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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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40 **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

41 ## 1. Introduction

42 The metabolic syndrome (MetS), as defined by a
43 cluster of metabolic risk factors such as high blood
44 pressure, high blood glucose, and high triglyceride
45 levels, increases the risk for developing cardiovascu-
46 lar disease (CVD) and type 2 diabetes (T2D) [1]. The
47 prevalence of MetS is rising all over the world, and the
48 estimated global prevalence is about one-quarter of
49 the world population [1], thereby posing an important
50 public health concern.
51 Concentrations of several circulating fatty acids
52 (FA) are emerging as novel, potentially modifiable
53 biomarkers for the risk of cardiometabolic diseases,
54 including the MetS [2, 3]. In fact, an altered FA pro-
55 file and estimated activities of main desaturases have
56 been associated with metabolic health [4] and the
57 development of MetS [5]. Nevertheless, those studies
58 have only assessed limited types of FA in popula-
59 tions with an elevated risk of CVD. Plus, the current
60 consideration of health risks associated with FA is
61 largely based on structural groups (e.g., saturated
62 FA, trans-FA, and unsaturated FA), but the evidence
63 is somewhat conflicting [6]. Thus, it is necessary to
64 assess a broader FA profile and understand the health
impact of each FA within the structural groups to 65
improve risk prediction for health outcomes more 66
efficiently rather than draw generalized conclusions 67
from pooling FA into structural groups. 68
Although an objective assessment of circulating 69
FA profiles in the blood can, to some extent, mitigate 70
the reporting bias of self-reported dietary lipids, the 71
biomarkers of FA in the blood cannot fully reflect 72
the dietary FA intake because it is also affected by 73
non-dietary factors [7]. One of the most critical fac- 74
tors is endogenous synthesis through desaturation by 75
three main desaturases: Δ^5 desaturase (D5D), Δ^6 76
desaturase (D6D), and Δ^9 or stearoyl-CoA desat- 77
urase (SCD) [8]. Therefore, circulating FA profiles 78
in the blood could reflect both diet and endogenous 79
metabolism. It is worth mentioning that other fac- 80
tors, such as sex, genotype, body mass index, alcohol 81
intake, smoking status, and physical activity, can also 82
interfere with circulating FA profiles [9, 10]. 83
In this exploratory study, we aimed to investigate 84
1) potential differences in circulating a wide-ranging 85
FA profile between individuals with and without the 86
MetS and the associations of circulating individual 87
FA with the prevalence of the MetS 2) and the associa- 88
tion of desaturase activities with the prevalence of the 89
MetS to glean insight into the endogenous synthesis 90
of FA. For this, we assessed FA in plasma phospho- 91
lipids (PL) in a general representative population. 92

2. Methods 93

2.1. Study design and population 94

The Lifelines cohort study is a multidisci- 95
plinary prospective population-based cohort study 96
that applies in a unique three-generation design of 97
the health and health-related behaviors of 167 729 98
persons living in The Netherlands. It employs a 99
broad range of investigative procedures in assess- 100
ing the biomedical, socio-demographic, behavioral, 101
physical, and psychological factors which contribute 102
to health and disease of the general population. In 103
short, the first group of participants was recruited 104
via local general practitioners. Then participants 105
could indicate whether their family members were 106
interested as well. Additionally, individuals who 107
were interested in the study could register via an 108
online registration system. Individuals with insuffi- 109
cient knowledge of the Dutch language, with severe 110
psychiatric or physical illness, were excluded from 111

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the study. Before study entry, a signed informed consent form was obtained from each participant. Adult participants ($\geq$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 ($18.5 \leq$ BMI<25 kg/m^2), overweight ($25 \leq$ BMI<30 kg/m^2), and obese (BMI $\geq$ 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

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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-administrated 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 (≥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 ± 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 ± 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

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303 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).

310 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

317 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; $p < 0.001$).

335 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).

348 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 ± 1.83%), total MUFA (12.9 ± 1.45%), and total TFA (0.21 ± 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).

365 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

385 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 for the presence of the MetS.

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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.

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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 of C18 : 0 via SCD-18 might have metabolic benefits

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.

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415 as SCD-18 converts the detrimental C18 : 0 to more
416 non-toxic forms, including C24 : 1n9, that was also
417 negatively associated with the MetS. Previous studies
418 found no difference or association between SCD-
419 18 and the MetS, and such inconsistency might be
420 related to the characteristics of the study popula-
421 tion, i.e., in men [29] or subjects at high risk of
422 CVD [5]. C18 : 1n7, another FA in de novo lipogen-
423 esis, was negatively associated with the MetS, which
424 corresponds to a longitudinal study that reported
425 C18 : 1n7 was associated with non-CVD mortality,
426 and, more specifically, cancer and dementia mor-
427 tality [18]. More studies are needed to confirm its
428 non-cardiometabolic detrimental health effects.

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			
	t1 ($n = 284$)	t2 ($n = 283$)	t3 ($n = 283$)	p-trend
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).

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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

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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 support the findings of this study, due to Lifelines data access permissions, but any researchers can apply to use Lifelines data, including the variables used in this investigation. Information about access to Lifelines data is given on their website: (https://www.lifelines.nl/researcher/how-to-apply).

CRediT author statement

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Supplementary data

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References

[1] Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Current Hypertension Reports. 2018;20(2):12. doi:10.1007/s11906-018-0812-z

[2] Jackson KH, Harris WS. Blood Fatty Acid Profiles: New Biomarkers for Cardiometabolic Disease Risk. Current Atherosclerosis Reports. 2018;20(5):22. doi:10.1007/s11883-018-0722-1

[3] Shramko VS, Polonskaya YV, Kashtanova EV, Stakhneva EM, Ragino YI. The Short Overview on the Relevance of Fatty Acids for Human Cardiovascular Disorders. Biomolecules. 2020;10(8):1127. doi:10.3390/biom10081127

[4] Svendsen K, Olsen T, Nordstrand Rusvik TC, Ulven SM, Holven KB, Retterstol K, Telle-Hansen VH. Fatty acid profile and estimated desaturase activities in whole blood are associated with metabolic health. Lipids Health Dis. 2020;19(1):102. doi:10.1186/s12944-020-01282-y

[5] Mayneris-Perxachs J, Guerendiain M, Castellote AI, Estruch R, Covas MI, Fito M, Salas-Salvado J, Martinez-Gonzalez MA, Aros F, Lamuela-Raventos RM, Lopez-Sabater MC, for PSI. Plasma fatty acid composition, estimated desaturase activities, and their relation with the metabolic syndrome in a population at high risk of cardiovascular disease. Clin Nutr. 2014;33(1):90-97. doi:10.1016/j.clnu.2013.03.001

[6] de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, Uleryk E, Budylowski P, Schünemann H, Beyene J, Anand SS. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 2015;351:h3978. doi:10.1136/bmj.h3978

[7] Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Progress in Lipid Research. 2008;47(5):348-380. doi:https://doi.org/10.1016/j.plipres.2008.03.003

[8] Nakamura MT, Nara TY. Structure, function, and dietary regulation of delta6, delta5, and delta9 desaturases. Annual Review of Nutrition. 2004;24(1):345-376. doi:10.1146/annurev.nutr.24.121803.063211

[9] Parry SA, Turner MC, Hodson L. Lifestyle interventions affecting hepatic fatty acid metabolism. Curr Opin Clin Nutr Metab Care. 2020;23(6):373-379. doi:10.1097/mco.0000000000000687

[10] Thifault E, Cormier H, Bouchard-Mercier A, Rudkowska I, Paradis AM, Garneau V, Ouellette C, Lemieux S, Couture P, Vohl MC. Effects of age, sex, body mass index and APOE genotype on cardiovascular biomarker response to an n-3 polyunsaturated fatty acid supplementation. J Nutrigenet Nutrigenomics. 2013;6(2):73-82. doi:10.1159/000350744

[11] Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, van Dijk F, van Zon SK, Wijmenga C, Wolffenbuttel BH, Stolk RP. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol. 2015;44(4):1172-1180. doi:10.1093/ije/dyu229

[12] Klijs B, Scholtens S, Mandemakers JJ, Snieder H, Stolk RP, Smidt N. Representativeness of the LifeLines Cohort Study. PLoS One. 2015;10(9):e0137203. doi:10.1371/journal.pone.0137203

[13] WHO. Obesity : preventing and managing the global epidemic : report of a WHO consultation. WHO Technical Report Series. World Health Organization, Geneva, Switzerland. 1999.

[14] Hoving EB, Jansen G, Volmer M, Van Doormaal JJ, Muskiet FA. Profiling of Plasma Cholesterol Ester and Triglyceride Fatty Acids as their Methyl Esters by Capillary Gas Chromatography, Preceded by a Rapid Aminopropyl-Silica Column Chromatographic Separation of Lipid Classes. Journal of Chromatography-Biomedical Applications. 1998;434(2):395-409

[15] Folch J, Lees M, Stanley GHS. A simple method for the isolation and purification of total lipids from animal tissues. Journal of Biological Chemistry. 1957;226(1):497-509. doi:https://doi.org/10.1016/S0021-9258(18)64849-5

[16] Kaluzny MA, Duncan LA, Merritt MV, Epps DE. Rapid separation of lipid classes in high yield and purity using bonded phase columns. Journal of Lipid Research. 1985;26: 135-140.

[17] Furtado JD, Beqari J, Campos H. Comparison of the Utility of Total Plasma Fatty Acids Versus those in Cholesteryl Ester, Phospholipid, and Triglyceride as Biomarkers of Fatty Acid Intake. Nutrients. 2019;11(9). doi:10.3390/nu11092081

[18] Lai Heidi TM, de Oliveira Otto Marcia C, Lee Y, Wu Jason HY, Song X, King Irena B, Psaty Bruce M, Lemaitre Rozenn N, McKnight B, Siscovick David S, Mozaffarian D. Serial plasma phospholipid fatty acids in the de novo lipogenesis pathway and total mortality, cause-specific mortality, and cardiovascular diseases in the cardiovascular health study. Journal of the American Heart Association. 2019;8(22):e012881. doi:10.1161/JAHA.119.012881

[19] International standard classification of education. United Nations Educational, Scientific, and Cultural Organization. 1997.

[20] RIVM. Dutch food composition table (NEVO). https://www.rivm.nl/nieuws/nieuwe-nevo-tabel-2011-beschikbaar. 2011.

[21] Molag ML, de Vries JHM, Duif N, Ock'e MC, Dagnelie PC, Goldbohm RA, van't Veer P. Selecting informative food items for compiling food-frequency questionnaires: comparison of procedures. British Journal of Nutrition. 2010;104(3):446-456. doi:10.1017/S0007114510000401

[22] Siebelink E, Geelen A, de Vries JH. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. Br J Nutr. 2011;106(2):274-281. doi:10.1017/S0007114511000067

[23] Byambasukh O. (Chapter 7) Physical activity and cardiometabolic health: Focus on domain-specific associations of physical activity over the life course. University of Groningen, Groningen. 2020.

[24] Alberti KGMM, Eckel Robert H, Grundy Scott M, Zimmet Paul Z, Cleeman James I, Donato Karen A, Fruchart J-C, James WPT, Loria Catherine M, Smith Sidney C. Harmonizing the Metabolic Syndrome. Circulation. 2009;120(16):1640-1645. doi:10.1161/CIRCULATIONAHA.109.192644

[25] Warensjö E, Sundström J, Lind L, Vessby B. Factor analysis of fatty acids in serum lipids as a measure of dietary fat quality in relation to the metabolic syndrome in men. The American Journal of Clinical Nutrition. 2006;84(2):442-448. doi:10.1093/ajcn/84.2.442

[26] Flock MR, Kris-Etherton PM. Diverse physiological effects of long-chain saturated fatty acids: implications for cardiovascular disease. Current Opinion in Clinical Nutrition & Metabolic Care. 2013;16(2).

[27] Imamura F, Fretts AM, Marklund M, Ardisson Korat AV, Yang W-S, Lankinen M, Qureshi W, Helmer C, Chen T-A, Virtanen JK, Wong K, Bassett JK, Murphy R, Tintle N, Yu CI, Brouwer IA, Chien K-L, Chen Y-y, Wood AC, del Gobbo LC, Djousse L, Geleijnse JM, Giles GG, de Goede J, Gudnason V, Harris WS, Hodge A, Hu F, InterAct C, Koulman A, Laakso M, Lind L, Lin H-J, McKnight B, Rajaobelina K, Riserus U, Robinson JG, Samieri C, Senn M, Siscovick DS, Soedamah-Muthu SS, Sotoodehnia N, Sun Q, Tsai MY, Tuomainen T-P, Uusitupa M, Wagenknecht LE, Wareham NJ, Wu JHY, Micha R, Lemaitre RN, Mozaffarian D, Forouhi NG. Fatty acids in the de novo lipogenesis pathway and incidence of type 2 diabetes: A pooled analysis of prospective cohort studies. PLOS Medicine. 2020;17(6):e1003102. doi:10.1371/journal.pmed.1003102

Uncorrected Author Proof

[28] Ameer F, Scandiuzzi L, Hasnain S, Kalbacher H, Zaidi N. De novo lipogenesis in health and disease. Metabolism. 2014;63(7):895-902. doi:https://doi.org/10.1016/j.metabol.2014.04.003

[29] Warensjö E, Ris'erus U, Vessby B. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men. Diabetologia. 2005;48(10):1999-2005. doi:10.1007/ s00125-005-1897-x

[30] Spector AA, Kim H-Y. Discovery of essential fatty acids. Journal of Lipid Research. 2015;56(1):11-21. doi:10.1194/jlr.R055095

[31] Kröger J, Schulze MB. Recent insights into the relation of Δ5 desaturase and Δ6 desaturase activity to the development of type 2 diabetes. Curr Opin Lipidol. 2012;23(1):4-10. doi:10.1097/MOL.0b013e32834d2dc5

[32] Kabagambe EK, Tsai MY, Hopkins PN, Ordovas JM, Peacock JM, Borecki IB, Arnett DK. Erythrocyte Fatty Acid Composition and the Metabolic Syndrome: A National Heart, Lung, and Blood Institute GOLDN Study. Clinical Chemistry. 2008;54(1):154-162. doi:10.1373/clinchem.2007.095059

[33] Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KH, Summerbell CD, Worthington HV, Song F, Hooper L. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2020;3:CD003177. doi:10.1002/14651858.CD003177.pub5

[34] Park I, Xun P, Tsinovoi CL, Klemmer P, Liu K, He K. Intakes of long-chain omega-3 polyunsaturated fatty acids and non-fried fish in relation to incidence of chronic kidney disease in young adults: a 25-year follow-up. Eur J Nutr. 2020;59(1):399-407. doi:10.1007/s00394-019-02022-4

[35] Zhang HJ, Gao X, Guo XF, Li KL, Li S, Sinclair AJ, Li D. Effects of dietary eicosapentaenoic acid and docosahexaenoic acid supplementation on metabolic syndrome: A systematic review and meta-analysis of data from 33 randomized controlled trials. Clin Nutr. 2021;40(7):4538-4550. doi:10.1016/j.clnu.2021.05.025

[36] Li K, Brennan L, McNulty BA, Bloomfield JF, Duff DJ, Devlin NFC, Gibney MJ, Flynn A, Walton J, Nugent AP. Plasma fatty acid patterns reflect dietary habits and metabolic health: A cross-sectional study. Molecular Nutrition & Food Research. 2016;60(9):2043-2052. doi:https://doi.org/10.1002/mnfr.201500711

[37] Imamura F, Sharp SJ, Koulman A, Schulze MB, Kroger J, Griffin JL, Huerta JM, Guevara M, Sluijs I, Agudo A, Ardanaz E, Balkau B, Boeing H, Chajes V, Dahm CC, Dow C, Fagherazzi G, Feskens EJM, Franks PW, Gavrila D, Gunter M, Kaaks R, Key TJ, Khaw KT, Kuhn T, Melander O, Molina-Portillo E, Nilsson PM, Olsen A, Overvad K, Palli D, Panico S, Rolandsson O, Sieri S, Sacerdote C, Slimani N, Spijkerman AMW, Tjonneland A, Tumino R, van der Schouw YT, Langenberg C, Riboli E, Forouhi NG, Wareham NJ. A combination of plasma phospholipid fatty acids and its association with incidence of type 2 diabetes: The EPIC-InterAct case-cohort study. PLoS Med. 2017;14(10):e1002409. doi:10.1371/journal.pmed.1002409

[38] Liu M, Zuo L-S-Y, Sun T-Y, Wu Y-Y, Liu Y-P, Zeng F-F, Chen Y-M. Circulating very-long-chain saturated fatty acids were inversely associated with cardiovascular health: a prospective cohort study and meta-analysis. Nutrients. 2020;12(9). doi:10.3390/nu12092709

[39] Lee YS, Cho Y, Shin M-J. Dietary Very Long Chain Saturated Fatty Acids and Metabolic Factors: Findings from the Korea National Health and Nutrition Examination Survey 2013. Clin Nutr Res. 2015;4(3):182-189.

[40] Fox TE, Bewley MC, Unrath KA, Pedersen MM, Anderson RE, Jung DY, Jefferson LS, Kim JK, Bronson SK, Flanagan JM, Kester M. Circulating sphingolipid biomarkers in models of type 1 diabetes. Journal of Lipid Research. 2011;52(3):509-517. doi:10.1194/jlr.M010595

[41] Keppley LJW, Walker SJ, Gademsey AN, Smith JP, Keller SR, Kester M, Fox TE. Nervonic acid limits weight gain in a mouse model of diet-induced obesity. The FASEB Journal. 2020;34(11):15314-15326. doi:https://doi.org/10.1096/fj.202000525R

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