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Plasma phospholipid fatty acid profile, estimated desaturase activities and prevalence of the metabolic syndrome in a general population cohort: A cross-sectional study

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Abstract.
BACKGROUND: An altered plasma fatty acid (FA) profile and desaturase activities have been associated with several metabolic diseases, including the MetS, but studies in the general populations are lacking, and only few studies have investigated a broad spectrum of FA in plasma phospholipids (PL).
OBJECTIVE: We investigated, cross-sectionally, the relationship of the FA profile and desaturase activities in plasma PL with the prevalence of MetS in a general population in The Netherlands.
METHODS: Baseline characteristic data from 850 participants (male: 50.2%) aged 38-68 years recruited in the Lifelines cohort study were obtained. The FA profile was determined in fasting plasma PL, and desaturase activities were estimated from product/precursor ratios. The MetS was defined according to International Diabetes Federation. Logistic regressions were used to examine the relation of the FA profile with the prevalence of MetS, and Bonferroni correction was applied to account for multiple testing.
RESULTS: 151 participants (17.7%) had the MetS. After adjustment for several confounders and Bonferroni correction, higher tertiles of C18 : 0 (the early precursor of *de novo lipogenesis* pathway), C18 : 3n6 and C20 : 3n6 (both consistent with a high Δ^6 desaturase (D6D) activity), and D6D activity itself were associated with a higher prevalence of MetS, while higher tertiles of C18 : 1n7, C24 : 0, and C24 : 1n9 (very long chain FA) as well as stearoyl-CoA desaturase (SCD)-18 were inversely associated with the MetS.
CONCLUSIONS: This study shows that a wide-ranging plasma PL FA profile and estimated desaturase activities were different between adults with and without the MetS in a general representative population and implicates the importance of monitoring individual FAs and desaturase activities as novel modifiable biomarkers for the MetS.

Keywords: Phospholipids, lipids, fatty acids, metabolic syndrome, fatty acid desaturases

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List of abbreviations

MetS	metabolic syndrome
PL	phospholipids
SCD	stearoyl-CoA desaturase
D6D	Δ^6 desaturase
D5D	Δ^5 desaturase
BP	blood pressure
WC	waist circumference
TC	total cholesterol
TGL	total triglycerides
FAME	fatty acid methyl esters
EDTA	ethylenediaminetetraacetic acid
ISCED	International Standard Classification of Education
FFQ	food frequency questionnaire
MVPA	non-occupational moderate-to-vigorous physical activity
IDF	International Diabetes Federation
IQR	interquartile range
OR	the odds ratios
SAFA	saturated fatty acids
TFA	trans fatty acids
VLC	very long chain

1. Introduction

The metabolic syndrome (MetS), as defined by a cluster of metabolic risk factors such as high blood pressure, high blood glucose, and high triglyceride levels, increases the risk for developing cardiovascular disease (CVD) and type 2 diabetes (T2D) [1]. The prevalence of MetS is rising all over the world, and the estimated global prevalence is about one-quarter of the world population [1], thereby posing an important public health concern.

Concentrations of several circulating fatty acids (FA) are emerging as novel, potentially modifiable biomarkers for the risk of cardiometabolic diseases, including the MetS [2, 3]. In fact, an altered FA profile and estimated activities of main desaturases have been associated with metabolic health [4] and the development of MetS [5]. Nevertheless, those studies have only assessed limited types of FA in populations with an elevated risk of CVD. Plus, the current consideration of health risks associated with FA is largely based on structural groups (e.g., saturated FA, trans-FA, and unsaturated FA), but the evidence is somewhat conflicting [6]. Thus, it is necessary to assess a broader FA profile and understand the health impact of each FA within the structural groups to improve risk prediction for health outcomes more efficiently rather than draw generalized conclusions from pooling FA into structural groups.

Although an objective assessment of circulating FA profiles in the blood can, to some extent, mitigate the reporting bias of self-reported dietary lipids, the biomarkers of FA in the blood cannot fully reflect the dietary FA intake because it is also affected by non-dietary factors [7]. One of the most critical factors is endogenous synthesis through desaturation by three main desaturases: Δ^5 desaturase (D5D), Δ^6 desaturase (D6D), and Δ^9 or stearoyl-CoA desaturase (SCD) [8]. Therefore, circulating FA profiles in the blood could reflect both diet and endogenous metabolism. It is worth mentioning that other factors, such as sex, genotype, body mass index, alcohol intake, smoking status, and physical activity, can also interfere with circulating FA profiles [9, 10].

In this exploratory study, we aimed to investigate 1) potential differences in circulating a wide-ranging FA profile between individuals with and without the MetS and the associations of circulating individual FA with the prevalence of the MetS, and 2) the association of desaturase activities with the prevalence of the MetS to glean insight into the endogenous synthesis of FA. For this, we assessed FA in plasma phospholipids (PL) in a general representative population.

2. Methods

2.1. Study design and population

The Lifelines cohort study is a multidisciplinary prospective population-based cohort study that applies in a unique three-generation design of the health and health-related behaviors of 167 729 persons living in The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical, and psychological factors which contribute to health and disease of the general population. In short, the first group of participants was recruited via local general practitioners. Then participants could indicate whether their family members were interested as well. Additionally, individuals who were interested in the study could register via an online registration system. Individuals with insufficient knowledge of the Dutch language, with severe

psychiatric or physical illness, were excluded from the study. Before study entry, a signed informed consent form was obtained from each participant. Adult participants (≥18 years) were asked to complete several self-administered questionnaires regarding various aspects, including demographics, socioeconomic status, lifestyle factors, and medication use. The Lifelines study was conducted according to the principles of the Declaration of Helsinki and approved by the Medical Ethics Committee of the Institutional Review Board of the University Medical Center Groningen, The Netherlands (2007/152). A detailed description of the Lifelines cohort study can be found elsewhere [11, 12]. For the current study, a subset of 864 participants from the Lifelines baseline database was randomly selected. Cases with missing or invalid data on circulating FA or daily energy intake were removed before analyses, leaving 850 participants with complete data (Supplementary Figure S1).

2.2. Clinical measurements

Anthropometric measurements and blood pressure (BP) were measured by well-trained staff. Anthropometric measurements were measured without shoes, in which body weight was measured to 0.1 kg by the SECA 761 scale (Seca GmbH, Hamburg, Germany); height was measured to 0.5 cm using the Frankfort Plane position by the SECA 222 stadiometer (Seca GmbH, Hamburg, Germany); and the waist circumference (WC) was measured to 0.5 cm by the SECA 200 measuring tape (Seca GmbH, Hamburg, Germany) [11]. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). The BMI was additionally categorized into underweight (BMI < 18.5 kg/m^2), normal (18.5 ≤ BMI<25 kg/m^2), overweight (25 ≤ BMI<30 kg/m^2), and obese (BMI ≥ 30 kg/m^2) [13]. BP was measured by Dynamap PRO 100V2 (GE Healthcare, Freiburg, Germany); systolic and diastolic BP were measured ten times within ten minutes, and each of the average values of the last three readings was used as BP parameters [11].

2.3. Biochemical measurements

For analyses of lipids and glucose, blood samples were drawn in the morning between 8:00 and 10:00 am after a period of overnight fasting at baseline. Serum levels of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured with an enzymatic colorimetric method, while low-density lipoprotein cholesterol (LDL-C) was measured with an enzymatic method, and total triglycerides (TGL) was measured with a colorimetric UV method, all on a Roche Modular P chemistry analyzer (Roche, Basel, Switzerland). Fasting blood glucose was measured using a hexokinase method. All biochemical measurements were performed in singles.

2.4. Fatty acids analyses and estimation of desaturase activities

Ethylenediaminetetraacetic acid (EDTA)-plasma samples were collected at baseline and stored at –80°C until analyses of fatty acids were carried out. Analyses of fatty acids were performed at the Department of Laboratory Medicine of the University Medical Center Groningen, The Netherlands, using the methodology as described by Hoving et al. [14]. In short, total lipids were extracted by the method of Folch et al., using 6 mL of chloroform-methanol (2 : 1) and a 200 μL EDTA-plasma sample [15]. Then, a shortened version of the method of Kaluzny et al. was used to isolate plasma cholesterol esters, triglycerides (TG), and phospholipids (PL), using aminopropyl SPE columns for the separation (Isolute, Biotage) [16]. Fatty acids were transmethylated with methanolic-HCL into fatty acid methyl esters (FAME). The samples were extracted with hexane and eventually redissolved into 100 μL hexane. 100 μL of internal standards for the quantification of fatty acids in cholesterol esters (17 : 0) (50.1 mg/100 mL chloroform-methanol, 2 : 1 v/v), and in triglycerides (19 : 0) (19.9 mg/100 mL chloroform-methanol, 2 : 1 v/v), both obtained from Sigma-Aldrich (Zwijndrecht, The Netherlands), were added before isolation of classes. For the quantification of fatty acids in PL, 100 μL of free fatty acid 19 : 0 (50.0 mg/100 mL methanol), obtained from Larodan (Solna, Sweden), was added after isolation of lipid classes according to an internal standard. To prevent fatty acid oxidation, 100 μL Butylated Hydroxytoluene (1 g/100 mL methanol) from Sigma-Aldrich (Zwijndrecht, The Netherlands) was added.

Aliquots of 2 μL were injected into an Agilent model 6890 gas chromatography equipped with a 200 m × 0.25 mm polar column (CP Select for FAME) and detected with an Agilent 7683 series

flame ionization detector. FAME was identified by comparing retention times with those of known standards (Supelco 37 component FAME mix (Sigma-Aldrich)). The precision of the measurements was tested by calculating the variation coefficient from 10 replicate quality-control samples (pooled plasma samples). We have only selected FA detected in plasma PL because it is the commonly used compartment to predict disease outcomes [17, 18]. FA in plasma PL were expressed as a relative percentage of total FA in PL (mol%).

Desaturase activity was estimated using the FA product/precursor ratio [8]. Thus, desaturase activities were estimated as the ratio of product to precursor of individual FA of plasma PL according to the following: SCD-16 = C16 : 1n7/C16 : 0, SCD-18 = C18 : 1n9/C18 : 0, D6D=C18 : 3n6/C18 : 2n6, and D5D=C20 : 4n6/C20 : 3n6.

2.5. Other covariates

Education, smoking status, and medication use were derived from self-administered questionnaires. Education, as defined by the highest educational level achieved, was categorized as: (1) low - junior general secondary education or lower (International Standard Classification of Education [ISCED] level 0, 1 or 2); (2) middle - secondary vocational education and senior general secondary education (ISCED level 3 or 4); and (3) high - higher vocational education or university (ISCED level 5 or 6) [19]. Smoking status was categorized into never, former, and current smoker. Medication use was binary classified and obtained from the question, "Do you use medicine that has been prescribed by a doctor?". Daily energy intake and alcohol intake were estimated from a semi-quantitative self-reported food frequency questionnaire (FFQ) by using the 2011 Dutch food composition database (NEVO) [20]. The FFQ was developed and validated by Wageningen University to assess the intake of 110 food items over the last month [21, 22]. Physical activity was indicated by non-occupational moderate-to-vigorous physical activity (MVPA), which was calculated in minutes per week from the validated Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) data, which incorporated leisure time and commuting physical activities, including sports, at moderate (4.0–6.4 metabolic equivalent of task [MET]) to vigorous ($\geq$6.5 MET) intensity [23].

2.6. Definition of the metabolic syndrome

The MetS was defined according to the International Diabetes Federation (IDF) which was WC > 94 cm (men) or > 80 cm (women) along with the presence of two or more of the following: 1) Blood glucose greater than 5.6 mmol/L or diagnosed diabetes; 2) HDL-C < 1.0 mmol/L in men, <1.3 mmol/L in women; 3) Blood TGL > 1.7 mmol/L; 4) BP > 130/85 mmHg or drug treatment for hypertension [1, 24].

2.7. Statistical analyses

Baseline characteristics were presented as mean $\pm$ standard deviation (SD) for parametric data, median (interquartile range [IQR]) for non-parametric distributes of the data, or frequencies (%) for nominal variables for the overall study population, and subjects with and without the MetS. Student's T-test, Mann–Whitney U test, and the Chi-Squared test were used to determine differences in baseline characteristics in participants with and without the MetS for parametric, non-parametric, and categorical variables, respectively. Metabolic risk factors, FA concentrations, and estimated desaturase activities were presented as mean $\pm$ SD for normally distributed variables and median (IQR) for variables with a skewed distribution. Differences in metabolic risk factors, FA concentrations, and estimated desaturase activities were analyzed by general linear models where log-transformation was applied for variables with a skewed distribution. And differences in the MetS components were assessed using a logistic regression model adjusting for age, sex, and energy intake for metabolic risk factors, and age and sex for FA concentrations and estimated desaturase activities. Correction for multiple comparisons at Bonferroni 2-tailed $a < 0.0014$ (33 FA and four desaturases activities = 37 exploratory comparisons).

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 tertiles of FA and estimated desaturase activities in plasma PL, considering the lowest tertile as the reference and controlling for potential confounding factors: age, sex, energy intake, alcohol intake, BMI, smoking status, medication use, education, and MVPA. Correction for multiple comparisons at Bonferroni

2-tailed $a < 0.0014$ (33 FA and four desaturases activities = 37 exploratory comparisons). Sensitivity analyses investigated the relationship between FA profile, estimated desaturase activities in plasma PL, and metabolic risk factors through partial correlation analysis controlling for age, sex, energy intake, alcohol intake, smoking status, medication use, education, MVPA, and BMI (Supplementary Table S1).

In multivariable logistic models, missing covariates (education, $n = 13$; medication, $n = 4$; energy and alcohol intake, $n = 86$; MVPA: $n = 81$) were imputed using chained multiple imputations. All analyses were performed with Stata, version 13.1 (StataCorp, Texas, USA).

3. Results

The baseline characteristics of the 850 participants (50.2% men) according to the MetS status are described in Table 1. The prevalence of MetS in the study population was 17.7% ($n = 151$). Of the total population, 56.4%, 56%, and 3.3% were overweight or obese, used prescribed medication, and had T2D, respectively. As expected, most of the characteristics associated with the MetS were different between participants with and without the MetS, except for daily energy intake, alcohol intake, and MVPA, for which no difference was observed ($p = 0.3$, 0.2, and 0.06, respectively). Participants with the MetS were older than those without the MetS (median [interquartile range]: 63 [58–67] vs. 54 [39–63], $p < 0.001$), had higher prevalence of obesity (39.7% vs. 8.9%, $p < 0.001$), T2D (11.9% vs. 1.4%, $p < 0.001$), and poorer education (18.5% vs. 38% for high education; 50.7% vs. 29.4% for low education; $p < 0.001$).

The metabolic risk factors between the MetS and non-MetS participants are detailed in Table 2. According to the definition of the MetS, the prevalence of MetS in the study population was 17.7% ($n = 151$), while that of its components was 62.3%, 15.4%, 10.9%, 39.5%, and 14.6%, for elevated WC, TGL, HDL-C, BP, and fasting glucose, respectively. Almost all metabolic risk factors and components contributing to the MetS, together with BMI, were different in participants with the MetS compared with those without the MetS ($p < 0.001$ for all), with the exception of TC and LDL-C ($p = 0.09$ and 0.07, respectively) (Table 2).

Table 3 compares the FA profile and estimated desaturase activities in plasma PL in participants with and without the MetS. There were, in total, 33 types of FA detected and quantified in plasma PL, including 11 saturated fatty acids (SAFA), six monounsaturated fatty acids (MUFA), seven omega-6 polyunsaturated fatty acids (PUFA), four omega-3 PUFA, and five trans fatty acids (TFA). Total SAFA accounted for almost half of the FA in plasma PL, followed by total PUFA ($37.1 \pm 1.83\%$), total MUFA ($12.9 \pm 1.45\%$), and total TFA ($0.21 \pm 0.068\%$) (Table 3). Participants with the MetS had lower levels of C17 : 0, C24 : 0 (Lignoceric acid), C18 : 1n7 (cis-Vaccenic acid), C24 : 1n9 (Nervonic acid), C18 : 1n7tr, SCD-18, and higher levels of C18 : 0 (Stearic acid), C18 : 3n6 (γ-Linolenic acid), C20 : 3n6 (Dihomo-γ-linolenic acid), C20 : 4n6, and D6D (Table 3).

The OR for having the MetS by tertiles of individual FA and estimated desaturase activities in plasma PL are shown in Table 4. After adjusting for covariates and performance of Bonferroni correction for multiple testing, logistic regression showed that higher tertiles of C18 : 0, C18 : 3n6, C20 : 3n6, and D6D remained independently associated with a higher prevalence of MetS, while higher tertiles of C24 : 0, C18 : 1n7, C24 : 1n9, and SCD-18 remained inversely associated with the MetS (Table 4). Partial correlation analyses, carried out as sensitivity analyses, showed correlations between the MetS-related FA, estimated desaturase activities, and several metabolic risk factors (Supplementary Table S1). C18 : 0, C18 : 3n6, C20 : 3n6, and D6D were also positively correlated with most metabolic risk factors, and C24 : 0, C18 : 1n7, C24 : 1n9, and SCD-18 were inversely correlated with several metabolic risk factors (Supplementary Table S1).

4. Discussion

In a group of representative and generally healthy adults in the Netherlands, we innovatively investigated the relations between a wide-ranging FA profile and the MetS in plasma PL. We found unique differences in the FA profile and estimated desaturase activities between participants with and without the MetS. Higher proportions of C18 : 0 (Stearic acid), C18 : 3n6 (γ-Linolenic acid), C20 : 3n6 (Dihomo-γ-linolenic acid), and D6D were associated with an increased risk for the presence of the MetS. In contrast, higher proportions of C24 : 0 (Lignoceric acid), C18 : 1n7 (cis-Vaccenic acid), C24 : 1n9 (Nervonic acid), and SCD-18 were associated with a lower risk

Table 1
Baseline characteristics of participants according to the metabolic syndrome (MetS) status

Characteristics	Total ($n=850$)	MetS ($n=151$)	No MetS ($n=699$)	p
Age, yrs	60 (42-64)	63 (58-67)	54 (39-63)	<0.001
Men, %	50.2	56.3	49	0.1
BMI, kg/m^2, %	26.0 ± 4.1	29.4 ± 4.2	25.2 ± 3.6	<0.001
Underweight	0.9	0	1.1	<0.001
Normal	42.7	11.9	49.4	
Overweight	42	48.3	40.6	
Obese	14.4	39.7	8.9	
Medication use, %	56	71.1	52.8	<0.001
T2D, %	3.3	11.9	1.4	<0.001
Smoking status, %				
Current smoker	15.3	16.6	15	0.04
Former smoker	41.8	49.7	40.1	
Never smoker	42.9	33.8	44.9	
Education, %				
Low	33.1	50.7	29.4	<0.001
Middle	32.3	30.8	32.6	
High	34.7	18.5	38	
Energy intake, kcal/d	1971.3 ± 625.1	1924.9 ± 535.8	1981.8 ± 643.6	0.3
Alcohol intake, g/d	6.2 (1.3-12.6)	5.9 (0.4-12)	6.2 (1.5-12.9)	0.2
MVPA, min/week	320 (150-660)	285 (120-600)	345 (160-670)	0.06

BMI: body mass index; T2D: type 2 diabetes; MVPA: non-occupational moderate-to-vigorous physical activity.

Table 2
Metabolic risk factors and the metabolic syndrome (MetS) components according to the MetS status

	Total ($n=850$)	MetS ($n=151$)	No MetS ($n=699$)	p*
Metabolic risk factors				
BMI, kg/m^2	26 ± 4.1	29.4 ± 4.2	25.2 ± 3.6	<0.001
WC, cm	91.6 ± 12.3	102.7 ± 10.3	89.2 ± 11.4	<0.001
TC, mmol/L	5.2 ± 1.0	5.5 ± 1.2	5.1 ± 1.0	0.09
HDL-C, mmol/L	1.5 ± 0.4	1.2 ± 0.3	1.6 ± 0.4	<0.001
LDL-C, mmol/L	3.3 ± 0.9	3.5 ± 1.1	3.2 ± 0.9	0.07
TGL, mmol/L	1.0 (0.8-1.4)	1.7 (1.3-2.5)	0.9 (0.7-1.2)	<0.001
SBP, mmHg	125.9 ± 17.1	140.1 ± 14.3	122.9 ± 16.1	<0.001
DBP, mmHg	73.4 ± 9.6	78.5 ± 9.7	72.2 ± 9.3	<0.001
Glucose, mmol/L	5.1 ± 0.7	5.8 ± 0.8	4.9 ± 0.6	<0.001
MetS components				
Elevated WC, %	62.3	100	54.2	/
Elevated TG, %	15.4	54.3	7.0	<0.001
Reduced HDL-C, %	10.9	39.1	4.9	<0.001
Elevated BP, %	39.5	88.7	28.9	<0.001
Elevated glucose, %	14.6	55.0	5.9	<0.001

BMI: body mass index; WC: waist circumference; TC: total cholesterol; HDL-C; high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TGL: total triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure. *p value for comparison between-groups calculated by general linear models and logistic regression models (both adjusted for age, sex, and energy intake) for the metabolic risk factors and the MetS component, respectively.

for the presence of the MetS.

As one of the main upstream FA in de novo lipogenesis, C18 : 0 was positively associated with the MetS in our study, agreeing with results reported by Warensjö et al. [25]. However, other studies found null associations of C18 : 0 with TC, LDL-C, and HDL-C [26] and the MetS [5], which could result from different types of population and FA compartments used in those studies. On the other hand, a higher level of C18 : 0 could indicate a more active de novo lipogenesis, which is an intricate and highly regulated pathway and can lead to adverse metabolic consequences when deregulated [27, 28]. Besides the positive association between C18 : 0 and the MetS, we observed a negative association between SCD-18 and the MetS. This indicates that endogenous metabolism

Table 3
Baseline fatty acid composition and estimated desaturase activities in the plasma phospholipids fraction according to the metabolic syndrome (MetS) status

Fatty acids (%)	Total ($n = 850$)	MetS ($n = 151$)	Non-MetS ($n = 699$)	p*
Total SAFA	49.5 ± 1.71	49.8 ± 1.47	49.4 ± 1.75	0.02
C14 : 0 (Myristic acid)	0.49 ± 0.13	0.49 ± 0.13	0.49 ± 0.13	0.6
C15 : 0 (Pentadecylic acid)	0.29 ± 0.069	0.27 ± 0.06	0.29 ± 0.071	0.002
C16 : 0 (Palmitic acid)	31.2 ± 1.76	30.9 ± 1.5	31.3 ± 1.81	0.1
C17 : 0 (Margaric acid)	0.40 ± 0.068	0.38 ± 0.074	0.40 ± 0.066	<0.001
C18 : 0 (Stearic acid)	13.3 ± 1.29	14.0 ± 1.18	13.1 ± 1.26	<0.001
C20 : 0 (Arachidic acid)	0.48 ± 0.12	0.46 ± 0.13	0.48 ± 0.12	0.4
C22 : 0 (Behenic acid)	1.47 ± 0.28	1.46 ± 0.31	1.47 ± 0.27	0.4
C23 : 0 (Tricosylic acid)	0.52 (0.41-0.64)	0.53 (0.42-0.64)	0.52 (0.41-0.64)	0.02
C24 : 0 (Lignoceric acid)	1.23 ± 0.24	1.19 ± 0.25	1.24 ± 0.24	0.003
C25 : 0 (Pentacosylic acid)	0.023 (0.013-0.037)	0.022 (0.012-0.038)	0.023 (0.013-0.037)	0.5
C26 : 0 (Cerotic acid)	0.0026 (0.0019-0.0040)	0.0024 (0.0018-0.0039)	0.0026 (0.0020-0.0040)	0.5
Total MUFA	12.9 ± 1.45	12.4 ± 1.36	13.0 ± 1.45	0.004
C16 : 1n7 (Palmitoleic acid)	0.57 ± 0.19	0.60 ± 0.21	0.56 ± 0.18	0.08
C18 : 1n7 (cis-Vaccenic acid)	1.22 ± 0.20	1.15 ± 0.21	1.23 ± 0.19	<0.001
C20 : 1n7 (Paullinic acid)	0.0034 (0.0025-0.0052)	0.0031 (0.0023-0.0050)	0.0034 (0.0025-0.0052)	0.3
C18 : 1n9 (Oleic acid)	8.78 ± 1.36	8.51 ± 1.24	8.84 ± 1.38	0.2
C20 : 1n9 (Gondoic acid)	0.14 ± 0.051	0.14 ± 0.051	0.14 ± 0.050	0.04
C24 : 1n9 (Nervonic acid)	2.16 ± 0.44	2.02 ± 0.48	2.19 ± 0.43	<0.001
Total PUFA	37.1 ± 1.83	37.2 ± 1.72	37.0 ± 1.85	0.5
C18 : 2n6 (Linoleic acid)	20.7 ± 2.56	19.9 ± 2.70	20.8 ± 2.50	0.002
C18 : 3n6 (γ-Linolenic acid)	0.073 (0.049-0.11)	0.096 (0.068-0.13)	0.070 (0.047-0.10)	<0.001
C20 : 2n6 (Eicosadienoic acid)	0.28 (0.25-0.32)	0.28 (0.25-0.31)	0.28 (0.25-0.32)	0.5
C20 : 3n6 (Dihomo-γ-linolenic acid)	2.88 ± 0.67	3.16 ± 0.68	2.81 ± 0.65	<0.001
C20 : 4n6 (Arachidonic acid)	8.41 ± 1.70	8.84 ± 1.94	8.32 ± 1.62	0.001
C22 : 4n6 (Docosatetraenoic acid)	0.25 ± 0.066	0.26 ± 0.072	0.24 ± 0.064	0.008
C22 : 5n6 (Osbond acid)	0.15 (0.11-0.18)	0.15 (0.11-0.18)	0.14 (0.11-0.18)	0.02
C18 : 3n3 (α-Linolenic acid)	0.25 (0.20-0.35)	0.24 (0.19-0.34)	0.26 (0.20-0.36)	0.08
C20 : 5n3 (Eicosapentaenoic acid)	0.87 (0.69-1.12)	0.93 (0.75-1.14)	0.87 (0.67-1.12)	0.3
C22 : 5n3 (Docosapentaenoic acid)	0.69 ± 0.17	0.73 ± 0.16	0.68 ± 0.074	0.6
C22 : 6n3 (Docosahexaenoic acid)	2.37 ± 0.82	2.47 ± 0.88	2.35 ± 0.81	0.7
Total TRANS	0.21 ± 0.068	0.19 ± 0.060	0.21 ± 0.070	0.001
C16 : 1n7tr (Palmitelaidic acid)	0.020 ± 0.0085	0.019 ± 0.0078	0.021 ± 0.0086	0.009
C18 : 1n9tr (Elaidic acid)	0.049 (0.038-0.063)	0.052 (0.041-0.066)	0.049 (0.038-0.063)	0.4
C18 : 1n7tr (trans-Vaccenic acid)	0.096 ± 0.041	0.087 ± 0.038	0.097 ± 0.042	0.001
C18 : 2n6trtr (Linoelaidic acid)	0.0037 (0.0027-0.0057)	0.0036 (0.0025-0.0057)	0.0037 (0.0027-0.0057)	0.8
CLA	0.031 (0.022-0.043)	0.030 (0.021-0.041)	0.032 (0.022-0.044)	0.05
Desaturase activity, arbitrary unit				
SCD-16	0.018 ± 0.0061	0.019 ± 0.0068	0.018 ± 0.0058	0.03
SCD-18	0.67 ± 0.14	0.61 ± 0.11	0.68 ± 0.14	<0.001
D6D	0.0036 (0.0023-0.0053)	0.0050 (0.0035-0.0073)	0.0033 (0.0021-0.0050)	<0.001
D5D	3.08 ± 0.94	2.94 ± 0.94	3.11 ± 0.94	0.02

SAFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; TRANS: trans fatty acids; CLA: conjugated linoleic acid; SCD-16: stearoyl-CoA desaturase-16; SCD-18: stearoyl-CoA desaturase-18; D5D: Δ5 desaturase; D6D: Δ6 desaturase. *p value for comparison between-groups calculated by general linear models adjusted for age and sex.

of C18 : 0 via SCD-18 might have metabolic benefits as SCD-18 converts the detrimental C18 : 0 to more non-toxic forms, including C24 : 1n9, that was also negatively associated with the MetS. Previous studies found no difference or association between SCD-18 and the MetS, and such inconsistency might be related to the characteristics of the study population, i.e., in men [29] or subjects at high risk of CVD [5]. C18 : 1n7, another FA in de novo lipogenesis, was negatively associated with the MetS, which corresponds to a longitudinal study that reported C18 : 1n7 was associated with non-CVD mortality, and, more specifically, cancer and dementia mortality [18]. More studies are needed to confirm its

Table 4
Odds ratio associated with having the metabolic syndrome (MetS) according to tertiles of fatty acids concentrations and estimated desaturase activities in the plasma phospholipids fraction

Fatty acids	Tertile			p-trend
	t1 ($n=284$)	t2 ($n=283$)	t3 ($n=283$)	
SAFA	1	1.42 (0.82-2.45)	1.93 (1.15-3.22)	0.01
C14 : 0 (Myristic acid)	1	1.31 (0.80-2.18)	1.06 (0.64-1.75)	0.8
C15 : 0 (Pentadecylic acid)	1	0.91 (0.56-1.47)	0.53 (0.32-0.89)	0.02
C16 : 0 (Palmitic acid)	1	1.07 (0.66-1.72)	0.63 (0.37-1.07)	0.1
C17 : 0 (Margaric acid)	1	0.71 (0.44-1.15)	0.54 (0.31-0.93)	0.02
C18 : 0 (Stearic acid)	1	1.73 (0.93-3.24)	4.61 (2.58-8.24)	<0.001
C20 : 0 (Arachidic acid)	1	1.25 (0.77-2.04)	0.69 (0.41-1.14)	0.2
C22 : 0 (Behenic acid)	1	0.52 (0.31-0.86)	0.56 (0.34-0.92)	0.02
C23 : 0 (Tricosylic acid)	1	0.73 (0.44-1.23)	0.54 (0.31-0.94)	0.03
C24 : 0 (Lignoceric acid)	1	0.42 (0.25-0.69)	0.42 (0.25-0.69)	<0.001
C25 : 0 (Pentacosylic acid)	1	0.61 (0.36-1.02)	0.84 (0.51-1.37)	0.5
C26 : 0 (Cerotic acid)	1	0.85 (0.52-1.39)	1.02 (0.62-1.66)	0.9
MUFA	1	0.72 (0.45-1.16)	0.52 (0.30-0.89)	0.02
C16 : 1n7 (Palmitoleic acid)	1	0.84 (0.50-1.41)	1.17 (0.71-1.95)	0.5
C18 : 1n7 (cis-Vaccenic acid)	1	0.52 (0.32-0.84)	0.38 (0.22-0.65)	<0.001
C20 : 1n7 (Paullinic acid)	1	0.75 (0.46-1.22)	0.96 (0.59-1.57)	0.8
C18 : 1n9 (Oleic acid)	1	0.71 (0.44-1.14)	0.84 (0.50-1.41)	0.4
C20 : 1n9 (Gondoic acid)	1	0.98 (0.60-1.58)	0.56 (0.33-0.93)	0.03
C24 : 1n9 (Nervonic acid)	1	0.41 (0.25-0.69)	0.34 (0.20-0.57)	<0.001
PUFA	1	1.37 (0.82-2.27)	1.10 (0.66-1.85)	0.8
C18 : 2n6 (Linoleic acid)	1	1.27 (0.80-2.03)	0.75 (0.44-1.29)	0.4
C18 : 3n6 (γ-Linolenic acid)	1	1.55 (0.87-2.76)	2.86 (1.65-4.96)	<0.001
C20 : 2n6 (Eicosadienoic acid)	1	0.98 (0.59-1.61)	1.05 (0.64-1.73)	0.8
C20 : 3n6 (Dihomo-γ-linolenic acid)	1	1.84 (1.05-3.24)	2.68 (1.55-4.63)	<0.001
C20 : 4n6 (Arachidonic acid)	1	0.79 (0.46-1.33)	1.22 (0.74-1.99)	0.4
C22 : 4n6 (Docosatetraenoic acid)	1	1.30 (0.77-2.16)	1.32 (0.79-2.19)	0.3
C22 : 5n6 (Osbond acid)	1	1.04 (0.63-1.72)	1.38 (0.83-2.29)	0.2
C18 : 3n3 (α-Linolenic acid)	1	0.99 (0.60-1.64)	0.75 (0.45-1.25)	0.3
C20 : 5n3 (Eicosapentaenoic acid)	1	1.12 (0.67-1.86)	1.29 (0.78-2.15)	0.3
C22 : 5n3 (Docosapentaenoic acid)	1	1.15 (0.68-1.95)	1.23 (0.72-2.10)	0.5
C22 : 6n3 (Docosahexaenoic acid)	1	0.91 (0.54-1.54)	0.91 (0.53-1.54)	0.7
TRANS	1	0.81 (0.50-1.31)	0.68 (0.40-1.14)	0.1
C16 : 1n7tr (Palmitelaidic acid)	1	1.02 (0.63-1.64)	0.65 (0.39-1.09)	0.1
C18 : 1n9tr (Elaidic acid)	1	1.18 (0.72-1.93)	0.81 (0.48-1.37)	0.4
C18 : 1n7tr (trans-Vaccenic acid)	1	0.58 (0.36-0.95)	0.51 (0.30-0.86)	0.01
C18 : 2n6trtr (Linoelaidic acid)	1	0.78 (0.48-1.28)	1.11 (0.68-1.81)	0.7
CLA	1	0.91 (0.56-1.48)	0.84 (0.50-1.39)	0.5
Desaturases				
SCD_16	1	0.83 (0.49-1.39)	1.16 (0.70-1.93)	0.5
SCD_18	1	0.66 (0.42-1.05)	0.39 (0.22-0.69)	0.001
D6D	1	1.62 (0.91-2.89)	2.83 (1.62-4.94)	<0.001
D5D	1	0.76 (0.47-1.23)	0.57 (0.35-0.95)	0.03

SAFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; TRANS: trans fatty acids; CLA: conjugated linoleic acid; SCD-16: stearoyl-CoA desaturase-16; SCD-18: stearoyl-CoA desaturase-18; D5D: Δ5 desaturase; D6D: Δ6 desaturase. Odds ratio (95% confidence interval) by logistic regression analysis adjusted by age, sex, education, smoking status, medication use, body mass index (BMI), energy intake, alcohol intake, and non-occupational moderate-to-vigorous physical activity (MVPA).

non-cardiometabolic detrimental health effects.

Omega-6 PUFA have been intensively studied for their health effects because most of them are sensitive to dietary intake and are considered an essential or conditionally essential FA [30]. In our study, C18 : 3n6 and C20 : 3n6, as a reflection of D6D activity, were positively associated with the MetS. D6D activity itself was also positively associated with the MetS. A similar association between D6D and metabolic health was also reported in previous studies

as a reflection of endogenous metabolism [5, 25]. It is worth mentioning that a strong positive association of D6D activity with diabetes incidence was reported previously [31]. As the MetS is mainly characterized by insulin resistance, our findings might indicate that the differences in omega-6 PUFA and desaturase activities observed here might be partly mediated by a relatively high degree of insulin resistance in individuals with the MetS. Of the four desaturase activities, SCD-16 and D5D were not associated with the MetS in the adjusted model. SCD-16 level was slightly higher in people with the MetS but was not associated with the MetS after adjusting for BMI and dietary factors. Since higher levels of SCD-16 might reflect a higher intake of SAFA and lower intake of PUFA, the slight difference in SCD-16 observed between individuals with and without the MetS was probably explained by dietary factors. Though not significant, D5D activity was decreased among individuals with the MetS, and individuals with increased D5D activity seemed less likely to have the MetS, which was in accordance with previous literature [25, 29].

Surprisingly, we did not observe any association between omega-3 PUFA and the MetS after adjusting for potential confounders. On the one hand, the result corresponds to previous studies that the association between omega-3 PUFA and the MetS seemed to be null [5, 32]. On the other hand, a meta-analysis of randomized controlled trials (RCTs) reported that increasing omega-3 PUFA slightly reduced the risk of coronary heart disease mortality and events, and reduced serum TGL [33], while mentioning that the conclusion was based on moderate- and low-certainty evidence. A 25-year follow-up study also found an inverse association between omega-3 FA intake and incidence of chronic kidney disease [34]. Thus, the evidence regarding omega-3 FA seems to be inconsistent, which could be attributable to the heterogeneity within the structural group, as indicated by another meta-analysis of RCTs, which showed that two omega-3 FA, i.e., EPA and DHA, had differential effects on MetS features: while EPA decreased serum TC, TGL, and LDL-C, DHA increased serum TC, LDL-C, and HDL-C [35]. Therefore, the reason for the null associations found of omega-3 FA with the MetS in our study remains unclear, and more research is warranted.

We found inverse associations between very long-chain FA (VLC FA) and the MetS, including C24 : 0 and C24 : 1n9. VLC SAFA are the main constituents of sphingolipids. Circulating C24 : 0 has been inversely associated with unfavorable metabolic profiles [36], insulin resistance [37], and cardiovascular health [38]. Studies have suggested that VLC SAFA could have positive effects on beta cells and lead to less apoptotic cell death and pancreatic dysfunction [36, 37]. Limited evidence exists regarding the mechanism behind circulating VLC SAFA, and their health effects are not entirely understood. In addition, circulating VLC SAFA are derived from limited dietary resources, such as canola oil and peanuts, and are influenced by genetic factors related to sphingolipid synthesis [38]. Nevertheless, a study reported an inverse association between dietary VLC SAFA and the MetS [39]. We also observed negative associations of C24 : 0 with the MetS, despite the fact that the associations between other VLC SAFA and the MetS were null. These null associations could be related to the FA fraction measured in this study, since plasma PL are considered less correlated with dietary intake compared with other plasma fractions [17]. We furthermore observed negative associations of C24 : 1n9 with BMI and fasting glucose. Recently, dietary supplementation of C24 : 1n9 was found to limit weight gain in a mouse model of diet-induced obesity [38, 40, 41], which to some extent supports the beneficial associations of C24 : 1n9 found in our study. Still, more research is needed to fill the knowledge gap regarding the relationship between these relatively uncharacterized FA and metabolic diseases.

This study has provided opportunities for future application. Individual FA from each FA group categorized by saturation levels might show different or contradictory relations with metabolic health, as demonstrated in our results. It will always be necessary to assess and report individual FA levels to understand the broad impact of metabolic diseases on the FA profile. Simply pooling individual FA into structural groups such as omega-6 PUFA, omega-3 PUFA, or total SAFA and drawing generalized conclusions about their effects on metabolic health will mislead policy makers and the public. A better understanding of the differences of various FA between metabolic health and disease could improve risk prediction for adverse events more efficiently and economically. In short, as new modifiable biomarkers for metabolic diseases emerge, individual FA from the most suitable fraction might provide information on how to modify the prevalence of the MetS by dietary means.

The main strength of this study is the well-characterized cohort of 850 individuals who were initially recruited from a representative general population cohort, which increases the possibility

for generalization of the results. Also, we have objectively assessed a broader range of FA and desaturase activities in PL, thereby showing more overall differences compared with previous studies. Thus, we were able to study the relationship between the FA profile and the MetS in a more comprehensive and comparative approach. Some limitations are worthy of mentioning. The cross-sectional nature of this study only allowed us to study associations, instead of possible causation, between FA profile, desaturase activities, and the MetS. In addition, we could not capture individual genetic and physiological effects on the FA profile as the FA profile is influenced by genetic, dietary, and physiological factors. Moreover, the use of product-to-precursor ratios of individual plasma FA as desaturase estimates may reflect FA metabolism, but may also be affected by dietary FA intake. Unfortunately, we were not able to provide such data due to the nature of the questionnaire design.

In conclusion, a wide-ranging FA profile and estimated desaturase activities differed between adults with and without the MetS in a general representative population. The early precursor of *de novo lipogenesis* pathway (C18 : 0) and a high D6D activity represented by higher levels of C18 : 3n6 and C20 : 3n6 were risk factors for the MetS, while VLC FA (C24 : 0 and C24 : 1n9), C18 : 1n7, and SCD-18 showed inverse associations with the MetS. Further studies are required to investigate the etiology of these observed differences in the FA profile during the MetS and the prospective effect of the FA profile on the incidence of the MetS.

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Conflict of interest

The authors have no conflict of interest to report.

Data availability

The authors do not have the authority to share the data that supports the findings of this study due to Lifelines data access permissions, but any researcher can apply to use Lifelines data, including the variables used in this investigation. Information about accessing Lifelines data is given on their website: (https://www.lifelines.nl/researcher/how-to-apply).

Author Contributions

Yinjie Zhu: Conceptualization, Methodology, Software, Formal analysis, Writing – Original Draft, Project administration; **Fabian A. Vogelpohl:** Methodology, Writing – Review & Editing; **M. Rebecca Heiner-Fokkema:** Resources, Data curation, Writing – Review & Editing; **Ilse G. Pranger**: Resources, Data curation, Writing – Review & Editing; **Isidor Minović:** Writing – Review & Editing; **Gerjan J. Navis:** Supervision, Writing – Review & Editing; **Stephan J.L. Bakker:** Conceptualization, Supervision, Writing – Review & Editing; **Ineke J. Riphagen:** Conceptualization, Writing – Review & Editing, Project administration.

Supplementary data

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/NHA-220155.

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