma FA proportions and estimated desaturase activities are shown in Table 4. The logistic regression model showed that higher quartiles of SFA, MA, PA, POA, and D6D were associated with an increased probability of the MetS, while higher quartiles of PUFA and LA were inversely associated with the MetS. Of note was that the most atherogenic FA were the most strongly associated with the MetS. In a crude logistic regression model, SCD-16 was also associated with increased prevalence of the MetS prevalence (P for trend = 0.047).

In a separate analysis, BMI and gender were shown to be the two variables that most attenuated the OR (data not shown) with respect to a crude model. Thus, we further analyzed the FA we found associated with having the MetS (including also GLA and DGLA, since they are typically related to the MetS in epidemiological studies) and estimated desaturase activities, repeating the above analyses separately in men and women and calculating the partial correlation coefficients with several metabolic risk factors as well. The results of logistic regression models showed that these FA and estimated desaturase activities were more strongly related to the MetS in women than in men. Thus, while LA quartiles were inversely related to having MetS in both genders (P for trend = 0.027 for men and 0.002 for women), higher quartiles of MA, PA, GLA, and D6D increased the probability of MetS in women (P for trend = 0.003, 0.011, 0.032, and 0.019, respectively) but not in men (P for trend = 0.37, 0.41, 0.95, and 0.33, respectively). When comparing the OR of the MetS across extreme quartiles, the highest quartiles of MA, PA, GLA, SCD-18, and D6D were associated with a higher likelihood of having the MetS in women compared to men (Table 5).

On the other hand, partial correlation coefficients showed significant associations between FA proportions and estimated desaturase activities and several metabolic risk factors (Table 6). MA and PA were positively associated with WC, BMI, TG, and glucose. In addition, PA was also positively related to TC. POA was adversely associated with most metabolic risk factors. In contrast, LA was beneficially associated with several metabolic risk factors, such as

Table 3
Baseline fatty acid composition and estimated desaturase activities in subjects with and without the MetS according to gender.

Fatty acid	No MetS				MetS					
	Men ($n = 62$)	Women ($n = 49$)	P[a]	All ($n = 112$)	Men ($n = 114$)	Women ($n = 201$)	P[a]	All ($n = 315$)	P sex[b]	P MetS[c]
SFA	28.9 ± 2.4*	28.5 ± 2.1**	0.27	28.7 ± 2.3	29.9 ± 3.2	29.7 ± 2.9	0.64	29.8 ± 3.0	0.79	<0.001
MA (C14:0)	0.53 ± 0.25	0.53 ± 0.21***	0.94	0.53 ± 0.24	0.60 ± 0.28	0.66 ± 0.30	0.038	0.64 ± 0.29	0.027	<0.001
PA (C16:0)	21.4 ± 2.0*	20.4 ± 1.5***	0.005	20.9 ± 1.9	22.1 ± 2.4	21.8 ± 2.3	0.18	21.9 ± 2.3	0.09	<0.001
MGA (C17:0)	0.29 ± 0.34	0.29 ± 0.24	0.99	0.29 ± 0.30	0.29 ± 0.41	0.27 ± 0.31	0.37	0.28 ± 0.35	0.42	0.82
SA (C18:0)	6.63 ± 0.87	7.09 ± 1.50	0.016	6.82 ± 1.18	6.64 ± 1.25	6.86 ± 1.11	0.08	6.78 ± 1.17	0.008	0.71
MUFA	28.0 ± 4.3	25.1 ± 3.7***	<0.001	26.7 ± 0.3	28.4 ± 4.6	27.4 ± 4.3	0.07	27.8 ± 4.5	0.004	0.019
POA (C16:1*n*-7)	1.15 ± 0.76	1.30 ± 0.44*	0.13	1.21 ± 0.64	1.31 ± 0.64	1.46 ± 0.63	0.020	1.40 ± 0.64	0.001	0.001
OA (C18:1*n*-9)	26.7 ± 4.1	23.8 ± 3.6**	<0.001	25.4 ± 4.1	26.9 ± 4.5	25.9 ± 4.3	0.06	26.3 ± 0.4	0.001	0.06
PUFA	41.8 ± 4.2**	44.7 ± 4.2***	0.001	43.0 ± 4.4	39.5 ± 5.8	41.3 ± 6.0	0.007	40.7 ± 6.0	0.002	<0.001
Series *n*-6										
LA (C18:2*n*-6)	29.5 ± 4.1**	31.1 ± 4.3**	0.06	30.2 ± 4.2	27.3 ± 5.3	28.3 ± 5.2	0.11	27.9 ± 5.3	0.14	<0.001
GLA (C18:3*n*-6)	0.36 ± 0.20	0.41 ± 0.20	0.23	0.38 ± 0.20	0.35 ± 0.14	0.45 ± 0.19	<0.001	0.41 ± 0.18	<0.001	0.17
DGLA (C20:3*n*-6)	1.38 ± 0.32	1.62 ± 0.38	<0.001	1.48 ± 0.36	1.34 ± 0.28	1.59 ± 0.35	<0.001	1.49 ± 0.35	<0.001	0.65
AA (C20:4*n*-6)	6.47 ± 1.53	7.06 ± 1.71	0.06	6.72 ± 1.63	6.36 ± 1.75	6.85 ± 1.72	0.016	6.67 ± 1.75	0.003	0.77
Series *n*-3										
ALA (C18:3*n*-3)	0.31 ± 0.13	0.34 ± 0.15	0.27	0.32 ± 0.14	0.32 ± 0.16	0.33 ± 0.15	0.39	0.33 ± 0.15	0.20	0.94
EPA (C20:5*n*-3)	0.73 ± 0.63	0.78 ± 0.62	0.57	0.75 ± 0.62	0.73 ± 0.82	0.71 ± 0.62	0.80	0.72 ± 0.70	0.94	0.48
DHA (C22:6*n*-3)	2.38 ± 0.76	2.74 ± 0.78*	0.012	2.53 ± 0.79	2.36 ± 0.91	2.49 ± 0.79	0.16	2.44 ± 0.84	0.025	0.31
Estimated desaturases										
SCD-16 (C16:1/C16:0)	0.060 ± 0.030	0.067 ± 0.021	0.17	0.063 ± 0.026	0.063 ± 0.024	0.071 ± 0.025	0.002	0.068 ± 0.025	<0.001	0.009
SCD-18 (C18:1*n*-9/C18:0)	4.03 ± 0.95	3.36 ± 0.80**	<0.001	3.72 ± 0.94	4.09 ± 1.07	3.80 ± 0.98	0.016	3.90 ± 1.02	<0.001	0.10
D6D (C18:3*n*-6/C18:2*n*-6)	0.012 ± 0.008	0.013 ± 0.007*	0.53	0.013 ± 0.008	0.013 ± 0.007	0.016 ± 0.008	0.001	0.015 ± 0.007	<0.001	0.009
D5D (AA/C20:3*n*-6)	4.71 ± 1.62	4.36 ± 1.53	0.21	4.55 ± 1.59	4.74 ± 1.77	4.31 ± 1.38	0.013	4.46 ± 1.55	0.005	0.57

AA, arachidonic acid; ALA, α-linolenic acid; D5D, Δ^5 desaturase; D6D, Δ^6 desaturase; DGLA, dihommo-γ-linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid; LA, linoleic acid; MA, myristic acid; MetS, metabolic syndrome; MGA, margaric acid; OA, oleic acid; PA, palmitic acid; POA, palmitoleic acid; SA, stearic acid; SCD, stearoyl coenzyme A desaturase.

Values of fatty acids are expressed as adjusted geometric mean (% of total fatty acids) ± SD.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (compared to the MetS group for the same gender).

[a] P value for comparison between-groups calculated by general linear models adjusted for age and energy intake.

[b] Additionally adjusted for MetS status.

[c] Additionally adjusted for gender.

Table 4
Odds ratio associated with having the MetS according to quartiles of fatty acid concentrations and estimated desaturase activities.

Fatty acid	Quartile				*P* trend
	1 ($n = 107$)	2 ($n = 107$)	3 ($n = 107$)	4 ($n = 106$)	
SFA	1.00	0.70 (0.39, 1.23)	1.56 (0.84, 2.90)	2.65 (1.34, 5.26)**	0.001
MA (C14:0)	1.00	1.52 (0.59, 2.68)	2.54 (1.38, 4.66)**	3.77 (1.95, 7.29)***	<0.001
PA (C16:0)	1.00	1.22 (0.69, 2.16)	1.49 (0.83, 2.69)	3.56 (1.79, 7.10)***	0.003
MGA (C17:0)	1.00	0.50 (0.27, 0.94)*	0.76 (0.40, 1.46)	0.64 (0.34, 1.22)	0.17
SA (C18:0)	1.00	0.69 (0.37, 1.28)	0.61 (0.33, 1.12)	0.83 (0.44, 1.56)	0.41
MUFA	1.00	1.57(0.87, 2.84)	1.57 (0.87, 2.84)	2.25 (1.21, 4.18)*	0.08
POA (C16:1*n*-7)	1.00	0.94 (0.53, 1.67)	1.61 (0.88, 2.97)	2.34 (1.22, 4.47)*	0.018
OA (C18:1*n*-9)	1.00	1.38 (0.77, 2.85)	1.58 (0.87, 2.88)	2.13 (1.14, 3.97)*	0.11
PUFA	1.00	0.44 (0.21, 0.92)*	0.24 (0.12, 0.48)***	0.28 (0.14, 0.56)***	<0.001
Series *n*-6					
LA (C18:2*n*-6)	1.00	0.52 (0.25, 1.10)	0.26 (0.13, 0.52)**	0.23 (0.11, 0.46)***	<0.001
GLA (C18:3*n*-6)	1.00	1.23 (0.67, 2.25)	1.47 (0.76, 2.82)	2.39 (1.20, 4.79)*	0.10
DGLA (C20:3*n*-6)	1.00	1.30 (0.71, 2.37)	1.63 (0.87, 3.04)	0.97 (0.54, 1.75)	0.33
AA (C20:4*n*-6)	1.00	0.72 (0.40, 1.33)	0.92 (0.49, 1.71)	0.92 (0.49, 1.71)	0.74
Series *n*-3					
ALA (C18:3*n*-3)	1.00	1.43 (0.77, 2.65)	1.08 (0.60, 1.97)	1.14 (0.62, 2.07)	0.71
EPA (C20:5*n*-3)	1.00	0.73 (0.50, 1.36)	0.76 (0.41, 1.41)	0.76 (0.41, 1.41)	0.75
DHA (C22:6*n*-3)	1.00	0.79 (0.42, 1.47)	0.75 (0.40, 1.40)	0.68 (0.37, 1.27)	0.67
Estimated desaturases					
SCD-16 (C16:1/C16:0)	1.00	1.03 (0.58, 1.84)	1.55 (0.84, 2.85)	1.75 (0.94, 3.26)	0.19
SCD-18 (C18:1*n*-9/C18:0)	1.00	0.85 (0.47, 1.53)	0.91 (0.50, 1.66)	1.76 (0.92, 3.39)	0.12
D6D (C18:3*n*-6/C18:2*n*-6)	1.00	1.47 (0.83, 2.60)	2.16 (1.18, 3.96)*	3.10 (1.63, 5.87)**	0.003
D5D (AA/C20:3*n*-6)	1.00	0.94 (0.51, 1.74)	0.93 (0.50, 1.72)	0.89 (0.48, 1.63)	0.98

AA, arachidonic acid; ALA, α-linolenic acid; D5D, Δ^5 desaturase; D6D, Δ^6 desaturase; DGLA, dihommo-γ-linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid; LA, linoleic acid; MA, myristic acid; MetS, metabolic syndrome; MGA, margaric acid; OA, oleic acid; PA, palmitic acid; POA, palmitoleic acid; SA, stearic acid; SCD, stearoyl coenzyme A desaturase.
Odds ratio (95% confidence interval) by logistic regression analysis adjusted by gender, age, energy intake, BMI, smoking status (current; past, 0–1 year; past, 1–5 year; past, >5 years; never), occupation (worker, unemployed or unfit, retired), and educational level (none, primary school, secondary school, university).
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

HDL-C, TG, and fasting glucose. Regarding the other PUFA considered, GLA showed non-significant associations with the metabolic risk factors, while DGLA was positively associated with TC, HDL-C, and low-density lipoprotein cholesterol (LDL-C). In what refers to estimated desaturase activities, SCD-16, SCD-18, and D6D were adversely associated with several metabolic risk factors, whereas D5D showed beneficial associations. When partial correlation coefficients were also controlled for BMI, most of the associations remained significant, except for WC, which only remained significant for PA. .

Table 5
Odds ratio associated with having the MetS for the highest quartile of the fatty acid concentrations and estimated desaturase activities according to gender.

	Men ($n = 177$)	Women ($n = 250$)
Fatty acid		
MA (C14:0)	2.23 (0.80, 6.20)	5.84 (2.01, 17.0)**
PA (C16:0)	2.05 (0.75, 5.62)	27.7 (3.5, 223.0)***
POA (C16:1*n*-7)	1.83 (0.71, 4.71)	2.21 (0.74, 6.61)
LA (C18:2*n*-6)	0.27 (0.09, 0.79)*	0.15 (0.05, 0.47)**
GLA (C18:3*n*-6)	1.20 (0.45, 3.15)	4.56 (1.56, 13.3)**
DGLA (C20:3*n*-6)	0.98 (0.41, 2.30)	2.75 (0.91, 8.33)
Estimated desaturases		
SCD-16 (C16:1/C16:0)	1.50 (0.57, 3.94)	1.10 (0.39, 3.11)
SCD-18 (C18:1*n*-9/C18:0)	0.97 (0.33, 2.87)	4.64 (1.42, 15.1)*
D6D (C18:3*n*-6/C18:2*n*-6)	2.34 (0.89, 6.13)	4.49 (1.66, 12.1)**
D5D (AA/C20:3*n*-6)	1.44 (0.57, 3.65)	1.09 (0.42, 2.86)

D5D, Δ^5 desaturase; D6D, Δ^6 desaturase; DGLA, dihommo-γ-linoleic acid; GLA, γ-linolenic acid; LA, linoleic acid; MA, myristic acid; MetS, metabolic syndrome; PA, palmitic acid; POA, palmitoleic acid; SCD, stearoyl coenzyme A desaturase.
Odds ratio (95% confidence interval) by logistic regression analysis, which included age, BMI, smoking status (current; past, 0–1 year; past, 1–5 year; past, >5 years; never), occupation (worker, unemployed or unfit, retired), and educational level (none, primary school, secondary school, university).
The lowest quartile was taken as the reference (OR = 1.00).
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

4. Discussion

In the current study, subjects with the MetS showed higher proportions of total SFA and lower levels of total PUFA than those without the MetS. Particularly, the concentrations of MA, PA, and POA in the participants with the MetS were significantly higher and those of LA lower than their counterparts. In contrast, the levels of MUFA and LC-PUFA (AA, EPA, and DHA) showed no significant differences between the two groups. These findings confirm the results of previous studies in which the FA composition of subjects with and without the MetS was significantly different.[9–15] In these studies patients with the MetS presented a high content of SFA, especially PA, and a low content of PUFA, especially LA, while in all these studies the proportions of AA, EPA and DHA were not significantly different according to MetS status. We also found that MA, SA, and POA were directly associated with an increased probability of having the MetS, whereas high levels of LA were significantly associated with a lower MetS probability. Moreover, increased levels of MA, PA, POA, and DGLA, in addition to low proportions of LA, were associated with adverse profiles of several metabolic risk factors.

In agreement with our results, Warensjö et al.[12] reported that a dietary SFA factor, comprised mainly of PA and SA in serum cholesterol esters (CE), was associated with a higher risk of having the MetS in Swedish men, independently of BMI, smoking status and physical activity. Likewise, Kabagambe et al.[18] found the highest quartile of SFA in erythrocytes to be directly associated with

Table 6
Partial correlation coefficients between plasma fatty acids, estimated desaturase activities and metabolic risk factors ($n = 427$).

	WC	BMI	TC	HDL-C[a]	LDL-C	TG[a]	SBP	DBP	Glucose
Fatty acid									
MA (C14:0)	0.13**	0.17**	0.08	−0.08	0.01	0.34***	0.06	0.03	0.11*
PA (C16:0)	0.24***	0.19***	0.10*	0.01	−0.00	0.37***	0.08	0.04	0.15**
POA (C16:1*n*-7)	0.16***	0.18***	0.18***	0.05	0.07	0.35***	0.06	0.12*	0.11*
LA (c18:2*n*-6)	−0.02	−0.06	0.07	0.10*	0.16**	−0.37***	0.04	−0.01	−0.12*
GLA (C18:3*n*-6)	0.03	0.00	0.08	0.09	0.04	0.07	−0.03	0.02	0.02
DGLA (C20:3*n*-6)	0.05	0.09	0.15**	0.20***	0.11*	−0.05	0.03	−0.01	−0.09
Estimated desaturases									
SCD-16 (C16:1/C16:0)	0.11*	0.15**	0.18***	0.05	0.08	0.30***	0.04	0.13**	0.08
SCD-18 (C18:1*n*-9/C18:0)	−0.02	0.00	−0.01	−0.29***	−0.04	0.43***	−0.00	0.08	0.12*
D6D (C18:3*n*-6/C18:2*n*-6)	0.03	0.02	0.05	0.05	−0.02	0.18***	−0.04	0.02	0.06
D5D (AA/C20:3*n*-6)	−0.08	−0.10**	−0.15**	0.01	−0.07	−0.28***	−0.06	−0.08	0.02

D5D, Δ^5 desaturase; D6D, Δ^6 desaturase; DBP, diastolic blood pressure; DGLA, dihommo-γ-linoleic acid; GLA, γ-linolenic acid; HDL-C, high-density lipoprotein cholesterol; LA, linoleic acid; LDL-C, low-density lipoprotein cholesterol; MA, myristic acid; PA, palmitic acid; POA, palmitoleic acid; SBP, systolic blood pressure; SCD, stearoyl coenzyme A desaturase; TC, total cholesterol; WC, waist circumference.
Adjusted for sex, age, energy intake, smoking status, occupation, educational level, and medication for hypercholesterolemia, blood pressure, and diabetes.
When adjustment included BMI, relationships of fatty acids and estimated desaturase activities with metabolic parameters remained significant, although somewhat attenuated, with the exception of WC, which only remained significant for PA.
*$P < 0.050$,**$P < 0.010$,***$P < 0.001$.
[a] Log-transformed for normality.

the MetS compared with the lower quartile after adjusting for several confounders. In the current study, we found that MA and PA were positively correlated with TG, even after adjustment for BMI. Positive associations of TG concentrations with individual and total SFA have also been found in adolescents[19] and adults.[20] Other studies have shown a strong and positive correlation between SFA intake and sagittal abdominal diameter, WC and BMI,[6,21] and measurement of glucose metabolism.[22] In addition, two recent studies evaluating the association of FA composition of erythrocytes with the MetS[10,18] also showed significant positive correlations of TG, BMI, WC, and glucose with total and individual SFA, respectively.

Also in agreement with data from previous studies in adolescents[19] and adults free of known metabolic diseases,[7] our results showed that POA levels were strongly and positively associated with most metabolic risk factors. In opposition, we found that PUFA and its main contributor, LA, were associated with a lower probability of having the MetS. Similarly, in the GOLDN Study both the highest quartile of PUFA and *n*-6 PUFA content in erythrocyte membranes were significantly associated with a lower probability of having the MetS compared to the lowest quartile after adjusting for confounders.[18] In fact, LA has shown to be protective against the MetS and several other CVD risk factors.[12,21,23] In our study, LA was also negatively correlated with TG. Others have found similar results in adults[18] and adolescents.[19] The level of plasma TG will be determined by both its secretion into blood and the efficiency of clearance. Since TG did not correlate with energy, fat, protein or carbohydrate intake, high TG levels may be due to increases in their biosynthesis in the body. This process is mediated by SCD, an enzyme that is down-regulated by PUFA.[5] In fact, we found that both SCD-16 and SCD-18 showed strong negative correlations with plasma LA ($r = -0.45$, $P < 0.001$; and $r = -0.59$, $P < 0.001$, respectively) and dietary LA ($r = -0.18$, $P < 0.001$; and $r = -0.11$, $P = 0.029$, respectively). Consequently, a greater deficiency of LA would lead to greater biosynthesis of TG. In addition, the efficiency of TG clearance may be reduced in people with insulin resistance and thus the MetS. Therefore, the lower LA levels found in people with MetS could also contribute to its negative correlation with TG.

Although a higher concentration of OA, GLA and DGLA is a rather consistent finding in patients with the MetS,[9–12,14,15] we failed to observe such situation. Moreover, Warensjö et al.[12] reported that a low-LA factor (directly associated with the MetS) comprised, among others, positive contributions of OA and GLA, whereas the *n*-3 PUFA factor (inversely associated with the MetS) had a negative loading of DGLA. Nevertheless, we did not find significant associations between the odds of having the MetS and these FA. However, we must take into account that olive oil, which is characterized by high levels of MUFA oleic acid (comprising between 55 and 85% of its FA content), was the largest contributor to total fat in our population. Therefore, the proportion of OA in our population is likely to reflect a dietary intake more than endogenous synthesis, which could result in the lack of difference in the proportions of participants with and without the MetS. In addition, Western societies obtain their OA content mainly from animal products, which contain large amounts of SFA. Therefore, it is likely that the findings for OA are confounded with SFA in Western populations. This is not the case of our study population, since plasma levels of OA correlated negatively with SFA intake ($r = -0.118$, $P = 0.015$).

Regarding GLA and DGLA, there are three aspects to consider. First, due to the high consumption of olive oil in our population, MUFA accounted for most of the fat content (50%), with only 15.6% coming from PUFA. Second, our subjects consumed 98.8 g/d of seafood, which represented 0.82 g/d or 0.35% of energy from marine *n*-3 PUFA, considerably higher than worldwide consumption.[24] Overall, this resulted in lower proportions of *n*-6 PUFA in our subjects compared with other Western studies. Finally, since dietary PUFA suppresses the activity and expression of desaturases,[5] the high consumption of fish in our population may contribute to high GLA and DGLA levels through low D5D expression in subjects without the MetS. Hence, the combination of these three factors might have led to the non-significant difference in the proportions of these FA between subjects with and without the MetS and the lack of association with the MetS.

Since dietary intake in the MetS group did not differ from that in subjects without the MetS, the differences in the plasma FA profile in the MetS group probably resulted from endogenous FA synthesis involving desaturases. In fact, subjects with the MetS showed higher values of SCD-16 and D6D than those without the MetS in the present study. In addition, high estimated SCD-16 and D6D activities were significantly associated with having the MetS in a crude logistic regression model. Conversely, SCD-18 and D5D neither differed among MetS groups nor showed a significant association with the odds of having the MetS. Similarly, in all the

previous studies that also investigated the association between estimated desaturase activities and the MetS, SCD-16 and D6D activities were consistently increased in subjects with the MetS.[9,11,12,14,15] A high estimated SCD-16 may both reflect a high intake of SFA and low PUFA and a high SCD-16 activity due to metabolic disorders.[25] Since only estimated D6D activity remained significant after adjustment for BMI, a marker of overall adiposity, the increase in the probability of having the MetS associated with higher SCD-16 activities is mainly explained by obesity due to an unhealthy diet. Similar results were found in Swedish men,[14] although in this population D6D was also dependent on BMI. However, Warensjö et al.[12] also carried out a principal factor analysis in Swedish men and found that both SCD-16 and D6D contributed with positive loadings to the low-LA factor, which was directly associated with having the MetS even after adjustment for BMI and other lifestyle factors.

Also consistent with our findings, in previous studies estimated SCD-18 activity did not differ between subjects with and without the MetS[9,11,12,14,15] and the predictive value of SCD-18 for MetS development was not significant either in Swedish[14] or in Japanese[9] men. This could also be explained by the high dietary proportion of OA, which affects the estimated SCD activity when using the ratio OA/SA. However, in opposition to our results, D5D activity was decreased in patients with the MetS in these previous studies. Moreover, low estimated D5D activity predicted the development of MetS independent lifestyle factors in Swedish men,[14] as well as the development of abdominal obesity, but not of the MetS from abdominal obesity in Japanese men.[9] In addition, the protective *n*-3 PUFA factor found in Swedish men comprised a positive loading from D5D.[12] As already stated, the high consumption of fish in our population, which might down-regulate D5D expression, along with the low proportions of *n*-6 PUFA due to high MUFA intake from olive oil, could explain the non-significant association between D5D and the MetS.

We found positive associations between SCD-16 and WC, BMI, TC, TG, and DBP, while SCD-18 was only correlated positively with TG but negatively with HDL-C. Moreover, while D6D was positively associated with TG, estimated D5D activity correlated negatively with BMI, TC, and TG. However, after adjustment for BMI, strong associations in desaturases remained for TG and TC. In humans, OA is the preferred substrate for the synthesis of TG and CE.[5] Since, OA is the major product of SCD, SCD plays a vital role in the de novo lipogenesis to store excess energy in a TG form and in cholesterol metabolism by providing a substrate for CE synthesis to temporarily store excess cholesterol in the liver. Thus, both SCD-16 and SCD-18 have been shown to correlate with TG levels in normal and hypertriglyceridemic adults,[26] and were strong predictors of TG ($P < 0.001$) and TC ($P < 0.05$) in healthy adolescents.[27] Our results are also consistent with some other studies in adolescents[19] and adults.[11]

Interestingly, we found that compared with men, women with the MetS presented a FA pattern and estimated desaturase activities closer to the typical profile of patients with the MetS. In contrast, we observed few strong differences in the FA and estimated desaturase activities between men and women without the MetS. Furthermore, women with the MetS presented higher TC values than men with MetS. We also found that FA and estimated desaturase activities were more strongly related to the MetS in women than in men. Therefore, our results demonstrate a greater impact of the MetS in women. An explanation for these gender-related differences may involve the influence of sex hormones. We must take into account that all women in the study were >60 y and, therefore, menopausal. Menopause is associated with an increase in all single components of the MetS.[28] People with the MetS are at increased risk of developing CVD. Although CVD is rare among women younger than 45 years, women older than 55 years are more likely to have CVD than men. Alterations in lipid metabolism are thought to be a substantial component of CVD risk in postmenopausal women.[28] However, it is unclear whether the transition to menopause increases CVD risk in all women or only in those who develop features of the MetS.[28] We found that only in the presence of the MetS women present a more proatherogenic FA and lipid profile than men. These results are in agreement with several studies that have shown that the effects of the MetS on CVD,[29] and all-cause mortality[30] are stronger in women than in men.

The main limitation of our study is its cross-sectional nature. Therefore, we cannot make statements about causation but only generate hypotheses for the associations between FA composition, desaturase activities and the MetS. However, some other limitations and strengths are worthy of mention. First, the disparity of results may reflect the different research models, different populations studied with different health status and dietary intakes. In addition, genetic determinants may interact with FA metabolism and contribute to FA composition, desaturase activities and MetS features. Second, although comprehensive data on diet, lifestyle, and other risk factors allowed us to adjust our statistical models for potential confounders, we could not rule out residual confounding. Third, the use of product-to-precursor ratios of individual plasma FA as estimates, which may reflect FA metabolism but may also be affected by dietary FA intake. Finally, our sample included adults > 55 y at high risk of CVD and may not be representative of the general Catalan population.

In conclusion, FA composition and estimated desaturase activities differed between Mediterranean adults with and without the MetS, thus confirming results of previous studies in other populations. MA, PA, POA, GLA, DGLA, SCD-16, SCD-18, and D6D were adversely associated with the MetS or several metabolic risk factors, while LA and D5D showed the opposite behavior. Therefore, our results contribute to the present knowledge and support current dietary recommendations to reduce the intake of SFA and increase that of PUFA. Since FA composition does not depend on diet alone, further research investigating FA and the MetS should include the effects of non-dietary factors such as genetics or younger populations (<50 y) with a healthier status. Interestingly, we found a stronger impact of the MetS in women. The basis for these sex-based differences warrants further research.

Conflict of interest

No conflicts of interest.

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