

Circulating plasma phospholipid fatty acids and risk of pancreatic cancer in a large European cohort

Corresponding author:

Dr Veronique Chajès, PhD

Nutritional Epidemiology Group

International Agency for Research on Cancer

150, Cours Albert-Thomas, 69372 Lyon CEDEX 08, France

Tel: +33 (0)4 72 73 80 14

E-mail: chajesv@iarc.fr

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Abbreviations: FA (fatty acid); SFA (saturated fatty acid); MUFA (monounsaturated fatty acid); PUFA (polyunsaturated fatty acid); TFA (*trans* fatty acid); PC (pancreatic cancer); EPIC (European Prospective Investigation into Cancer and Nutrition); OR (odds ratio); CI (confidence interval).

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Novelty and Impact

This is the first study exploring the association between biomarkers of fatty acids and pancreatic cancer risk in an epidemiological setting. Our findings confirm previous findings on the association between dairy products, seed and marine food and the risk of pancreatic cancer, which may be driven by specific fatty acid isomers. The influence of some fatty acid isomers on the development of pancreatic cancer may be sex-specific and modulated by smoking. This study highlights the importance of using circulating biomarkers to identify the potential fatty acid isomers and their biological effects leading to this deadly disease.

Authors:

Matejcic M¹, Lesueur F^{2,3,4,5}, Biessy C¹, Renault AL^{2,3,4,5}, Mebirouk N^{2,3,4,5}, Yasmine S¹, Keski-Rahkonen P¹, Li K¹, Hémon B¹, Weiderpass E^{6,21,22,32}, Rebours V⁷, Boutron-Ruault MC^{8,9}, Carbonnel F^{8,9,10}, Kaaks R¹¹, Katzke V¹¹, Kuhn T¹¹, Boeing H¹², Trichopoulou A^{13,14}, Palli D¹⁵, Agnoli C¹⁶, Panico S¹⁷, Tumino R¹⁸, Sacerdote C¹⁹, Quirós JR²³, Duell EJ²⁴, Porta M²⁵, Sánchez MJ^{26,27}, Chirlaque MD^{28,27,29}, Barricarte A^{30,27,31}, Amiano P^{32,27}, Ye W^{33,34}, Peeters PH^{35,38}, Khaw KT³⁶, Perez-Cornago A³⁷, Key TJ³⁷, Bueno-de-Mesquita HB^{38,20}, Riboli E³⁸, Vineis P³⁹, Romieu I¹, Gunter MJ^{1*}, Chajès V¹

*Co-senior authors

Affiliations of authors:

¹International Agency for Research on Cancer, Lyon, France

²Genetic Epidemiology of Cancer team, Inserm, U900, Paris, France

³Institut Curie, Paris, France

⁴PSL University, Paris, France

⁵Mines ParisTech, Fontainebleau, France

⁶Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland

⁷Department of Gastroenterology and Pancreatology, Beaujon Hospital, University Paris 7, Clichy, France

⁸INSERM, Centre for Research in Epidemiology and Population Health, U1018, Health across Generations Team, Institut Gustave Roussy, Villejuif, France

⁹Université Paris Sud, UMRS 1018, Villejuif, France

¹⁰Department of Gastroenterology, Bicêtre University Hospital, Assistance Publique des Hôpitaux de Paris, Le Kremlin Bicêtre, France

¹¹Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

¹²Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Nuthetal, Germany

¹³Hellenic Health Foundation, Athens, Greece

¹⁴WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece

¹⁵Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute – ISPO, Florence, Italy

¹⁶Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

¹⁷Clinical Medicine and Surgery Department, Università degli Studi di Napoli Federico II, Naples, Italy

¹⁸Cancer Registry and Histopathology Department, "Civic - M.P. Arezzo" Hospital, ASP Ragusa, Italy

¹⁹Unit of Cancer Epidemiology, Citta' della Salute e della Scienza Hospital, University of Turin and Centre for Cancer Prevention (CPO), Turin, Italy

²⁰Department of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

²¹Department of Community Medicine, Faculty of Health Sciences, University of Tromsø – The Arctic University of Norway, Tromsø, Norway

²²Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway

²³EPIC Asturias, Public Health Directorate, Asturias, Spain

²⁴Unit of Nutrition and Cancer, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain

²⁵Hospital del Mar Research Institute - IMIM, CIBER Epidemiología y Salud Pública (CIBERESP) and Universitat Autònoma de Barcelona, Barcelona, Spain

²⁶Escuela Andaluza de Salud Pública. Instituto de Investigación Biosanitaria ibs.GRANADA. Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain

²⁷CIBER in Epidemiology and Public Health (CIBERESP), Madrid, Spain

²⁸Department of Epidemiology, Regional Health Council, IMIB-Arrixaca, Murcia, Spain

²⁹Department of Health and Social Sciences, Universidad de Murcia, Murcia, Spain

³⁰Navarra Institute for Health Research (IdiSNA), Pamplona, Spain

³¹Navarra Public Health Institute, Pamplona, Spain

³²Public Health Division of Gipuzkoa, BioDonostia Research institute, San Sebastian, Spain

³³Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

³⁴The Medical Biobank at Umeå University, Umeå, Sweden

³⁵Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

³⁶University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom

³⁷Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

³⁸Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, UK

³⁹MRC-PHE Center for Environment and Health, School of Public Health, Imperial College, London, UK

Abstract

There are both limited and conflicting data on the role of dietary fat and specific fatty acids in the development of pancreatic cancer. In this study, we investigated the association between plasma phospholipid fatty acids and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. The fatty acid composition was measured by gas chromatography in plasma samples collected at recruitment from 375 incident pancreatic cancer cases and 375 matched controls. Associations of specific fatty acids with pancreatic cancer risk were evaluated using multivariable conditional logistic regression models with adjustment for established pancreatic cancer risk factors. Statistically significant inverse associations were found between pancreatic cancer incidence and levels of heptadecanoic acid (OR_{T3-T1} [odds ratio for highest versus lowest tertile]=0.63; 95%CI[confidence interval]=0.41–0.98; P_{trend} =0.036), n-3 polyunsaturated α -linolenic acid (OR_{T3-T1} =0.60; 95%CI=0.39–0.92; P_{trend} =0.02) and docosapentaenoic acid (OR_{T3-T1} =0.52; 95%CI=0.32–0.85; P_{trend} =0.008). Industrial trans-fatty acids were positively associated with pancreatic cancer risk among men (OR_{T3-T1} =3.00; 95%CI=1.13–7.99; P_{trend} =0.029), while conjugated linoleic acids were inversely related to pancreatic cancer among women only (OR_{T3-T1} =0.37; 95%CI=0.17–0.81; P_{trend} =0.008). Among current smokers, the long-chain n-6/n-3 polyunsaturated fatty acids ratio was positively associated with pancreatic cancer risk (OR_{T3-T1} =3.40; 95%CI=1.39–8.34; P_{trend} =0.007). Results were robust to a range of sensitivity analyses. Our findings suggest that higher circulating levels of saturated fatty acids with an odd number of carbon atoms and n-3 polyunsaturated fatty acids may be related to lower risk of pancreatic cancer. The influence of some fatty acids on the development of pancreatic cancer may be sex-specific and modulated by smoking.

Introduction

Pancreatic cancer (PC) is increasingly more common in developed regions and approximately 104,000 new cases were diagnosed in Europe in 2012¹. The late presentation and unspecific symptoms of PC together with a lack of effective screening tests result in extremely poor prognosis². In addition, PC is the only major neoplasm showing an unfavorable mortality trend in both sexes over the last few decades in Europe³.

Several factors have been linked with the risk of PC, including tobacco smoking, alcohol, chronic pancreatitis, history of diabetes, obesity, family history of PC, and some common genetic variants⁴⁻⁶. A role for dietary fat and fatty acids (FAs) in PC development has been suggested by experimental studies⁷⁻¹⁰, but previous epidemiological analyses of dietary FA intake have produced inconclusive results¹¹⁻¹⁴. Of these, the NIH-AARP Diet and Health Study is the largest prospective study on dietary fat intake and PC risk to date where higher intakes of total, monounsaturated and saturated fat were significantly associated with increased risk¹¹. Interestingly, recent data from the Women's Health Initiative demonstrated a reduction in PC incidence among overweight women randomized to a low-fat dietary intervention although the association may be due to chance and no association was observed for the effect of the low-fat dietary pattern overall¹⁵. However, a recent meta-analysis of case-control and cohort studies has shown that healthy dietary patterns, characterized by high intakes of vegetables, fruits, and fish, and low-fat dairy, were associated with decreased risk of PC, whereas an increased risk was reported with a western-type pattern high in fat, particularly saturated and trans fats¹⁶.

The inconsistency of epidemiological findings relating fatty acid intake to PC may be due to methodological limitations of dietary questionnaires^{17,18}, and no study to date has explored the relationship between circulating concentrations of FAs and PC risk. The use of biomarkers may offer a more valid estimation of the contribution of FAs to the etiology of PC¹⁹. The FA composition of plasma phospholipids reflects medium-term intake of some FAs²⁰, particularly of those not endogenously synthesized^{21,22}. Furthermore, the ratio of monounsaturated fatty acids (MUFAs) to saturated fatty acids (SFAs), also known as the desaturation index, measured in blood phospholipids is used as surrogate

marker of the activity of hepatic stearoyl-CoA desaturase-1 (SCD-1), a key enzyme in the synthesis of MUFAs from SFAs^{23,24}, which has previously been associated with cancer risk and mortality^{25,26}.

We conducted a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to estimate the association of specific plasma phospholipid levels of relevant FAs and PC risk. In addition, we used the desaturation index as an indicator of endogenous MUFA synthesis^{23,27} to investigate the association between fat metabolism and pancreatic carcinogenesis.

Methods

Study design

The EPIC cohort includes 521,330 participants recruited between 1992 and 2000 from 23 centers in 10 European countries to investigate the relationship between diet, lifestyle and genetic factors and the incidence of cancer and other chronic diseases. The study design, recruitment procedures and data collection have been described previously²⁸. Briefly, socio-demographic, lifestyle and dietary data were collected at enrolment from all study participants by country-specific questionnaires. Baseline anthropometric measurements and peripheral blood samples were also collected. Procedures for sample collection, processing and storage are described in detail elsewhere²⁹. All participants signed an informed consent for the use of their blood samples and data. The EPIC study was approved by the Ethical Review Board of the IARC and by all local centres.

Outcome assessment

Participants were followed from the date of enrolment until first cancer diagnosis at any site, death, emigration or end of the follow-up period, whichever occurred first. Incident PC cases were identified through population cancer registries (Italy except Naples, the Netherlands, Norway, Spain, Sweden and the United Kingdom) or a combination of methods including health insurance records, cancer and pathology registries, and active follow-up in three countries (France, Germany, Greece and Naples). Cases were identified up to the end of 2010.

In the current study, 61% of PC cases were confirmed by histological or cytological examination, whereas the remainder were diagnosed through clinical observation, imaging results, autopsy, or death certificate. Clinical and tumour characteristics were defined according to the codes of the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD). Diagnosis of cancer cases in EPIC was based on the 3rd revision of the International Classification of Diseases for Oncology (ICD-O-3). Mortality data were coded according to the 10th

revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10). The most common histological subtype of PC was adenocarcinoma (77.6%), while the less common endocrine form accounted for less than 1%. The remaining PC cases were of unknown (21.3%) or mixed (0.8%) origin.

Lifestyle data collection

Participants completed a baseline lifestyle questionnaire providing information on reproductive history, use of oral contraceptives and hormonal replacement therapy, education, socio-economic status, occupation, family history of cancer, history of previous illness (e.g., diabetes), physical activity, dietary intake, alcohol consumption and smoking status in the year prior to enrolment²⁹.

Selection of study subjects

Of 521,330 subjects (aged 35-70 y) recruited to the EPIC study, the current analysis excluded subjects with prevalent cancer at any anatomic site (n=23,785) or those lost to follow-up (n=4365). A total of 1013 incident PC cases identified after a median follow-up of 11.7 years (min-max: 1 day-17.8 years).

A nested case-control study was initially designed with 1013 eligible cases who provided a blood sample and completed the lifestyle and dietary questionnaires at recruitment. Plasma samples from Denmark were not included in this analysis, leading to 417 PC cases. Each case was individually matched to one control subject (ratio 1:1) using an incidence density sampling approach while fulfilling the following matching criteria: study center, sex, age at blood collection (± 3 months), date and time at blood collection, length of follow-up, fasting status and, for women, use of pill/hormonal replacement treatment. After exclusion of subjects with inadequate FA measurements and incomplete pairs, 375 cases with PC (153 men and 222 women) and 375 controls were available for analysis.

Fatty acid quantification

Gas chromatography was used to determine plasma phospholipid concentrations of sixty FAs from short-chain SFAs to long-chain PUFAs, including fifteen *trans* fatty acids (TFAs) from industrial processes and natural animal sources³⁰. Briefly, total lipids were extracted from plasma samples with chloroform-methanol 2:1 (vol/vol) containing antioxidant butylated hydroxytoluene and L- α -phosphatidylcholine-dimyristoyl-d54 as an internal standard. Phospholipids were purified by adsorption chromatography on SPE columns, and then converted to their methyl esters (FAMES) at room temperature using Meth-Prep II reagent. FAMES were extracted in hexane and transferred to small vials until being injected into the gas chromatograph (Agilent 7890A GC). The Select for FAME Capillary GC Columns (Agilent) were used for separation of FAMES. Samples from cases and control subjects were processed in the same batch, and laboratory staff was blinded to any participant characteristics. Identification of individual FAMES was obtained by comparison with the relative retention time of commercially available pure standard mixtures (Sigma, St. Louis, MO). The relative amount of each FA was expressed as percentage of total FAs and as absolute plasma concentration ($\mu\text{mol/l}$) based on the amount of the internal standard.

The within-day coefficients of variation (CVs), which were calculated using standard quality control samples, ranged from 1.81% to 9.75%. All laboratory analyses were performed at the International Agency for Research on Cancer (Lyon, France).

Using concentrations of individual FAs, we calculated the plasma phospholipid percentage of the following groups: SFAs (14:0, 15:0, 16:0, 17:0, 18:0, 20:0, 22:0, 24:0), *cis* MUFAs (14:1n-5, 15:1, 16:1n-7/9, 17:1, 18:1n-5/7, n-9, 20:1n-9, 22:1n-9, 24:1n-9), *cis* n-6 PUFAs (18:2n-6, 18:3n-6, 20:2n-6, 20:3n-6, 20:4n-6, 22:4n-6, 22:5n-6), *cis* n-3 PUFAs (18:3n-3, 20:5n-3, 22:5n-3, 22:6n-3), long-chain n-6/n-3 PUFA ratio, ruminant TFAs (16:1n-7*t*, 18:1n-7*t*, CLA 9*c*11*t*, 10*t*12*c*) and industrial TFAs (16:1n-9*t*, 18:1n-8*t*;n-9*t*;n-12*t*, 18:2n-6*t*, 18:3n-3*t*). The desaturation indexes as the ratio of oleic acid (18:1n-9) to stearic acid (18:0) (DI₁₈) and the ratio of palmitoleic acid (16:1n-7) to palmitic acid (16:0) (DI₁₆) were also computed as previously reported²³.

Statistical methods

Baseline lifestyle and dietary characteristics of cases and control individuals were compared using paired t-test for continuous variables, and the Chi-squared test from unadjusted conditional logistic regression for categorical variables. All missing values were excluded from these calculations. Distributions of plasma phospholipid FAs were transformed to the natural log scale. Geometric means (\pm SD) of plasma phospholipid FAs expressed as percentage and absolute concentration ($\mu\text{mol/l}$) were presented for descriptive purposes.

Multivariable conditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) according to percentage of FAs assessed continuously (log transformed) and as tertiles based on the distribution in controls (the lowest tertile was used as the reference category). Associations between FAs expressed in $\mu\text{mol/l}$ and PC risk were also evaluated (data not shown). Tests for linear trend were performed by entering the median value of each tertile as continuous term in the multivariable models. Analyses were also stratified by sex because of differences in metabolic profile between men and women in response to nutritional interventions³¹. We used a chi-squared statistic to test for heterogeneity between log transformed percentiles of plasma phospholipid FAs by sex comparing the deviations of logistic beta-coefficients observed in each subgroup relative to the overall beta-coefficient³². All multivariable models were adjusted for an *a priori* set of confounding factors that included BMI, height, alcohol intake (as continuous variables), history of diabetes mellitus (yes; no; 14.7% unknown), smoking status (never smokers; former smokers; current smokers; 1.5% unknown), education (none or primary school; secondary school; higher education; 3.7% unknown), and physical activity (inactive; moderately inactive; moderately active; active; 2.4% unknown, according to the Cambridge Physical Activity Index). Unknown categories of the above-mentioned variables were included in the models using indicator variables. There were only modest differences in results between models with and without adjustment for potential confounders, and only adjusted models are presented. Simultaneous adjustment for FAs that share common food sources was also performed to assess their independent effects. The false discovery rate (FDR, Q-values) was computed on P-trends based on 26 individual FAs or subgroups to control for multiple comparisons.

Subgroup analyses were conducted by median level of BMI and by smoking status (never/former smokers vs. current smokers) at recruitment. Tests for interaction between log transformed percentiles of plasma phospholipid FAs and potential risk factors as dichotomous variables were computed by including a cross-product term in the multivariable model and evaluating the influence of this term by a likelihood ratio test.

Sensitivity analyses excluding cases with blood samples drawn less than two years or five years before diagnosis, subjects with fasting status at blood collection, subjects with the non-adenocarcinoma subtype, subjects with blood HbA1c levels $\geq 6.5\%$, or subjects with a history of diabetes mellitus were performed. Models were further adjusted for biomarkers of hyperinsulinemia (C-peptide; a biomarker of endogenous insulin secretion³³) and glycosylated hemoglobin (HbA1c; a stable and long-term marker for glucose, independent of fasting status³⁴) measured at recruitment in 320 and 344 study subjects, respectively. Further adjustment for calcium and vitamin D in models that included FAs primarily derived from dairy products was also performed.

Statistical tests were two-sided, and *P* values below 0.05 were considered statistically significant. All analyses were performed using STATA 12.1 (StataCorp. 2011, Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

Results

Baseline characteristics of study participants by case-control status are summarized in Table 1. The mean lag time between blood collection and PC diagnosis was 7.1 (± 3.6) years. Cases were significantly more likely to be smokers at recruitment compared to controls. Among women only, significantly higher weight, BMI, waist to hip ratio and tobacco use was observed in cases compared with controls (Supplementary Table 1).

The baseline distributions of plasma phospholipid FAs in cases and controls are presented in Table 2. Palmitic acid (16:0) and linoleic acid (18:2n-6) represented almost half of the total measured FAs, and the addition of stearic acid (18:0), oleic acid (18:1n-9) and arachidonic acid (20:4n-6) accounted for more than 80% of the total FA fraction. Each of the remaining FAs was found at proportions below 5%.

Table 3 presents overall and sex-stratified risk estimates by tertiles of plasma phospholipid FAs expressed as percentage of total FAs. Overall, we found a significant inverse association between heptadecanoic acid (17:0) and PC risk ($OR_{T3-T1}=0.63$; 95% CI=0.41–0.98; $P_{trend}=0.036$). Concentrations of pentadecanoic acid (15:0) were also inversely associated with the risk of PC, although the risk estimate did not quite attain statistical significance ($OR_{T3-T1}=0.63$; 95% CI=0.38–1.04; $P_{trend}=0.058$). Among individual *cis* n-3 PUFAs, α -linolenic acid (18:3n-3; $OR_{T3-T1}=0.60$; 95% CI=0.39–0.92; $P_{trend}=0.02$) and docosapentaenoic acid (22:5n-3; $OR_{T3-T1}=0.52$; 95% CI=0.32–0.85; $P_{trend}=0.008$) were significantly inversely associated with PC risk, while there was no evidence of association for total *cis* n-3 PUFAs (Table 3). In sex-stratified analyses, conjugated linoleic acid (CLA 9*c*11*t*; 10*t*12*c*) was associated with reduced PC risk among women ($OR_{T3-T1}=0.37$; 95% CI=0.17–0.81; $P_{trend}=0.008$) but not among men ($P_{heterogeneity}=0.056$), and total industrial TFAs was associated with PC development among men only ($OR_{T3-T1}=3.00$; 95% CI=1.13–7.99; $P_{trend}=0.029$; $P_{heterogeneity}=0.030$). None of the associations remained significant after controlling for multiple testing ($Q\text{-value}>0.05$).

In smoking-stratified analysis, we observed significant interactions between several FAs and smoking status on the risk of PC ($P_{interaction}\leq 0.01$; Supplementary Table 2). Specifically, among current smokers, the long-chain n-6/n-3 PUFA ratio was positively associated with PC risk ($OR_{T3-T1}=3.40$;

95%CI=1.39–8.34; $P_{\text{trend}}=0.007$), while an inverse association was found for docosahexaenoic acid (22:6n-3; $\text{OR}_{\text{T3-T1}}=0.31$; 95%CI=0.13–0.76; $P_{\text{trend}}=0.009$) and total *cis* n-3 PUFAs ($\text{OR}_{\text{T3-T1}}=0.26$; 95%CI=0.11–0.62; $P_{\text{trend}}=0.002$). None of these FAs were significantly associated with PC risk among non-smokers. Results show a statistically significant interaction ($P_{\text{interaction}}<0.05$) for 15:0, 17:0 and 18:3n-6 although no clear associations were found when looking at the trends for the two different BMI categories (Supplementary Table 3).

In sensitivity analyses, the risk estimates did not substantially alter when analyses were restricted to the adenocarcinoma subtype of PC (n=291). The associations between individual FAs and PC risk did not differ following adjustment for C-peptide or HbA1c levels and constituents of dairy products (data not shown). Risk estimates did not substantially change after (i) exclusion of subjects with blood HbA1c levels $\geq 6.5\%$ (n=32) or those with a history of diabetes mellitus (n=51), (ii) exclusion of cases with blood samples drawn less than two years (n=42) or five years (n=115) before diagnosis of PC, (iii) exclusion of subjects with fasting status at blood collection (n=350), and (iii) mutual adjustment for FAs that share common food sources (data not shown).

Discussion

In this prospective analysis of prediagnostic plasma phospholipid FA levels and PC development, we present results for total families of FAs that have biologically plausible links with PC (SFAs, *cis* MUFAs, *cis* n-6 PUFAs, *cis* n-3 PUFAs, long-chain n-6/n-3 PUFA ratio, ruminant TFAs and industrial TFAs), and for individual FAs for which there is experimental and epidemiological evidence for association with PC^{7,9,11,14} or other cancers^{35,36}. We found evidence of significantly reduced risk of PC among subjects with higher levels of saturated heptadecanoic acid (17:0) and pentadecanoic acid (15:0), as well as with *cis* n-3 polyunsaturated α -linolenic acid (18:3n-3) and docosapentaenoic acid (22:5n-3). However, the inverse associations did not withstand correction for multiple testing. In sex-stratified analysis, industrial TFAs were positively associated with PC risk among men, while conjugated linoleic acids conferred a significantly reduced risk among women. Finally, there was a significantly higher risk of PC associated with the long-chain n-6/n-3 PUFA ratio among smokers, whereas no association emerged among non-smokers.

SFAs comprised of an odd number of carbon atoms (15:0 and 17:0) cannot be synthesized *de novo* and are primarily derived from ruminant products³⁷. Previous cross-sectional studies performed in the EPIC cohort reported a positive correlation between plasma phospholipid levels of pentadecanoic acid and heptadecanoic acid and dairy products intake^{38,39}. The NIH-AARP Diet and Health Study found a positive association between saturated fat from animal sources and PC risk albeit the study was based on questionnaire data and the association was mainly attributed to the 16:0 and 18:0 isoforms, which are major FAs present in the diet¹¹. However, the inverse association with SFAs in our study concerns the SFAs 15:0 and 17:0 present specifically in dairy foods. While it is possible that the association between FAs and PC risk may be attributed to other constituents of dairy products such as calcium⁴⁰ and vitamin D⁴¹, the inverse association with 15:0 and 17:0 in our study remained significant after further adjustment for calcium and vitamin D intake, supporting an independent effect of these FAs on PC risk. Our findings are supported by recent studies reporting an inverse association between circulating levels of 15:0 and/or 17:0 and type 2 diabetes^{42,43}, with a potential involvement of these specific FAs in metabolic pathways that needs to be addressed in appropriate experimental studies.

The polyunsaturated α -linolenic acid (18:3n-3) is an essential n-3 PUFA primarily found in green leafy vegetables, seed and vegetable oils, nuts and meat. Intake of α -linolenic acid has not been linked to PC risk in prospective studies based on dietary questionnaires^{11,12,14}, which might be a result of poor assessment¹⁸. However, our findings are in agreement with *in vitro* and *in vivo* studies reporting an inhibitory effect of α -linolenic acid on tumor development^{44,45}. Further, we observed a significant inverse association between the n-3 PUFA docosapentaenoic acid and PC risk. Fish oil supplements and ingredients, oily fish, and grass-fed beef are primary docosapentaenoic acid sources in the general population⁴⁶. Since docosapentaenoic acid levels in fish oils are substantially lower than those of other n-3 PUFAs, previous epidemiological studies based on self-reported dietary intake were likely unable to fully capture the availability of this compound in foods. While there is a lack of robust experimental evidence linking docosapentaenoic acid with PC development, interestingly, a study on the effect of individual n-3 PUFAs on human colorectal carcinoma cells reported strong anti-proliferative and pro-apoptotic effects of this FA isomer⁴⁷. More extensive research is required to elucidate the role of docosapentaenoic acid in pancreatic carcinogenesis.

Tobacco-specific nitrosamines have been shown to induce pancreatic tumors in animal models^{48,49}, and the carcinogenic effect of these compounds was enhanced when animals were fed a high-fat diet⁵⁰. The n-3 and n-6 PUFAs have opposing effects in modulating signal transduction and gene expression involved in systemic inflammation⁵¹. Our finding of a statistically significant interaction between the long-chain n-6/n-3 PUFA ratio and smoking status may be due to the ability of these FAs and smoking-derived compounds to modulate similar inflammatory pathways that promote pancreatic carcinogenesis⁵². Caution needs to be taken in interpreting these findings given the low number of smokers and additional studies or experimental models are required for validation.

The sex-specific associations between industrial TFAs, conjugated linoleic acids and PC risk that we found in our analysis may reflect differences in hormone levels and dietary patterns between men and women³¹. However, the sample size may have been insufficient to detect robust statistical heterogeneity between genders and it is also possible that the results are due to chance. Replication in study populations with a larger number of cases or a wider intake of these FAs are required to confirm our findings.

Strengths of this study are the prospective and multi-center study design, the ability to distinguish various FA isomers, the relatively long follow-up time and the detailed information on lifestyle factors. The study also had some limitations including the low number of cases in subgroup analyses, the lack of information on family history of PC, and the single collection of blood samples at baseline. However, a previous study in a population of healthy women has shown high reliability of serum phospholipid FA levels from samples collected over time⁵³.

In conclusion, this study based on biomarkers of FA exposure provides support for a possible inverse relationship between specific FA isomers present in dairy products, seeds and marine foods on the development of PC. In addition, we found evidence of potential interactions of specific FAs with sex and smoking status on the risk of PC. Our findings support the conclusions of the WCRF Pancreatic Cancer 2012 Report⁵⁴ that concluded there is suggestive evidence of a link between intake of SFAs with PC, but go beyond this by highlighting the role of individual FA isomers in PC susceptibility. The use of circulating biomarkers of fatty acids could provide new insights into the biological mechanism underlying the association between fat, obesity and PC risk, as well as enable the development of more effective strategies for targeted screening and prevention.

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Table 1. Baseline characteristics of study population*

	Controls (n=375)	Cases (n=375)	P value†
Sex, n (%)			
Men	153 (40.8%)	153 (40.8%)	-
Women	222 (59.2%)	222 (59.2%)	-
Mean age (y) at			
Blood collection	57.44 ± 8.28	57.44 ± 8.30	-
Diagnosis		64.59 ± 8.87	-
Anthropometric measures			
Mean adult weight (kg)	72.62 ± 14.11	74.35 ± 13.50	0.087
Mean adult height (cm)	165.19 ± 8.95	165.93 ± 8.84	0.251
Mean body mass index (kg/m ²)	26.55 ± 4.43	26.99 ± 4.40	0.18
Waist to hip ratio	0.87 ± 0.10	0.88 ± 0.09	0.261
Nutrient intake			
Total energy intake (kcal)	2064.96 ± 598.26	2069.97 ± 666.98	0.914
Alcohol intake (g/d)‡	16.17 ± 22.05	16.56 ± 21.27	0.823
History of diabetes mellitus, n (%)			0.631
No	292 (77.9)	297 (79.2)	
Yes	27 (7.2)	24 (6.4)	
Unknown≠	56 (14.9)	54 (14.4)	
Smoking status, n (%)			0.001
Never smokers	183 (48.8)	164 (43.7)	
Former smokers	123 (32.8)	100 (26.7)	
Current smokers	65 (17.3)	104 (27.7)	
Unknown≠	4 (1.1)	7 (1.9)	
Physical activity, n (%)			0.743
Inactive	41 (10.9)	38 (10.1)	
Moderately inactive	118 (31.5)	107 (28.5)	
Moderately active	184 (49.1)	191 (50.9)	
Active	24 (6.4)	29 (7.7)	
Unknown≠	8 (2.1)	10 (2.7)	
Education, n (%)			0.062
Low	150 (40.0)	175 (46.7)	
Medium	146 (38.9)	120 (32.0)	
High	67 (17.9)	64 (17.1)	
Unknown≠	12 (3.2)	16 (4.3)	

*Data are presented as means (±SD) or proportions (percentages).

†Statistical significance for differences between cases and control individuals was tested using paired t-test for continuous variables and the Chi-squared test from unadjusted conditional logistic regression for categorical variables; P-values were not computed for matching factors.

‡Alcohol intake in grams/day among subjects who consumed alcohol at recruitment (84%).

≠Unknown subjects were excluded from calculations.

Table 2. Baseline plasma proportions and levels of fatty acids in the study population*

	Controls (n=375)		Cases (n=375)	
	Percentage [†]	Level (μmol/l)	Percentage [†]	Level (μmol/l)
Saturated fatty acids				
15:0 (pentadecanoic acid)	0.14 ± 1.74	8.93 ± 1.82	0.14 ± 1.67	8.71 ± 1.79
16:0 (palmitic acid)	25.06 ± 1.07	1588.61 ± 1.22	25.07 ± 1.07	1592.48 ± 1.24
17:0 (heptadecanoic acid)	0.37 ± 1.23	21.55 ± 1.28	0.35 ± 1.23	20.84 ± 1.28
18:0 (stearic acid)	14.07 ± 1.09	785.46 ± 1.24	14.04 ± 1.09	785.29 ± 1.26
<i>Cis</i> monounsaturated fatty acids				
16:1n-7 (palmitoleic acid)	0.67 ± 1.40	39.18 ± 1.56	0.70 ± 1.44	41.26 ± 1.62
18:1n-9 (oleic acid)	10.47 ± 1.21	577.18 ± 1.34	10.61 ± 1.22	585.99 ± 1.36
<i>Trans</i> monounsaturated fatty acids				
18:1n-9t/12t (elaidic acid)	0.25 ± 1.89	11.38 ± 2.00	0.26 ± 1.86	11.57 ± 1.91
18:1n-7t (vaccenic acid)	0.16 ± 1.88	7.09 ± 1.82	0.16 ± 1.87	7.03 ± 1.78
<i>Cis</i> n-6 polyunsaturated fatty acids				
18:2n-6 (linoleic acid)	22.07 ± 1.17	1224.16 ± 1.91	21.91 ± 1.16	1217.31 ± 1.26
18:3n-6 (γ-linolenic acid)	0.11 ± 1.57	6.08 ± 1.86	0.11 ± 1.55	6.22 ± 1.70
20:3n-6 (di-homo-γ-linolenic acid)	3.39 ± 1.28	197.62 ± 1.40	3.48 ± 1.26	203.44 ± 1.39
20:4n-6 (arachidonic acid)	10.78 ± 1.22	601.36 ± 1.31	10.78 ± 1.21	602.38 ± 1.32
Conjugated linoleic acids				
9c11t + 10t12c	0.19 ± 1.77	11.34 ± 1.86	0.19 ± 1.67	11.07 ± 1.79
<i>Cis</i> n-3 polyunsaturated fatty acids				
18:3n-3 (α-linolenic acid)	0.19 ± 1.55	11.25 ± 1.65	0.18 ± 1.52	10.60 ± 1.65
20:5n-3 (eicosapentaenoic acid)	1.05 ± 1.75	53.83 ± 1.85	1.03 ± 1.73	53.00 ± 1.84
22:5n-3 (docosapentaenoic acid)	1.02 ± 1.29	48.53 ± 1.40	0.99 ± 1.27	47.00 ± 1.40
22:6n-3 (docosahexaenoic acid)	4.55 ± 1.35	262.65 ± 1.41	4.55 ± 1.37	263.01 ± 1.43
Groupings				
Total saturated fatty acids	40.05 ± 1.03	2431.01 ± 1.21	40.00 ± 1.03	2433.91 ± 1.24
Total <i>cis</i> monounsaturated fatty acids	13.09 ± 1.19	717.05 ± 1.33	13.27 ± 1.19	728.71 ± 1.35

Total <i>cis</i> n-6 polyunsaturated fatty acids	37.71 ± 1.10	2103.94 ± 1.23	37.66 ± 1.09	2106.18 ± 1.23
Total <i>cis</i> n-3 polyunsaturated fatty acids	7.06 ± 1.30	389.75 ± 1.39	6.98 ± 1.32	386.83 ± 1.41
Long-chain n-6/n-3 PUFA ratio	2.23 ± 1.42	2.28 ± 1.43	2.27 ± 1.41	2.31 ± 1.41
Total <i>trans</i> ruminant fatty acids	0.73 ± 1.48	40.39 ± 1.53	0.73 ± 1.47	40.27 ± 1.50
Total <i>trans</i> industrial fatty acids	0.41 ± 1.69	18.64 ± 1.82	0.41 ± 1.63	18.89 ± 1.73
Desaturation index				
DI₁₆ (16:1n-7c/16:0)	0.03 ± 1.37	0.02 ± 1.37	0.03 ± 1.40	0.03 ± 1.41
DI₁₈ (18:1n-9c/18:0)	0.74 ± 1.26	0.73 ± 1.26	0.76 ± 1.26	0.75 ± 1.26

*Geometric means (±SD) of plasma fatty acids are presented.

†Relative amount expressed as percentage of total fatty acids.

Table 3. Multivariable odds ratios (ORs) and 95% confidence intervals (CIs) for plasma phospholipid fatty acids (percentage of total fatty acids) associated with pancreatic cancer risk

Plasma phospholipid fatty acids	Continuous†	Tertiles of plasma phospholipid fatty acids*			P-trend‡	P-heterogeneity§	Q-values§
		T1 (Ref)	T2	T3			
Saturated fatty acids							
15:0 (pentanoic acid)						0.691	
Total	0.72 (0.42; 1.26)	1.00	0.88 (0.56; 1.37)	0.63 (0.38; 1.04)	0.058		0.377
Men	0.95 (0.36; 2.52)	1.00	1.14 (0.58; 2.26)	0.78 (0.34; 1.77)	0.523		0.959
Women	0.65 (0.30; 1.44)	1.00	0.79 (0.46; 1.37)	0.62 (0.34; 1.15)	0.132		0.572
16:0 (palmitic acid)						0.756	
Total		1.00	0.71 (0.47; 1.06)	1.05 (0.69; 1.59)	0.787		0.853
Men		1.00	0.74 (0.39; 1.42)	1.06 (0.50; 2.22)	0.871		0.966
Women		1.00	1.21 (0.69; 2.11)	1.25 (0.70; 2.20)	0.466		0.884
17:0 (heptanoic acid)						0.547	
Total	0.32 (0.13; 0.82)	1.00	0.56 (0.37; 0.84)	0.63 (0.41; 0.98)	0.036		0.312
Men	0.55 (0.14; 2.21)	1.00	0.49 (0.25; 0.95)	0.84 (0.41; 1.71)	0.523		0.959
Women	0.23 (0.06; 0.85)	1.00	0.63 (0.37; 1.05)	0.60 (0.34; 1.06)	0.075		0.390
18:0 (stearic acid)						0.580	
Total	0.50 (0.06; 3.85)	1.00	0.89 (0.60; 1.31)	0.92 (0.61; 1.38)	0.686		0.853
Men		1.00	0.59 (0.32; 1.09)	1.13 (0.57; 2.25)	0.798		0.966
Women	0.56 (0.05; 7.00)	1.00	1.37 (0.79; 2.37)	0.87 (0.49; 1.52)	0.578		0.884
Cis monounsaturated fatty acids							
16:1n-7 (palmitoleic acid)						0.723	
Total	1.70 (1.00; 2.87)	1.00	1.08 (0.71; 1.64)	1.17 (0.77; 1.79)	0.461		0.853
Men	1.59 (0.72; 3.55)	1.00	1.12 (0.60; 2.09)	1.35 (0.65; 2.81)	0.425		0.959
Women	1.91 (0.90; 4.04)	1.00	1.04 (0.57; 1.87)	1.13 (0.63; 2.02)	0.662		0.930
18:1n-9 (oleic acid)						0.642	
Total	1.30 (0.52; 3.24)	1.00	1.33 (0.90; 1.95)	1.10 (0.71; 1.69)	0.561		0.853
Men	0.88 (0.21; 3.68)	1.00	1.35 (0.73; 2.48)	0.78 (0.38; 1.61)	0.655		0.966

Women	1.34 (0.39; 4.59)	1.00	1.17 (0.71; 1.91)	1.03 (0.59; 1.81)	0.848		0.930
<i>Trans</i> monounsaturated fatty acids							
18:1n-9t/12t (elaidic acid)						0.409	
Total	1.11 (0.76; 1.62)	1.00	1.12 (0.73; 1.71)	1.24 (0.72; 2.15)	0.439		0.853
Men	1.39 (0.75; 2.59)	1.00	1.20 (0.62; 2.34)	1.74 (0.74; 4.12)	0.218		0.959
Women	0.97 (0.58; 1.61)	1.00	1.14 (0.67; 1.94)	1.03 (0.49; 2.15)	0.894		0.930
18:1n-7t (vaccenic acid)						0.860	
Total	1.05 (0.74; 1.49)	1.00	0.94 (0.61; 1.45)	1.12 (0.66; 1.89)	0.648		0.853
Men	1.17 (0.65; 2.09)	1.00	0.87 (0.42; 1.78)	1.38 (0.53; 3.62)	0.547		0.959
Women	1.01 (0.64; 1.60)	1.00	1.39 (0.78; 2.46)	1.24 (0.64; 2.39)	0.577		0.884
<i>Cis</i> n-6 polyunsaturated fatty acids							
18:2n-6 (linoleic acid)						0.088	
Total	1.15 (0.68; 1.93)	1.00	1.01 (0.70; 1.47)	0.93 (0.61; 1.43)	0.768		0.853
Men		1.00	1.21 (0.62; 2.37)	1.67 (0.79; 3.55)	0.178		0.959
Women	1.15 (0.67; 1.99)	1.00	0.82 (0.50; 1.35)	0.73 (0.42; 1.27)	0.254		0.826
18:3n-6 (γ-linolenic acid)						0.195	
Total	1.13 (0.79; 1.60)	1.00	0.96 (0.65; 1.44)	1.10 (0.71; 1.69)	0.692		0.853
Males	1.11 (0.57; 2.16)	1.00	1.07 (0.59; 1.93)	1.74 (0.85; 3.57)	0.156		0.959
Females	1.08 (0.67; 1.72)	1.00	0.85 (0.49; 1.46)	0.90 (0.50; 1.63)	0.721		0.930
20:3n-6 (di-homo-γ-linolenic acid)						0.717	
Total	1.38 (0.67; 2.86)	1.00	1.03 (0.69; 1.55)	1.14 (0.75; 1.73)	0.534		0.853
Men	1.29 (0.43; 3.85)	1.00	1.15 (0.61; 2.17)	1.30 (0.69; 2.44)	0.416		0.959
Women	1.69 (0.61; 4.63)	1.00	1.14 (0.65; 1.99)	1.12 (0.64; 1.95)	0.725		0.930
20:4n-6 (arachidonic acid)						0.201	
Total	0.89 (0.38; 2.10)	1.00	0.86 (0.58; 1.28)	1.14 (0.76; 1.71)	0.534		0.853
Men	0.38 (0.10; 1.55)	1.00	1.29 (0.70; 2.38)	0.80 (0.41; 1.57)	0.535		0.959
Women	1.58 (0.51; 4.97)	1.00	0.74 (0.43; 1.27)	1.48 (0.86; 2.56)	0.197		0.732
Conjugated linoleic acids							
9c11t + 10t12c						0.056	
Total	0.87 (0.58; 1.32)	1.00	0.80 (0.52; 1.25)	0.70 (0.42; 1.16)	0.175		0.758

Men	1.06 (0.57; 1.97)	1.00	1.01 (0.51; 1.98)	1.02 (0.48; 2.15)	0.958		0.966
Women	0.80 (0.44; 1.45)	1.00	0.74 (0.38; 1.43)	0.37 (0.17; 0.81)	0.008		0.104
<i>Cis</i> n-3 polyunsaturated fatty acids							
18:3n-3 (α -linolenic acid)						0.773	
Total	0.59 (0.38; 0.92)	1.00	0.69 (0.46; 1.03)	0.60 (0.39; 0.92)	0.020		0.260
Men	0.57 (0.29; 1.13)	1.00	0.64 (0.32; 1.27)	0.63 (0.33; 1.20)	0.152		0.959
Women	0.55 (0.30; 0.99)	1.00	0.46 (0.27; 0.79)	0.55 (0.31; 0.99)	0.043		0.371
20:5n-3 (eicosapentaenoic acid)						0.174	
Total	0.95 (0.69; 1.30)	1.00	0.73 (0.50; 1.09)	0.71 (0.48; 1.07)	0.091		0.473
Males	1.20 (0.72; 2.00)	1.00	0.54 (0.28; 1.05)	1.08 (0.57; 2.07)	0.875		0.966
Females	0.80 (0.52; 1.23)	1.00	0.74 (0.44; 1.25)	0.58 (0.33; 1.02)	0.057		0.371
22:5n-3 (docosapentaenoic acid)						0.147	
Total	0.43 (0.18; 1.04)	1.00	0.76 (0.48; 1.21)	0.52 (0.32; 0.85)	0.008		0.208
Men	0.72 (0.16; 3.35)	1.00	0.54 (0.25; 1.15)	0.72 (0.32; 1.60)	0.553		0.959
Women	0.26 (0.08; 0.85)	1.00	0.83 (0.45; 1.53)	0.36 (0.18; 0.74)	0.004		0.104
22:6n-3 (docosahexaenoic acid)						0.932	
Total	1.10 (0.62; 1.94)	1.00	0.81 (0.55; 1.20)	1.14 (0.76; 1.72)	0.506		0.853
Men	0.87 (0.34; 2.26)	1.00	0.81 (0.43; 1.51)	1.01 (0.53; 1.93)	0.949		0.966
Women	1.15 (0.54; 2.46)	1.00	1.07 (0.64; 1.80)	0.99 (0.57; 1.72)	0.949		0.949
Groupings							
Total saturated fatty acids						0.791	
Total		1.00	0.99 (0.67; 1.48)	0.99 (0.62; 1.59)	0.977		0.977
Men		1.00	0.94 (0.48; 1.83)	1.11 (0.48; 2.58)	0.824		0.966
Women		1.00	1.15 (0.67; 1.98)	1.27 (0.68; 2.37)	0.451		0.884
Total <i>cis</i> monounsaturated fatty acids						0.339	
Total	1.49 (0.55; 4.09)	1.00	1.27 (0.87; 1.86)	1.07 (0.70; 1.64)	0.701		0.853
Men	0.95 (0.20; 4.52)	1.00	1.26 (0.69; 2.29)	0.61 (0.29; 1.30)	0.307		0.959
Women	1.55 (0.39; 6.12)	1.00	1.03 (0.61; 1.74)	1.07 (0.63; 1.84)	0.800		0.930
Total <i>cis</i> n-6 polyunsaturated fatty acids						0.776	
Total	0.76 (0.11; 5.54)	1.00	0.87 (0.60; 1.26)	0.87 (0.58; 1.30)	0.474		0.853

Men		1.00	0.65 (0.33; 1.28)	0.83 (0.41; 1.72)	0.629		0.966
Women		1.00	0.99 (0.62; 1.60)	0.95 (0.56; 1.61)	0.860		0.930
Total <i>cis</i> n-3 polyunsaturated fatty acids						0.694	
Total	0.95 (0.50; 1.80)	1.00	0.58 (0.39; 0.86)	0.92 (0.62; 1.35)	0.692		0.853
Men	1.08 (0.37; 3.18)	1.00	0.66 (0.35; 1.24)	0.96 (0.50; 1.84)	0.966		0.966
Women	0.80 (0.34; 1.88)	1.00	0.50 (0.30; 0.84)	0.82 (0.49; 1.38)	0.491		0.884
Long-chain n-6/n-3 PUFA ratio						0.232	
Total	1.03 (0.61; 1.73)	1.00	0.87 (0.59; 1.30)	1.02 (0.68; 1.54)	0.928		0.965
Males	0.75 (0.33; 1.72)	1.00	0.89 (0.49; 1.62)	0.69 (0.35; 1.34)	0.276		0.959
Females	1.39 (0.68; 2.86)	1.00	0.96 (0.56; 1.64)	1.19 (0.67; 2.11)	0.567		0.884
Total <i>trans</i> ruminant fatty acids						0.531	
Total	1.08 (0.59; 1.97)	1.00	0.92 (0.60; 1.41)	0.84 (0.50; 1.42)	0.520		0.853
Men	1.75 (0.66; 4.65)	1.00	1.02 (0.49; 2.14)	1.12 (0.46; 2.72)	0.817		0.966
Women	0.77 (0.34; 1.77)	1.00	0.99 (0.57; 1.71)	0.77 (0.39; 1.52)	0.460		0.884
Total <i>trans</i> industrial fatty acids						0.030	
Total	1.15 (0.71; 1.87)	1.00	1.32 (0.86; 2.02)	1.07 (0.62; 1.84)	0.728		0.853
Men	1.60 (0.71; 3.61)	1.00	1.32 (0.60; 2.93)	3.00 (1.13; 7.99)	0.029		0.754
Women	0.99 (0.52; 1.88)	1.00	1.06 (0.60; 1.86)	0.73 (0.33; 1.58)	0.485		0.884
Desaturation index							
DI₁₆ (16:1n-7c/16:0)						0.698	
Total	1.91 (1.07; 3.39)	1.00	1.27 (0.85; 1.90)	1.09 (0.70; 1.70)	0.752		0.853
Men	1.77 (0.74; 4.21)	1.00	1.08 (0.57; 2.01)	1.10 (0.53; 2.28)	0.793		0.966
Women	2.19 (0.95; 5.04)	1.00	1.76 (0.99; 3.13)	1.41 (0.77; 2.61)	0.348		0.884
DI₁₈ (18:1n-9c/18:0)						0.501	
Total	1.31 (0.62; 2.74)	1.00	1.07 (0.72; 1.57)	1.18 (0.78; 1.79)	0.438		0.853
Men	0.93 (0.28; 3.07)	1.00	1.23 (0.68; 2.23)	1.22 (0.59; 2.54)	0.529		0.959
Women	1.32 (0.49; 3.56)	1.00	0.74 (0.43; 1.29)	0.93 (0.54; 1.61)	0.768		0.930

Conditional logistic regression adjusted for body mass index, height, history of diabetes mellitus, smoking status, alcohol intake, education, and physical activity. Cases are individually matched to controls for study center, sex, age at blood collection (± 3 months), date and time at blood collection, length of follow-up, fasting status and, for women, use of pill/hormonal replacement treatment.

*Cut-points of tertiles determined on control individuals.

†OR (95% CI) for an increment of one unit percentage of plasma phospholipid fatty acids as continuous variable (log transformed); estimates with extreme confidence intervals are omitted.

‡Obtained by modelling the median of each tertile as continuous variable.

×Tests of heterogeneity between log transformed percentiles of plasma phospholipid FAs in men and in women based on Chi-squared statistics calculated as the deviations of logistic beta-coefficients observed in each of the subgroups relative to the overall beta-coefficient.

§False discovery rate (FDR) corrected P-trend.

Supplementary Table 1. Baseline characteristics of the study population by sex*

	Males			Females		
	Controls (n=153)	Cases (n=153)	<i>P</i> value†	Controls (n=222)	Cases (n=222)	<i>P</i> value†
Mean age (y) at						
Blood collection	56.44 ± 8.32	56.48 ± 8.36	0.971	58.13 ± 8.20	58.11 ± 8.21	0.973
Diagnosis		63.38 ± 8.62			65.42 ± 8.97	
Anthropometric measures						
Mean adult weight (kg)	81.40 ± 12.25	80.37 ± 11.18	0.446	66.58 ± 11.99	70.20 ± 13.41	0.003
Mean adult height (cm)	171.82 ± 6.81	172.37 ± 7.50	0.500	160.62 ± 7.23	161.50 ± 6.70	0.184
Mean body mass index (kg/m ²)	27.55 ± 3.71	27.06 ± 3.47	0.230	25.86 ± 4.75	26.93 ± 4.96	0.020
Waist to hip ratio	0.96 ± 0.06	0.95 ± 0.06	0.669	0.80 ± 0.07	0.82 ± 0.07	0.017
Nutrient intake						
Energy intake (kcal)	2314.86 ± 604.54	2410.08 ± 678.00	0.197	1892.29 ± 530.13	1837.10 ± 550.20	0.283
Alcohol intake (g/d)‡	23.94 ± 28.35	26.12 ± 26.54	0.510	9.76 ± 11.65	9.15 ± 11.55	0.624
History of diabetes mellitus, n (%)			0.493			1
No	119 (77.8)	116 (75.8)		178 (80.2)	176 (79.3)	
Yes	13 (8.5)	16 (10.5)		11 (5.0)	11 (5.0)	
Unknown#	21 (13.7)	21 (13.7)		33 (14.9)	35 (15.8)	
Smoking status, n (%)			0.070			0.008
Never smokers	48 (31.4)	43 (28.1)		135 (60.8)	121 (54.5)	
Former smokers	66 (43.1)	53 (34.6)		57 (25.7)	47 (21.2)	
Current smokers	36 (23.5)	52 (34.0)		29 (13.1)	52 (23.4)	
Unknown#	3 (2.0)	5 (3.3)		1 (0.5)	2 (0.9)	
Physical activity, n (%)			0.295			0.668
Inactive	29 (19.0)	20 (13.1)		12 (5.4)	18 (8.1)	
Moderately inactive	50 (32.7)	46 (30.1)		68 (30.6)	61 (27.5)	
Moderately active	61 (39.9)	67 (43.8)		123 (55.4)	124 (55.9)	
Active	9 (5.9)	16 (10.5)		15 (6.8)	13 (5.9)	
Unknown#	4 (2.6)	4 (2.6)		4 (1.8)	6 (2.7)	

Education, n (%)			0.125		0.180
Low	53 (34.6)	67 (43.8)		97 (43.7)	108 (48.7)
Medium	59 (38.6)	49 (32.0)		87 (39.2)	71 (32.0)
High	39 (25.5)	32 (20.9)		28 (12.6)	32 (14.4)
Unknown [‡]	2 (1.3)	5 (3.3)		10 (4.5)	11 (5.0)

*Data are presented as means (\pm SD) or proportions (percentages).

[†]Statistical significance for differences between cases and control individuals was tested using paired t-test for continuous variables and the Chi-squared test from unadjusted conditional logistic regression for categorical variables; P-value was not computed for matching factors.

[‡] Alcohol intake in grams/day among subjects who consumed alcohol at recruitment (84%).

[‡]Unknown subjects are excluded from calculations.

Supplementary Table 2. Multivariable odds ratios (ORs) and 95% confidence intervals (CIs) for association between plasma phospholipid fatty acid (percentage of total fatty acids) and pancreatic cancer risk stratified by smoking status at recruitment

Percentage of total fatty acids, and pancreatic cancer risk stratified by smoking status at recruitment						
Plasma phospholipid fatty acids	Continuous†	Tertiles of plasma phospholipid fatty acids*			P-trend‡	P-interaction§
		T1 (Ref)	T2	T3		
Saturated fatty acids						
15:0 (pentanoic acid)						0.551
Non-smokers§	0.94 (0.73; 1.21)	1 (ref)	1.15 (0.76; 1.72)	0.79 (0.49; 1.28)	0.386	
Current smokers	0.84 (0.41; 1.70)	1 (ref)	0.69 (0.31; 1.54)	0.90 (0.36; 2.23)	0.743	
16:0 (palmitic acid)						0.509
Non-smokers		1 (ref)	0.94 (0.62; 1.44)	1.05 (0.68; 1.62)	0.831	
Current smokers		1 (ref)	0.68 (0.28; 1.68)	1.18 (0.53; 2.64)	0.617	
17:0 (heptanoic acid)						0.3945
Non-smokers	0.40 (0.15; 1.10)	1 (ref)	0.61 (0.40; 0.93)	0.72 (0.46; 1.15)	0.147	
Current smokers	0.39 (0.07; 2.15)	1 (ref)	1.15 (0.51; 2.56)	0.58 (0.23; 1.47)	0.289	
18:0 (stearic acid)						0.9878
Non-smokers	0.46 (0.06; 3.86)	1 (ref)	0.87 (0.57; 1.33)	0.93 (0.60; 1.44)	0.761	
Current smokers		1 (ref)	1.38 (0.62; 3.10)	0.84 (0.35; 2.02)	0.755	
Cis monounsaturated fatty acids						
16:1n-7 (palmitoleic acid)						0.6394
Non-smokers	1.70 (1.01; 2.86)	1 (ref)	1.07 (0.71; 1.63)	1.21 (0.79; 1.85)	0.385	
Current smokers	1.99 (0.76; 5.20)	1 (ref)	1.61 (0.68; 3.79)	2.01 (0.87; 4.68)	0.109	
18:1n-9 (oleic acid)						0.3055
Non-smokers	1.10 (0.44; 2.73)	1 (ref)	1.15 (0.76; 1.73)	0.97 (0.63; 1.48)	0.887	
Current smokers		1 (ref)	1.55 (0.67; 3.58)	1.93 (0.82; 4.53)	0.136	
Trans monounsaturated fatty acids						
18:1n-9t/12t (elaidic acid)						0.6216
Non-smokers	0.90 (0.65; 1.25)	1 (ref)	1.00 (0.64; 1.55)	1.01 (0.63; 1.63)	0.97	
Current smokers	1.87 (0.98; 3.57)	1 (ref)	2.78 (1.16; 6.70)	3.27 (1.21; 8.84)	0.023	
18:1n-7t (vaccenic acid)						0.9143
Non-smokers	0.94 (0.68; 1.29)	1 (ref)	1.07 (0.70; 1.64)	1.13 (0.71; 1.79)	0.604	

Current smokers	1.21 (0.68; 2.15)	1 (ref)	1.25 (0.55; 2.88)	1.18 (0.50; 2.78)	0.693	
<i>Cis</i> n-6 polyunsaturated fatty acids						
18:2n-6 (linoleic acid)						0.6949
Non-smokers	1.08 (0.73; 1.62)	1 (ref)	0.72 (0.47; 1.09)	0.72 (0.47; 1.10)	0.12	
Current smokers		1 (ref)	2.55 (1.10; 5.89)	1.68 (0.70; 4.06)	0.279	
18:3n-6 (γ-linolenic acid)						0.0895
Non-smokers	1.04 (0.78; 1.38)	1 (ref)	0.99 (0.65; 1.51)	0.91 (0.61; 1.38)	0.674	
Current smokers	1.71 (0.80; 3.66)	1 (ref)	0.79 (0.34; 1.83)	1.40 (0.65; 3.02)	0.399	
20:3n-6 (di-homo-γ-linolenic acid)						0.3143
Non-smokers	1.41 (0.65; 3.03)	1 (ref)	1.24 (0.81; 1.89)	1.30 (0.84; 2.03)	0.242	
Current smokers	2.09 (0.53; 8.20)	1 (ref)	0.85 (0.36; 1.98)	1.30 (0.57; 3.00)	0.519	
20:4n-6 (arachidonic acid)						0.9972
Non-smokers	1.01 (0.42; 2.43)	1 (ref)	0.85 (0.55; 1.30)	1.17 (0.77; 1.77)	0.428	
Current smokers	0.49 (0.07; 3.59)	1 (ref)	1.30 (0.56; 3.01)	1.20 (0.50; 2.88)	0.689	
Conjugated linoleic acids						
9c11t + 10t12c						0.661
Non-smokers	0.95 (0.66; 1.36)	1 (ref)	0.84 (0.55; 1.28)	0.77 (0.48; 1.22)	0.259	
Current smokers	1.40 (0.71; 2.74)	1 (ref)	1.91 (0.85; 4.33)	1.63 (0.60; 4.40)	0.304	
<i>Cis</i> n-3 polyunsaturated fatty acids						
18:3n-3 (α-linolenic acid)						0.6917
Non-smokers	0.76 (0.50; 1.15)	1 (ref)	0.82 (0.54; 1.24)	0.75 (0.48; 1.15)	0.183	
Current smokers	0.82 (0.32; 2.11)	1 (ref)	0.82 (0.35; 1.89)	0.62 (0.25; 1.52)	0.295	
20:5n-3 (eicosapentaenoic acid)						0.1384
Non-smokers	1.11 (0.82; 1.52)	1 (ref)	0.80 (0.53; 1.22)	0.96 (0.63; 1.45)	0.833	
Current smokers	0.57 (0.29; 1.12)	1 (ref)	0.83 (0.38; 1.83)	0.37 (0.16; 0.89)	0.034	
22:5n-3 (docosapentaenoic acid)						0.4051
Non-smokers	0.71 (0.32; 1.56)	1 (ref)	0.96 (0.63; 1.47)	0.61 (0.38; 0.98)	0.046	
Current smokers	0.45 (0.10; 2.01)	1 (ref)	0.98 (0.43; 2.25)	0.72 (0.29; 1.75)	0.469	
22:6n-3 (docosahexaenoic acid)						0.0025
Non-smokers	1.70 (0.95; 3.04)	1 (ref)	0.93 (0.60; 1.43)	1.43 (0.95; 2.17)	0.074	

Current smokers	0.17 (0.05; 0.56)	1 (ref)	0.49 (0.21; 1.14)	0.31 (0.13; 0.76)	0.009	
Groupings						
Total saturated fatty acids						0.4101
Non-smokers		1 (ref)	1.24 (0.81; 1.88)	1.08 (0.69; 1.69)	0.736	
Current smokers		1 (ref)	0.70 (0.30; 1.61)	0.94 (0.41; 2.16)	0.897	
Total <i>cis</i> monounsaturated fatty acids						0.4011
Non-smokers	1.30 (0.47; 3.58)	1 (ref)	1.06 (0.70; 1.60)	0.98 (0.64; 1.50)	0.941	
Current smokers		1 (ref)	1.88 (0.80; 4.37)	1.70 (0.72; 4.02)	0.249	
Total <i>cis</i> n-6 polyunsaturated fatty acids						0.2998
Non-smokers	0.35 (0.05; 2.55)	1 (ref)	0.89 (0.59; 1.33)	0.68 (0.44; 1.05)	0.087	
Current smokers		1 (ref)	0.73 (0.32; 1.67)	1.41 (0.63; 3.18)	0.401	
Total <i>cis</i> n-3 polyunsaturated fatty acids						0.0033
Non-smokers	1.62 (0.84; 3.13)	1 (ref)	0.76 (0.49; 1.17)	1.34 (0.89; 2.02)	0.14	
Current smokers	0.13 (0.03; 0.52)	1 (ref)	0.41 (0.18; 0.93)	0.26 (0.11; 0.62)	0.002	
Long-chain n-6/n-3 PUFA ratio						0.0097
Non-smokers	0.74 (0.44; 1.25)	1 (ref)	0.88 (0.58; 1.34)	0.79 (0.52; 1.22)	0.291	
Current smokers	3.26 (1.19; 8.92)	1 (ref)	1.81 (0.75; 4.38)	3.40 (1.39; 8.34)	0.007	
Total <i>trans</i> ruminant fatty acids						0.5255
Non-smokers	1.04 (0.63; 1.71)	1 (ref)	0.92 (0.60; 1.41)	0.89 (0.56; 1.40)	0.608	
Current smokers	1.15 (0.48; 2.77)	1 (ref)	2.21 (0.94; 5.15)	1.00 (0.40; 2.50)	0.929	
Total <i>trans</i> industrial fatty acids						0.5833
Non-smokers	0.88 (0.59; 1.31)	1 (ref)	1.09 (0.71; 1.68)	0.88 (0.55; 1.42)	0.605	
Current smokers	1.94 (0.89; 4.23)	1 (ref)	1.53 (0.65; 3.58)	2.04 (0.79; 5.23)	0.139	
Desaturation index						
DI₁₆ (16:1n-7c/16:0)						0.7081
Non-smokers	1.83 (1.05; 3.19)	1 (ref)	1.14 (0.75; 1.73)	1.17 (0.76; 1.80)	0.471	
Current smokers	2.20 (0.78; 6.25)	1 (ref)	1.81 (0.79; 4.14)	1.79 (0.76; 4.20)	0.186	
DI₁₈ (18:1n-9c/18:0)						0.3981
Non-smokers	1.17 (0.55; 2.48)	1 (ref)	1.02 (0.67; 1.55)	1.06 (0.70; 1.62)	0.77	

Current smokers	1 (ref)	1.32 (0.55; 3.18)	2.80 (1.18; 6.64)	0.017
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Unconditional logistic regression adjusted for matching variables (study center, sex, age at blood collection, data and time at blood collection, length of follow-up, fasting status, pill/hormone replacement treatment), body mass index, height, history of diabetes mellitus, alcohol intake, education and physical activity.

*Cut-points of tertiles determined on control individuals.

†OR (95% CI) for an increment of one unit percentage of plasma phospholipid fatty acids as continuous variable (log transformed); estimates with extreme confidence intervals are omitted.

‡Obtained by modelling the median of each tertile as continuous variable.

§Obtained by modelling the interaction term between log transformed percentiles of plasma phospholipid FAs and smoking status as dichotomous variable by including a cross-product term in the multivariable model and evaluating the influence of this term by a likelihood ratio test.

§Non-smokers includes former and never smokers at recruitment.

Supplementary Table 3. Multivariable odds ratios (ORs) and 95% confidence intervals (CIs) for association between plasma phospholipid fatty acid (percentage of total fatty acids) and pancreatic cancer risk stratified by levels of BMI at recruitment

Percentage of total fatty acids, and pancreatic cancer risk stratified by levels of BMI at recruitment						
Plasma phospholipid fatty acids	Continuous†	Tertiles of plasma phospholipid fatty acids*			P-trend‡	P-interaction§
		T1 (Ref)	T2	T3		
Saturated fatty acids						
15:0 (pentanoic acid)						0.0304
BMI <26.1 kg/m ²	0.74 (0.49; 1.10)	1 (ref)	0.92 (0.55; 1.56)	0.61 (0.35; 1.09)	0.109	
BMI ≥26.1 kg/m ²	1.01 (0.75; 1.37)	1 (ref)	1.98 (1.18; 3.34)	1.43 (0.81; 2.52)	0.189	
16:0 (palmitic acid)						0.6337
BMI <26.1 kg/m ²		1 (ref)	0.70 (0.40; 1.23)	1.40 (0.81; 2.44)	0.221	
BMI ≥26.1 kg/m ²		1 (ref)	1.05 (0.61; 1.80)	1.07 (0.62; 1.87)	0.805	
17:0 (heptanoic acid)						0.0403
BMI <26.1 kg/m ²	0.15 (0.04; 0.53)	1 (ref)	0.67 (0.38; 1.17)	0.62 (0.35; 1.08)	0.084	
BMI ≥26.1 kg/m ²	0.85 (0.25; 2.94)	1 (ref)	0.60 (0.34; 1.05)	0.70 (0.41; 1.20)	0.181	
18:0 (stearic acid)						0.2868
BMI <26.1 kg/m ²	0.33 (0.02; 4.66)	1 (ref)	0.74 (0.43; 1.25)	0.79 (0.46; 1.36)	0.387	
BMI ≥26.1 kg/m ²	0.20 (0.01; 3.19)	1 (ref)	1.21 (0.71; 2.06)	0.84 (0.47; 1.50)	0.55	
Cis monounsaturated fatty acids						
16:1n-7 (palmitoleic acid)						0.3207
BMI <26.1 kg/m ²	2.08 (1.05; 4.14)	1 (ref)	1.08 (0.63; 1.83)	1.08 (0.62; 1.88)	0.798	
BMI ≥26.1 kg/m ²	1.69 (0.90; 3.19)	1 (ref)	0.99 (0.58; 1.68)	1.31 (0.77; 2.25)	0.319	
18:1n-9 (oleic acid)						0.6549
BMI <26.1 kg/m ²	1.10 (0.31; 3.93)	1 (ref)	0.92 (0.54; 1.58)	1.06 (0.61; 1.84)	0.838	
BMI ≥26.1 kg/m ²	2.04 (0.70; 5.99)	1 (ref)	1.74 (1.03; 2.93)	1.26 (0.74; 2.17)	0.402	
Trans monounsaturated fatty acids						
18:1n-9t/12t (elaidic acid)						0.8431
BMI <26.1 kg/m ²	1.13 (0.75; 1.71)	1 (ref)	0.91 (0.53; 1.56)	1.16 (0.64; 2.13)	0.649	
BMI ≥26.1 kg/m ²	1.11 (0.73; 1.68)	1 (ref)	0.75 (0.43; 1.30)	1.21 (0.66; 2.21)	0.59	

18:1n-7t (vaccenic acid)						0.1029
BMI <26.1 kg/m ²	0.82 (0.54; 1.25)	1 (ref)	0.94 (0.54; 1.63)	0.83 (0.45; 1.52)	0.541	
BMI ≥26.1 kg/m ²	1.13 (0.77; 1.66)	1 (ref)	0.89 (0.53; 1.49)	1.27 (0.72; 2.23)	0.448	
<i>Cis</i> n-6 polyunsaturated fatty acids						
18:2n-6 (linoleic acid)						0.9159
BMI <26.1 kg/m ²	1.14 (0.66; 1.98)	1 (ref)	0.98 (0.57; 1.67)	0.77 (0.44; 1.34)	0.353	
BMI ≥26.1 kg/m ²	0.70 (0.17; 2.85)	1 (ref)	1.20 (0.72; 2.01)	0.87 (0.51; 1.50)	0.644	
18:3n-6 (γ-linolenic acid)						0.0281
BMI <26.1 kg/m ²	1.24 (0.82; 1.88)	1 (ref)	0.95 (0.56; 1.62)	1.16 (0.68; 1.98)	0.588	
BMI ≥26.1 kg/m ²	0.79 (0.46; 1.36)	1 (ref)	0.94 (0.56; 1.57)	0.99 (0.58; 1.68)	0.951	
20:3n-6 (di-homo-γ-linolenic acid)						0.1433
BMI <26.1 kg/m ²	1.49 (0.57; 3.85)	1 (ref)	1.23 (0.72; 2.10)	1.39 (0.80; 2.41)	0.247	
BMI ≥26.1 kg/m ²	1.32 (0.51; 3.42)	1 (ref)	1.03 (0.60; 1.77)	1.01 (0.59; 1.72)	0.98	
20:4n-6 (arachidonic acid)						0.828
BMI <26.1 kg/m ²	1.01 (0.31; 3.32)	1 (ref)	1.02 (0.59; 1.77)	1.49 (0.87; 2.53)	0.133	
BMI ≥26.1 kg/m ²	0.65 (0.21; 1.98)	1 (ref)	0.74 (0.43; 1.28)	0.82 (0.48; 1.41)	0.502	
Conjugated linoleic acids						
9c11t + 10t12c						0.7158
BMI <26.1 kg/m ²	1.12 (0.69; 1.84)	1 (ref)	0.97 (0.57; 1.65)	0.89 (0.51; 1.56)	0.692	
BMI ≥26.1 kg/m ²	1.08 (0.71; 1.64)	1 (ref)	0.90 (0.53; 1.54)	0.94 (0.51; 1.74)	0.809	
<i>Cis</i> n-3 polyunsaturated fatty acids						
18:3n-3 (α-linolenic acid)						0.9587
BMI <26.1 kg/m ²	0.70 (0.39; 1.24)	1 (ref)	0.65 (0.39; 1.09)	0.58 (0.33; 1.03)	0.052	
BMI ≥26.1 kg/m ²	0.84 (0.50; 1.42)	1 (ref)	0.82 (0.48; 1.40)	0.89 (0.51; 1.57)	0.647	
20:5n-3 (eicosapentaenoic acid)						0.4445
BMI <26.1 kg/m ²	0.98 (0.65; 1.45)	1 (ref)	0.65 (0.39; 1.10)	0.81 (0.47; 1.38)	0.383	
BMI ≥26.1 kg/m ²	1.06 (0.71; 1.59)	1 (ref)	0.87 (0.52; 1.45)	0.75 (0.44; 1.29)	0.304	

22:5n-3 (docosapentaenoic acid)						0.9322
BMI <26.1 kg/m ²	0.72 (0.25; 2.10)	1 (ref)	0.69 (0.41; 1.17)	0.54 (0.30; 0.98)	0.04	
BMI ≥26.1 kg/m ²	0.69 (0.27; 1.75)	1 (ref)	0.69 (0.40; 1.18)	0.67 (0.37; 1.18)	0.16	
22:6n-3 (docosahexaenoic acid)						0.7261
BMI <26.1 kg/m ²	0.95 (0.48; 1.89)	1 (ref)	1.04 (0.61; 1.80)	1.05 (0.61; 1.81)	0.862	
BMI ≥26.1 kg/m ²	1.05 (0.48; 2.31)	1 (ref)	0.77 (0.44; 1.32)	1.33 (0.80; 2.23)	0.248	
Groupings						
Total saturated fatty acids						0.0653
BMI <26.1 kg/m ²		1 (ref)	1.10 (0.63; 1.90)	1.36 (0.78; 2.40)	0.273	
BMI ≥26.1 kg/m ²		1 (ref)	0.78 (0.46; 1.32)	0.76 (0.44; 1.31)	0.308	
Total <i>cis</i> monounsaturated fatty acids						0.653
BMI <26.1 kg/m ²	1.32 (0.32; 5.38)	1 (ref)	0.98 (0.57; 1.67)	1.14 (0.66; 1.97)	0.645	
BMI ≥26.1 kg/m ²	2.50 (0.75; 8.33)	1 (ref)	2.19 (1.28; 3.75)	1.56 (0.90; 2.70)	0.141	
Total <i>cis</i> n-6 polyunsaturated fatty acids						0.8736
BMI <26.1 kg/m ²	0.70 (0.06; 8.72)	1 (ref)	0.84 (0.49; 1.44)	0.88 (0.51; 1.53)	0.665	
BMI ≥26.1 kg/m ²	0.24 (0.02; 3.36)	1 (ref)	0.76 (0.46; 1.29)	0.68 (0.40; 1.16)	0.151	
Total <i>cis</i> n-3 polyunsaturated fatty acids						0.9876
BMI <26.1 kg/m ²	0.88 (0.40; 1.94)	1 (ref)	0.67 (0.39; 1.15)	0.87 (0.51; 1.48)	0.568	
BMI ≥26.1 kg/m ²	1.07 (0.45; 2.56)	1 (ref)	0.74 (0.44; 1.26)	1.07 (0.64; 1.79)	0.802	
Long-chain n-6/n-3 PUFA ratio						0.9243
BMI <26.1 kg/m ²	1.12 (0.59; 2.11)	1 (ref)	1.01 (0.58; 1.74)	1.22 (0.70; 2.12)	0.482	
BMI ≥26.1 kg/m ²	0.89 (0.45; 1.76)	1 (ref)	0.89 (0.53; 1.51)	0.88 (0.52; 1.50)	0.648	
Total <i>trans</i> ruminant fatty acids						0.3703
BMI <26.1 kg/m ²	0.80 (0.44; 1.45)	1 (ref)	0.90 (0.52; 1.55)	0.73 (0.41; 1.30)	0.288	
BMI ≥26.1 kg/m ²	1.34 (0.70; 2.56)	1 (ref)	1.11 (0.65; 1.87)	1.25 (0.69; 2.25)	0.464	
Total <i>trans</i> industrial fatty acids						0.8295
BMI <26.1 kg/m ²	1.17 (0.72; 1.91)	1 (ref)	1.22 (0.71; 2.12)	1.18 (0.66; 2.13)	0.574	

BMI ≥ 26.1 kg/m ²	1.09 (0.65; 1.83)	1 (ref)	1.10 (0.65; 1.87)	1.06 (0.57; 1.95)	0.83	
Desaturation index						
DI₁₆ (16:1n-7c/16:0)						0.3111
BMI <26.1 kg/m ²	2.14 (1.03; 4.44)	1 (ref)	1.09 (0.64; 1.87)	1.26 (0.73; 2.18)	0.395	
BMI ≥ 26.1 kg/m ²	1.81 (0.92; 3.57)	1 (ref)	1.53 (0.90; 2.59)	1.57 (0.90; 2.73)	0.115	
DI₁₈ (18:1n-9c/18:0)						0.4474
BMI <26.1 kg/m ²	1.26 (0.45; 3.57)	1 (ref)	0.86 (0.49; 1.48)	1.25 (0.73; 2.14)	0.415	
BMI ≥ 26.1 kg/m ²	1.98 (0.80; 4.91)	1 (ref)	1.63 (0.96; 2.77)	1.40 (0.81; 2.41)	0.237	

Unconditional logistic regression adjusted for matching variables (study center, sex, age at blood collection, data and time at blood collection, length of follow-up, fasting status, pill/hormone replacement treatment), height, history of diabetes mellitus, smoking status, alcohol intake, education and physical activity.

*Cut-points of tertiles determined on control individuals.

†OR (95% CI) for an increment of one unit percentage of plasma phospholipid fatty acids as continuous variable (log transformed); estimates with extreme confidence intervals are omitted.

‡Obtained by modelling the median of each tertile as continuous variable.

×Obtained by modelling the interaction term between log transformed percentiles of plasma phospholipid FAs and BMI as dichotomous variable by including a cross-product term in the multivariable model and evaluating the influence of this term by a likelihood ratio test.