Supplementary Appendix

Supplementary Approaches

Cohort descriptions, assessments of fatty acids, genotyping information, and diabetes ascertainment and diagnostic criteria

Age, Gene/Environment Susceptibility-Reykjavik study (AGESR), Iceland[1,2]

The AGESR is a random sample of 5,764 men and women who were drawn from an established single center population-based cohort; the Reykjavik Study, begun in 1967 to study heart disease. AGES-Reykjavik Study was designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. At study baseline (2002–2006), participants were aged 66–96 years. A total of 753 adults with available data on circulating fatty acids and diabetes were eligible for the current analysis.

Blood samples were collected at baseline after an overnight fast and stored at -80 °C. Fatty acids were measured in plasma phospholipids at the Fred Hutchinson Cancer Research Center. Phospholipids were separated from other lipids by using one-dimensional thin-layer chromatography. Fatty acid methyl esters were prepared by direct transesterification and separated by using gas chromatography (Agilent Technologies 7890 Gas Chromatograph flame ionization detector; Supelco fusedsilica 100-m capillary column SP-2560; initially at 160 °C for 16 min, ramped up at 3.0 °C/min to 240 °C, and held for 15 min). The identification, precision, and accuracy were continuously evaluated by using both model mixtures of known fatty acid methyl esters and established in-house control pools. Fatty acids were expressed as the weight percentage of the total phospholipid fatty acids analyzed. The CV from pooled quality-control samples for major polyunsaturated fatty acids were all 2.5%. CVs for other major fatty acids were 0.77% (palmitic), 0.47% (stearic), and 0.42% (oleic).

Participants were seen in clinic ~5 years after baseline. Prevalent diabetes at the clinic visit were determined from self-reported diabetes, diabetes medication use or fasting plasma glucose ≥7.0mmol/L. Time to incident diabetes was defined as the median time between baseline and follow-up visit.

Alpha Omega Cohort (AOC), the Netherlands[3,4]

AOC is a cohort of 4837 non-hospitalized patients who experienced a myocardial infarction up to 10 years before enrolment. The study includes a trial phase (Alpha Omega Trial, 3-year intervention with low doses of n-3 fatty acids, until 2009). It is now used as prospective cohort study for risk prediction in post-MI patients. The patients were recruited in collaboration with cardiologists from 32 Dutch hospitals. At baseline (2002-2006), data were collected on diet, lifestyle, cardiovascular risk factors, medical history, and medication use. Subjects were physically examined by trained research nurses, which included anthropometry, blood pressure, heart rate, and blood sampling. Examinations were repeated after 20 months (midterm examination in n=800) and 40 months (final examination). Patients have been continuously followed for cause-specific mortality, also after the trial ended.

Baseline blood samples of 10 mL of non-fasting venous blood were drawn at the patients' home or at the hospital. For cholesteryl ester fatty acid analysis, blood was collected in EDTA containing vacutainers, packed in a sealed envelope and sent over postal mail to a central laboratory. At the laboratory, the EDTA samples were centrifuged for 10 minutes at 1200 g and plasma was stored at -80°C. Fatty acids were measured in plasma cholesteryl esters and plasma phospholipids (for the last 998 participants) by gas chromatography. In short, to isolate cholesteryl esters and phospholipids, lipids from EDTA plasma were dissolved and separated by solid phase extraction silica columns (Chrompack, Middelburg, The Netherlands). The fatty acids were identified by comparison with known standards (Nu-chek prep, Inc. Elysian, MN, USA). Fatty acids were expressed as mass percentages of total fatty acid methyl esters (g/100 g). A quality control plasma pool was analysed in duplicate in each run.

Incident diabetes during the trial phase was defined as either a self-reported physician diagnosis or use of antidiabetic medication (based on telephone interviews at 12 and 24 months or examinations at 20 months (midterm examination; n=800) or 40 months (final examination).

Atherosclerosis Risk in Communities Study (ARIC), USA[5,6]

ARIC is a multi-center prospective investigation of atherosclerotic disease in a predominantly bi-racial population7. Mmen and women aged 45- 64 years at baseline were recruited from 4 communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban areas of Minneapolis, Minnesota; and Washington County, Maryland. A total of 15,792 individuals participated in the baseline examination in 1987-1989, but only baseline fasting blood from the Minnesota field center were analyzed for participants with all data plus plasma fatty acids (n=3494).

Fatty acids were measured in EDTA plasma that had been frozen at -70˚C. Fatty acid assays were performed at the Collaborative Studies Clinical Laboratory at Fairview University Medical Center (Minneapolis, MN) as previously described 8. Lipids were extracted with chloroform/methanol and separated by thin layer chromatography. Fatty acid methyl esters were prepared from the phospholipid fraction and separated by gas chromatography using an HP-5890 gas chromatograph (Hewlett- Packard, Palo Alto, CA) with a 100-m capillary Varian CP7420 column. We identified 29 fatty acids. The concentration of each fatty acid was expressed as to percentage of total fatty acids.

ARIC Study samples were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0 (Santa Clara, California. Autosomal SNPs were used for imputation after exclusion of SNPs with HWE deviation $p<1 \times 10^{-5}$, call rate <95%, or MAF<1%.

Participants were enrolled and measurements taken at baseline 1987-1989 and at 3 subsequent exams (3 years apart). Medication use was assessed at each study exam. Fasting glucose was measured at the study baseline (1987–1989) and in subsequent visits 1990–1992, 1993 – 1995, and 1996-98. Type 2 diabetes was defined as a single measure of fasting glucose concentration $\geqslant$ 7.0mmol/L, or new use of an insulin or oral hypoglycemic medication, or self-report of physician diagnosis.

Chin-Shan Community Cardiovascular Cohort (CCCC), Taiwan[7,8]

CCCC began in 1990, following 1703 men and 1899 women aged 35 years old and above, homogenous in Chinese ethnicity, in Northern Taiwan for the study of cardiovascular diseases. The cohort was assembled from the registry data of the bureaucracy and the participants were recruited by house-to-house visits. The study was approved by the IRB in the National Taiwan University Hospital. Participants received baseline health examination at the community health center. We recruited the subjects by volunteer basis and respondent rates were up to 83%. In the survey, all of the study participants were individually interviewed from a structured questionnaire, for the information on socio-demographic characteristics, physical activity, smoking, alcohol drinking habits, dietary characteristics, personal and family histories of diseases and hospitalizations. With informed consent, the participants underwent physical examinations and laboratory tests. The examiners undertook training in the questionnaire collections and measures.

10-mL tubes of EDTA-anticoagulated blood were collected, refrigerated on-site, and forwarded to the core laboratory of the National Taiwan University Hospital within 3 h. The blood was centrifuged at 800×g for 10 min, whereupon plasma was separated, dispensed into aliquots, and frozen at –70 ºC. All analyses of fatty acid content were performed by the same technician. After thawing the plasma, 0.5 mL samples were extracted and combined with 0.5 mL methanol followed by 1.0 mL chloroform under a nitrogen atmosphere. The lipid extract was then filtered to remove proteins and methyl esters were separated and measured using a 5890 gas chromatograph (Hewlett Packard, Avondale, PA) equipped with a 30 m-FFAT WCOT glass capillary column (J & W Scientific, Folsom, CA) and a flame ionization detector. A total of 29 individual fatty acids were identified by comparing the retention times of peaks to the retention times of synthetic FA standards with known compositions (Supelco 37 Comp. FAME Mix, 47885-U; Bellefonte, PA, USA). The relative quantity of each FA (% of total FAs) was determined by integrating the area beneath the peak, and dividing the result by the total area for all FAs.

Participants were enrolled and measurements taken at baseline (1992-1993) and at 2 subsequent exams (1994-1995 and 1999-2000). Type 2 diabetes was defined as fasting glucose levels ≥ 7.0mmol/L or with use of hypoglycemic medication.

Cardiovascular Health Study (CHS), USA[9-11]

The CHS is a population-based longitudinal study of risk factors for cardiovascular disease and stroke in adults 65 years of age or older, recruited at four field centers (Forsyth County, NC; Sacramento County, CA; Washington County, MD; Pittsburgh, PA). Overall, 5201 predominantly Caucasian individuals were recruited in 1989-1990 from random samples of Medicare eligibility lists, followed by an additional 687 African-Americans recruited in 1992-1993 (total n=5,888). Fatty acids were measured on samples collected in the third year of follow-up. Investigators of CHS can be found at http://www.chs-nhlbi.org.

Blood was drawn after a 12-hour fast and stored at -70ºC. Plasma phospholipid fatty acids were measured at the Fred Hutchinson Cancer Research Center (Seattle, WA) using stored blood samples from 1992-1993. Total lipids were extracted from plasma using the methods of Folch.[10]

A one dimensional thin-layer chromatography was used to separate phospholipids from neutral lipids. Phospholipids fraction was directly trans-esterified using the Lepage and Roy method to prepare fatty acid methyl esters, and individual fatty acid methyl esters were separated using gas chromatography (Agilent 5890 Gas Chromatograph flame ionization detector, Agilent Technologies, Palo Alto, CA; fused silica capillary column SP-2560 [100m x 0.25mm, 0.2μm], Supelco Belefonte, PA; initial 160 degrees Celsius for 16 min, ramp 3 degrees Celsius/min to 240 degrees Celsius, hold 15 minutes). For this analysis, levels of each individual fatty acid are expressed as a weight percentage of total phospholipid fatty acids analyzed. CVs were <3% for most fatty acids.

Participants were followed by means of annual study clinic examinations with interim phone contacts for 10 y and telephone contacts every 6 mo thereafter. Medication use was assessed annually. Fasting glucose was measured at the study baseline (1992–1993) and in 1996–1997, 1998–1999, and 2005–2006; nonfasting glucose was measured in 1994–1995. Type 2 diabetes was defined as a single measure of fasting glucose concentration ≥7.0mmol/L, nonfasting or 2-h postchallenge glucose concentration ≥11.1mmol/L, or new use of an insulin or oral hypoglycemic medication.

European Prospective Investigation into Cancer-InterAct Consortium, eight European countries[12,13]

The EPIC-InterAct consortium is a case-cohort study derived from 340,234 people with 3.99 million person-years of follow-up (1991-2007) in eight countries of the EPIC study (France, Italy, Spain, the United Kingdom, the Netherlands, Germany, Sweden, and Denmark). In total, 12,403 cases of type 2 diabetes were verified. From the European Prospective Investigations into Cancer and Nutrition cohort, 16,835 people with baseline plasma samples were randomly selected as a sub-cohort. After exclusions for prevalent diabetes and uncertain diabetes status, 16,154 individuals remained in the sub-cohort, including 778 with incident type 2 diabetes during follow-up. From this case-cohort of 27,779 participants, 27,296 adults were available for analysis (12,132 cases of type 2 diabetes and 15,919 sub-cohort participants including 755 incident cases of type 2 diabetes within the sub-cohort). When providing results to the FORCE Consortium, a single InterAct estimate was derived by conducting country-specific Prentice-weighted Cox proportional hazard analysis and pooling country-specific estimates by random-effects meta-analysis – a standard approach in InterAct.

Fatty acids were profiled at the Medical Research Council Human Nutrition Research (Cambridge, UK); profiling involved analysis of plasma samples stored at baseline at −196°C (or −150°C in Denmark). The assay methods were previously described and included hydrolysis and methylation to convert phospholipid fatty acids into more volatile fatty acid methyl esters and separation of the different fatty acids by gas chromatography (J&W HP-88, 30 m length, 0.25 mm internal diameter [Agilent Technologies, CA, USA]) equipped with flame ionisation detection (7890N GC [Agilent Technologies]). Samples from people with type 2 diabetes and subcohort participants were processed in random order by centre, and laboratory staff were masked to all participant characteristics by the use of anonymised aliquots. Thirty seven different fatty acids were identified with their retention times compared with those of commercial standards and expressed each level as percentage of total phospholipid fatty acids (mol%). Pentadecanoic acid (15:0) showed

coefficient of variation 11.9%; palmitic acid (16:0), 1.6%; heptadecanoic acid (17:0), 4.2%; stearic acid (18:0), 2.0%; arachidic acid (20:0), 15.3%; behenic acid (22:0), 10.3%; tricosanoic acid (23:0), 18.9%; and lignoceric acid (24:0), 14.7%. We used human and equine plasma (Sera Laboratories International, West Sussex, UK) for quality control.

Ascertainment of incident T2D involved a review of the existing EPIC datasets at each centre using multiple sources of evidence including self-report, linkage to primary-care registers, secondary-care registers, medication use (drug registers), hospital admissions and mortality data.

Finnish Diabetes Prevention Study (FDPS), Finland[14-16]

The Finnish DPS is a was a randomised study aimed at preventing type 2 diabetes through intensive lifestyle intervention, carried out at five study clinics in Finland. The randomised trial started in November 1993, the recruitment period lasted until June 1998 and the intervention period lasted until the end of 2001. The last follow-up data has been collected in 2009 with a follow-up over 13 years from baseline. Participants were recruited at five field centers (Kuopio, Helsinki, Tampere, Turku and Oulu). The cohort consists of 522 non-institutionalized men and women. Originally, subjects at baseline were all with impaired glucose tolerance defined by repeated oral glucose tolerance tests (OGTT) (mean value of 2-hour plasma glucose concentrations 7.8-11.0 mmol/l in two OGTTs). For the fatty acid measurements, only subjects who were non-diabetic by the revised WHO 1999 criteria at baseline and had stored serum samples available from the active study period (n=407). From these, three subjects have lost follow-up and do not have data on diabetes incidence after baseline. Therefore, a total of 396 adults free of type 2 diabetes at baseline with available data on circulating fatty acids and diabetes incidence were eligible for the current analysis.

The total serum fatty acid composition was measured by TETHYS Bioscience Inc. (Emeryville, CA) in 2010 as in [Takkunen et al. Longitudinal associations of serum fatty acid composition with type 2 diabetes risk and markers of insulin secretion and sensitivity in the Finnish Diabetes Prevention Study. Eur J Nutr 2016 55:967-79), using stored (-80 oC) serum samples taken during the active intervention period. The lipids from serum were extracted in the presence of authentic internal standards by the method of Folch et al. [Folch J, Lees M, Sloane Stanley GH (1957) A simple method for the isolation and purification of total lipides from animal tissues. J Biol Chem 226:497-509] using chloroform:methanol (2:1 v/v). The total lipid extract was trans esterified in 1% sulfuric acid in methanol in a sealed vial under a nitrogen atmosphere at 100°C for 45 min. The resulting extract was neutralized with 6% potassium carbonate and the fatty acid methyl esters were extracted with hexane. The isolated fatty acid methyl ester extract was then prepared for gas chromatography by sealing the hexane extracts under nitrogen. The fatty acid methyl esters were separated and quantified by capillary gas chromatography (Agilent Technologies model 6890) equipped with a 30 m DB 88MS capillary column (Agilent Technologies) and a flame ionization detector. Proportions of fatty acids are expressed as molar percentages (mol/mol of all fatty acids). The intra- and inter-assay CV% for individual fatty acids were ≤10% and ≤12%, respectively.

Genotypes of the studied SNPs were obtained by genotyping the Metabochip (Jääskeläinen et al., Genetic predisposition to obesity and lifestyle factors – the combined analyses of twenty-six known BMI- and fourteen known waist:hip ratio (WHR)-associated variants in the Finnish Diabetes Prevention Study. Br J Nutr (2013) 110:1856-1865), a custom Illumina iSelect array

which assays approximately 200 000 SNPs identified through genome-wide meta-analyses for metabolic and atherosclerotic/CVD and traits. 388 persons with FA data have given consent for DNA studies. From these, 352 subjects had DNA samples left for Metabochip analyses.

Diagnosis of diabetes was defined per the World Health Organization (WHO) 1985 criteria (plasma fasting glucose ≥7.8 or 2-h glucose ≥11.1). All diabetes diagnoses were ascertained by a repeated positive OGTT and confirmed by a physician.

Framingham Heart Study (FHS), USA[17-19]

FHS is a population based longitudinal study of families living in Framingham, Massachusetts. The offspring study was initiated in 1971 and consisted of a sample of 5,124 individuals, offspring of the original cohort and their spouses. Blood samples for fatty acid measurement and covariate data were collected during wave 8 of the study (2005-2008), and participants were followed till 2015.

The fatty acid composition of erythrocyte samples were analyzed by gas chromatography equipped with a SP 2560 capillary column after direct transesterification for 10 minutes in boron trifluoride/ methanol and hexane at 100 C as previously described.[18] This technique generates fatty acids primarily from erythrocyte glycerophospholipids. Erythrocytes were isolated from blood drawn after a 10–12 h fast and frozen at −80 °C immediately after collection. All fatty acids present at >1% abundance had CVs of ≤7%.

Genotyping was conducted using the Affymetrix 500K SNP chip, with imputation for markers with genotype call rates below 97% or small ($<1x10^{-6}$) HWE p-values using Mach and the CEU HapMap dataset for reference.

Incident diabetes was defined as fasting glucose concentration ≥ 7.0mmol/L, HBA1C ≥ 6.5 or new use of insulin or oral hypoglycemic medication ascertained during follow up examinations.

Health Professionals Follow-up Study (HPFS), USA[20,21]

The Health Professionals Follow-up Study (HPFS) started in 1986, with 51,529 male health professionals, who were 40 – 75 years of age at recruitment in 1986. Blood samples were collected from HPFS participants in 1994. For this study we utilized previously measured fatty acid concentrations in stored blood used for nested case-control studies of incident cardiovascular diseases. Subjects were free of cardiovascular diseases, cancer and diabetes at the time of blood sampling.

Blood samples were sent to the lab with an ice pack via overnight courier and the majority of the samples arrived within 24 hours. Upon arrival, samples were centrifuged and divided into aliquots for plasma, white blood cell, and red blood cells, and stored in liquid nitrogen freezers at ≤-130°C. Fatty acid concentrations were measured in stored total plasma and erythrocyte samples using gas-liquid chromatography. Concentrations of individual circulating fatty acids were expressed as a percentage of total fatty acids either in plasma or erythrocyte membranes Plasma intra-assay CVs

are as follows: EPA: 7%, DPA: 13%, DHA: 10%, ALA: 4%. The corresponding erythrocyte CVs are as follows: EPA: 12%, DPA: 13%, DHA: 14%, ALA: 12%.
Incident cases of diabetes are identified by self-reports on mail questionnaires and confirmed by supplementary information collected about the diagnosis using the following criteria from the National Diabetes Data Group (NDDG) up until 1998: (1) manifestation of classic symptoms such as excessive thirst, polyuria, weight loss and hunger, in conjunction with elevated fasting glucose ≥7.8mmol/L or non-fasting glucose levels ≥11.1mmol/L (2) asymptomatic but elevated plasma glucose in two separate occasions or abnormal glucose tolerance test results and (3) receiving any hypoglycemic treatment for diabetes. After 1998 a fasting glucose concentration ≥7.0mmol/L was adopted per the new diagnostic criteria of the American Diabetes Association (ADA). Medical records were obtained for a subset of the subjects diagnosed with diabetes to validate the information obtained by the supplemental questionnaire. This supplemental questionnaire has been validated as a confirmation tool for diabetes diagnosis with high reliability (>98% of cases confirmed for those who provided records).

Hisayama Study (Hisayama), Japan[22-24]

The Hisayama Study is an ongoing, population-based prospective cohort study of cardiovascular disease and its risk factors in the town of Hisayama, a suburb in the metropolitan in Japan. A total of 2172 residents who were aged 40-79 years older, completed 75g oral glucose tolerance test, were without diabetes at baseline, and had no missing values for serum fatty acid levels were enrolled in the present study.

Serum fatty acids levels were assayed by gas chromatography (SRL, Tokyo, Japan). Briefly, total lipids in plasma were extracted according to the Folch's procedure, followed by hydrolysis to free fatty acids. Free fatty acids were esterified with potassium methoxide/methanol and boron trifluorideemethanol. The methylated fatty acids were analyzed using GC-17A gas chromatograph (Shimadzu Corporation, Kyoto, Japan) with omegawax-250 capillary column (SUPELCO, SigmaeAldrich Japan, Tokyo, Japan). Reproducibility (i.e. the coefficient of variation) of the determination of serum EPA, DHA, and AA levels by this method was reported to be 4.4%, 2.3%, and 3.8%, respectively.

Genomic DNA was extracted from whole blood using a QIAmp DNA blood kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Extracted DNA was dissolved in 20 μL Tris-HCl buffer (10 mmol/L, pH 8.0) containing 1 mmol/L EDTA and was stored at -80°C until use. Genotyping was performed by using of either the multiplex polymerase chain reaction-based invader assay (Third Wave Technologies) 17 or TaqMan assay (Applied Biosystems) in a blinded manner to the clinical information of study subjects. The databases from the cohort of the Hisayama study has been scrutinized in order to identify subjects with information of genotype and phenotype regarding diabetic status. A total of 3,230 subjects who participated in the health examination in 2002 consented to a genomic research and were genotyped for tagging single nucleotide peptides (SNPs). Among them, 2,047 subjects were identified as genetically unrelated subjects by the analysis of Identity by State, and were performed genotype imputation using MINIMAC3. After excluding those aged ≥ 80 years, those who did not undergo 75g oral glucose tolerant test, those with diabetes mellitus at baseline, 1,432 were enrolled in the analysis.

New onset of T2DM was determined based on the OGTT data or the measurements of fasting or casual plasma glucose in the annual health examinations, plus the clinical information; namely, medical records and the use of antidiabetic medications. T2DM was defined as FPG ≥7.0 mmol/L, 2hPG or casual plasma glucose ≥11.1 mmol/L, and/or the use of antidiabetic medications (oral hypoglycemic agents, injectable glucagon-like peptide analogs, or insulin).

Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), Finland[25,26]

The KIHD study was designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in a population-based, randomly selected sample of men from eastern Finland. The baseline examinations were carried out in 1984-1989. A total of 2682 men who were 42, 48, 54 or 60 years old at baseline (82.9% of those eligible) were recruited in two cohorts. The first cohort consisted of 1166 men who were 54 years old, enrolled in 1984-1986, and the second cohort included 1516 men who were 42, 48, 54 or 60 years old, enrolled in 1986-1989. The baseline examinations were followed by the 4-year examination round (1991-1993) in which 1038 men from the second cohort (88% of the eligible) participated. At the 11-year examination round (1998-2001), all men from the second cohort were invited and 854 men (95% of the eligible) participated. These examinations were also the baseline for 920 postmenopausal women (78.4% of the 1173 eligible women) from the same area, aged 53-73 years. During the 20-year examination round, all eligible men from the first and second baseline cohorts and all women were invited to the study site. A total of 1241 men (80% of the eligible) and 634 women (81.0% of the eligible) participated.

Venous blood samples were collected between 8AM and 10AM after an overnight fast. Serum total fatty acids were determined from frozen samples with a NB-351 capillary column (HNU-Nordion, Helsinki, Finland) by a Hewlett-Packard 5890 Series II gas chromatograph (Hewlett-Packard Company, Avondale, Pa, USA, since 1999 Agilent Technologies Inc., USA) with a flame ionization detector. Serum was extracted with chloroform-methanol and fatty acids were methylated with methanol and sulphuric acid prior to gas chromatography. Each analyte had an individual reference standard and the analytes were quantified with an internal standard method using eicosane.

Type 2 diabetes was defined as a self-reported physician diagnosis and/or fasting plasma glucose ≥ 7.0mmol/L or 2-hour oral glucose tolerance test plasma glucose ≥ 11.1mmol/L at re-examination rounds 4, 11 and 20 years after the baseline, and by record linkage to the national hospital discharge registry, and to the Social Insurance Institution of Finland register for reimbursement of medicine expenses used for T2D for the entire study period until the end of the follow-up in Dec 31, 2010.

Melbourne Collaborative Cohort Study (MCCS), Australia[27,28]

MCCS is a prospective cohort study of 41,513 residents (17,044 men) of Melbourne, Australia aged between 27 and 75 years at baseline (99.3% were ages 40– 69 years). Italian and Greek migrants were deliberately recruited to extend the range of lifestyle exposures. Recruitment occurred between 1990 and 1994. Participants were recruited via the electoral rolls (registration to vote is compulsory for adults in Australia), advertisements, and community announcements in local media (e.g., television, radio, and newspapers). Comprehensive lists of Italian and Greek surnames also were used to target southern European migrants in the phone book and electoral

rolls. Blood was collected into sodium-heparin vacutainers from all subjects. After collection, blood was centrifuged immediately and plasma stored in liquid nitrogen at -120°C. Following an average of 9.0 (SD 1.2) years, samples for participants in the sub-cohort were defrosted at room temperature. Thawed samples were vortexed rapidly for a few seconds, then spun at 1000 rpm (210 x g) for 10 min at 4°C on a "Heraeus Megafuge 2.0R" bench top centrifuge. Samples were kept on ice until they were aliquotted. The aliquotted samples were also kept on ice. Liquid nitrogen was added to the tubes, which were sealed quickly, then frozen immediately at -80°C until shipment to the laboratory in cryoboxes. All samples were handled under red light conditions.

Biomarker fatty acids were measured in plasma collected at recruitment in a sub-group of around 6900 participants based on a random cohort of around 4000 people and cases of cancer, cardiovascular diseases and diabetes: the number of diabetes cases was 402 for the current study, informing a crude 4-year risk of 1.0% (402/41513). Total lipids were extracted from plasma with chloroform/methanol (2:1 by volume). Lipid extracts were separated by thin-layer chromatography (TLC) into phospholipids, triglyceride and cholesteryl esters classes on silica gel plates (Silica gel 60H Merck Darmstadt Germany). The TLC solvent system was petroleum spirit/diethyl ether/glacial acetic acid (180:30:2, by volume). Lipid classes were visualized with fluorescein 5-isothiocyanate against TLC standard 18-5 (NuChek Prep Inc: Elysian, MN) All solvents contained the anti-oxidant butylated hydroxyl anisole at 0.005% (wt/vol). Phospholipid fractions were transesterified by methanolysis (1% H2SO4 in methanol) for 3 h at 70°C. After cooling, the resulting FAME were extracted with n-heptane and transferred into gas chromatography vials containing anhydrous Na2SO4. FAME were separated and quantified with a Hewlett-Packard 5880 gas-liquid chromatograph using a capillary column equipped with fame ionization detection and Hewlett-Packard Chem-Station data system. Separation was achieved on a 50m×0.33mm ID BPX-70 column (SGE, Melbourne, Australia). Helium was the carrier gas at a column flow rate of 35 cm/s. The inlet split ratio was set at 30 to 35 cm/s. The oven temperature at injection was set at 140°C and programmed to rise to 200°C at 5°C/min. The injector and dejector temperatures were set to 250°C and 300°C, respectively. FAME were identified by comparison of retention times to authentic lipid standards (NuChek Prep Inc: Elysian, MN). The between batch coefficients of variation were between 1% and 12%.

Incident cases of diabetes were identified from a self-administered questionnaire mailed to participants about 4 years after baseline. Participants were asked: ''Has a doctor ever told you that you have had diabetes?'' and, if yes, for the year of diagnosis. For all self-reported incident cases, except those who reported a diagnosis date before baseline and who were excluded, confirmation of diagnosis was sought from physicians nominated by participants. Physicians were asked to specify if the participant had diabetes and, if so, to indicate whether it was type 1 or type 2.

Metabolic Syndrome in Men (METSIM), Finland[29,30]

The population-based METSIM study includes 10 197 Finnish men, aged from 45 to 73 y at the baseline study (2005-2010) and who were living in Kuopio or surrounding communities and were willing to participate in the study. Plasma FAs were measured in a random sample of 1364 men of the entire cohort.[29]

Lipids were extracted from plasma sample with chloroform–methanol (2:1) and lipid fractions

were separated using an aminopropyl column. Fatty acids in lipid fractions were transmethylated with 14% boron trifluoride in methanol. Finally, fatty acid methyl esters were analysed using a 7890A gas chromatograph (Agilent Technologies, Wilmington, DE, USA) equipped with a 25 m NEFA phase column (Agilent Technologies). Cholesteryl nonadecanoate (Nu-Chek Prep, Elysian, MA, USA), trinonadecanoin and dinonadecanoyl phosphatidylcholine (Larodan Fine Chemicals, Malmo, Sweden) served as internal standards.

Type 2 diabetes diagnosis was based on an oral glucose tolerance test (fasting plasma glucose ≥7.0mmol/L and/or 2 h plasma glucose ≥ 11.1mmol/L), or on HbA1c measurements (≥6.5 %) at the follow-up visit, or on the National Drug Reimbursement registry data (drug treatment started for diabetes during the follow-up).

Multiethnic Study of Atherosclerosis (MESA), USA[31-33]

MESA is a National Heart, Lung and Blood Institute-sponsored, population-based investigation of subclinical cardiovascular disease and its progression. A total of 6,814 individuals, aged 45 to 84 years, were recruited from six US communities (Baltimore City and County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St. Paul, MN) between July 2000 and August 2002. Participants were excluded if they had physician-diagnosed cardiovascular disease prior to enrollment, including angina, myocardial infarction, heart failure, stroke or TIA, resuscitated cardiac arrest or a cardiovascular intervention (e.g., CABG, angioplasty, valve replacement, or pacemaker/defibrillator placement). Pre-specified recruitment plans identified four racial/ethnic groups (White European-American, African-American, Hispanic-American, and Chinese-American) for enrollment, with targeted oversampling of minority groups to enhance statistical power. Investigators of MESA can be found at http://www.mesa-nhlbi.org.

Phospholipid fatty acids were extracted and measured at the University of Minnestoa (Minneapolis, MN). Plasma was diluted in saline and lipids were extracted from with a mixture of chloroform:methanol, and cholesterol, triglycerides and phospholipid subclasses were separated on a silica thin-layer chromatography plate in a solvent mixture of petroleum ether, diethyl ether, and glacial acetic acid. The band of phospholipids was harvested for the formation of methyl esters. FAME prepared with 14% boron trifluoride in methanol, incubated at 80ºC for 90 minutes, and extracted with petroleum ether. The final product was dissolved in heptane and injected onto a capillary Varian CP7420 100-m column with a Hewlett Packard 5890 gas chromatograph (GC) equipped with a HP6890A autosampler. The GC is configured for a single capillary column with a flame ionization detector and interfaced with HP chemstation software. Separation of individual fatty acids was obtained over an 80-minute run. Individual fatty acid values are expressed as percentage of total fatty acids. Inter-assay CVs were less than 10%.

Participants were followed by means of bi-annual study clinic examinations with yearly interim phone contacts for 10 y Fasting glucose was measured at the study baseline (2000-2002) and in 2002-2004,2004-2005, 2005-2007, and 2010–2011. Diabetes was defined as fasting plasma glucose ≥7.0mmol/L.

Nurses' Health Study (NHS), USA[20,21]

NHS was established in 1976 by recruiting 121,700 female nurses aged 30 to 55 who responded to a questionnaire with information related to their health, lifestyle practices and occurrence of

chronic diseases. Blood samples were collected from NHS participants in 1989-1990. For this study we utilized previously measured fatty acid concentrations in stored blood used for nested case-control studies of incident cardiovascular diseases. Subjects were free of cardiovascular diseases, cancer and diabetes at the time of blood sampling.

Blood samples were sent to the lab with an ice pack via overnight courier and the majority of the samples arrived within 24 hours. Upon arrival, samples were centrifuged and divided into aliquots for plasma, white blood cell, and red blood cells, and stored in liquid nitrogen freezers at ≤-130°C. Fatty acid concentrations were measured in stored total plasma and erythrocyte samples using gas-liquid chromatography. Concentrations of individual circulating fatty acids were expressed as a percentage of total fatty acids either in plasma or erythrocyte membranes. CVs were 10% for linoleic acid and arachidonic acid for erythrocyte membrane, 7% for linoleic in plasma, and 10% for arachidonic acid in plasma. Plasma intra-assay CVs are as follows: EPA: 7%, DPA: 6%, DHA: 3%, ALA: 3%. The corresponding erythrocyte CVs are as follows: EPA: 12%, DPA: 5%, DHA: 7%, ALA: 11%.

Incident cases of T2D are identified by self-reports on the mail questionnaires and confirmed by supplementary information collected about the diagnosis using the following criteria from the National Diabetes Data Group (NDDG) up until 1998: (1) manifestation of classic symptoms such as excessive thirst, polyuria, weight loss and hunger, in conjunction with elevated fasting glucose ≥7.8mmol/L or non-fasting glucose levels ≥11.1mmol/L (2) asymptomatic but elevated plasma glucose in two separate occasions or abnormal glucose tolerance test results and (3) receiving any hypoglycemic treatment for diabetes. After 1998 a fasting glucose concentration ≥7.0mmol/L was adopted per the new diagnostic criteria of the American Diabetes Association (ADA). Medical records were obtained for a subset of the subjects diagnosed with diabetes to validate the information obtained by the supplemental questionnaire. This supplemental questionnaire has been validated as a confirmation tool for diabetes diagnosis with high reliability (>98% of cases confirmed for those who provided records).

Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS), Sweden[34-36]

PIVUS was initiated in 2001 as a research collaboration between the Department of Medicine and the University Hospital in Uppsala with the primary aim to evaluate the usefulness of different measurements of endothelial function and other techniques to evaluate vascular function. In June 2004 the last subject was included in the cohort resulting in 1016 subjects aged 70 being randomly selected from the general population in the town of Uppsala. Several secondary aims have also been added to this prospective cohort study and several academic groups have been engaged in the evaluation of this cohort from different aspects.

Fatty acid composition in cholesterol esters and phospholipids were measured by gas chromatography. Serum (0.5 mL) was mixed with 2.5 mL methanol, 5 mL chloroform (with 0.005% added butylated hydroxytoluene, BHT) and 7.5 mL NaH2PO4 (0.2 mol/l) and stored in 4°C over night for lipid extraction. The chloroform phase was then removed with a syringe and evaporated to dryness on a 30°C heating block using nitrogen gas. The lipid residue was dissolved in chloroform and the lipid fractions were separated by thin-layer chromatography (TLC); the adsorbent containing POPOP as fluorescent agent. The TLC-plates were eluted at room

temperature with the solvent system petroleum ether/diethyl ether/acetic acid (81:18:1 by volume). The lipid fractions were visualized in UV light and the spots containing cholesterol esters and phospholipids were scraped off into vials and methylated at 60°C overnight after addition of 2 mL H2SO4 (5%) in methanol. The fatty acid methyl esters were extracted into 3 mL petroleum ether (0.005% BHT) after addition of 1.5 mL distilled water. The phases were separated after thorough mixing and centrifugation at 1500g for 10 minutes. The petroleum ether phase was pipetted off and the solvent was evaporated under nitrogen gas on a 30°C heating block. The fatty acid methyl esters were dissolved in 120 µL hexane and placed in vials. The fatty acid methyl esters were separated by gas-liquid chromatography on a 30-m glass capillary column coated with Thermo TR-FAME (Thermo Electron Corporation, USA) with helium gas as a carrier gas. An Agilent Technologies system consisting of model GLC 6890N, autosampler 7683 and Agilent ChemStation was used. The temperature was programmed to 150-260° C. The fatty acids were identified by comparing each peak´s retention time with fatty acid methyl ester standards Nu Check Prep (Elysian, MN, USA). Fatty acids are presented as the percent of total fatty acids analyzed in each compartment.

Diabetes incidence during follow-up was identified by medical records, repeated blood sampling and self-reports at follow-ups after 5 and 10 years. Type 2 diabetes was defined using one of four criteria: a) fasting blood glucose ≥ 6.1 mmol/L (corresponds to fasting plasma glucose ≥ 7.0 mmol/L), b) self-reported diabetes, c) diabetes diagnosis reported in medical records, d) use of insulin or oral hypoglycemic agents.

Three City Study (3C), France[37,38]

3C study is an ongoing multicenter prospective cohort study of vascular risk factors for dementia which started in 1999-2000 and included 9,294 community dwellers in three French cities: Bordeaux (n=2,104), Dijon (n=4,931) and Montpellier (n=2,259). Individuals living in one of these cities, aged 65 years and over and not institutionalized were eligible for recruitment into the 3C study. The protocol of the 3C study has been approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research of the Kremlin-Bicêtre University Hospital (Paris). All participants gave their written informed consent. The baseline data collection included socio-demographic and lifestyle characteristics, symptoms and complaints, main chronic conditions, medication use, neuropsychological testing, clinical examination including blood pressure measurement, electrocardiogram (ECG) and blood sampling. Four follow-up examinations were performed at 2, 4, 7, and 10 years after baseline. The present study is based on the 12 years of follow-up. Fatty acid composition of red blood cell membrane phospholipids were measured at baseline from fasting blood samples among 670 individuals from the Bordeaux and Montpellier centers.

Erythrocyte membrane phospholipid fatty acids were measured at the French Institute for fats and oils (ITERG). Total lipids from red blood cell membranes were extracted by using the method of Peuchant et al.[33] A one dimensional thin-layer chromatography was used to separate total phospholipids of red blood cells from neutral lipids. Total fatty acids of the red blood cell phospholipid fraction were methylated according to the procedure of Morrison and Smith,[39] to obtain fatty acid methyl esters. Individual fatty acid methyl esters were separated using a gas chromatograph (Focus GC, Thermo Scientific, France) equipped with a flam ionization detector and a split injector. A fused silica capillary column (BPX 70, 60m x 0.25mm internal diameter,

0.25mm film; Phenomenex, Germany) was used with H2 as the carrier gas (inlet pressure: 1 bar). The column temperature was programmed to increase from 150 to 200°C at 1.5°C/min for 25 min, and then from 200 to 225°C at 20°C/min and was held at 225°C until the completion of the analysis (20 min). The injection port and detector were maintained at 250 and 280°C, respectively. Data were integrated using the ChromQuest Software (Thermo Scientific). Individual fatty acid methyl esters were identified by comparing their retention times with those of authentic standards eluted in the same conditions (Sigma Chemical Co., Saint Quentin Fallavier, France). The results are expressed as a weight percentage of total fatty acids. The laboratory CV's were 0.5% for linoleic acid and 0.8% for arachidonic acid.

Participants were followed up at 2, 4,7,10,12 years post baseline. Type 2 diabetes was self - reported or defined by use of insulin or oral hypoglycemic medication.

Uppsala Longitudinal Study of Adult Men (ULSAM), Sweden[35,36,40]

ULSAM is a community-based cohort of men living in Uppsala county, Sweden. The origin of this longitudinal study was the "Uppsala Primary Preventive Study", carried out between September 1970 and September 1973. The study comprised all men living in the County of Uppsala born between 1920 and 1924 selected from the register of County Council. All men (n=2841) were invited for the investigation, 81.7% (n=2322) participated. The mean age at this baseline examination was 49.6 (SD +/- 0.6), hence this starting cohort was referred to as ULSAM-50. After this baseline examination, all men were invited to participate in follow-up investigations at the ages 70, 82 and 88. Between the age 50 and 70, 422 had died and 219 had moved out of the Uppsala region. Of the 1681 men invited, 460 did not participate in this follow up, leaving 1221 men who participated (response rate of 73%) aged around 70. The men were invited by a letter, which also explained the aim of the examination. They received the letter 7-10 days prior to the examination. Those born at the beginning of the year were called first. Six individuals were called every weekday except for the vacation period in Sweden between June 25 and August 15. A second invitation letter was sent at the end of the examination of each age class to those who had not come after the first invitation. The screening examination program included a medical questionnaire and interview, blood and urine sampling, blood pressure and anthropometric measurements, intravenous glucose tolerance test, ECG recording, chest X-ray and pure tone audiometry. At the baseline exam, fatty acid composition was assessed in serum cholesterol, whereas at the second exam 20 years later, fatty acids were measured in both cholesterol esters and adipose tissue. Dodecapenta and dodecahepta acids were measured only in adipose tissue lipids.

Adipose tissue fatty acid composition was initially analyzed in a random subsample of 318 men. In December 2008, 535 new samples were analyzed for adipose tissue fatty acid composition. Subcutaneous adipose tissue was collected with biopsy as described by Hirsch et al.[35] and Beynen et al.[36]. The subject lay face down and the biopsy was taken with a needle coupled to a vacuum tube from the upper, outer quadrant of the buttocks. The sample was collected in the connector between the needle and the tube, and stored at -70°C in the connector for some weeks until analysis. Prior to the fatty acid analysis the biopsy was weighed and homogenized. The fatty acid compositions of the subcutaneous adipose tissue were analyzed as described in detail by Carlson[37] and Boberg et al.[38]. An extraction with chloroform in the presence of methanol, butylated hydroxytoluene, and NaH2PO4 was conducted over night, and evaporated under nitrogen. The dry

extracts were dissolved in a few drops of chloroform and applicated on thin liquid chromatography plates for separation of the lipids in a solvent system consisting of petroleum ether:diethyl ether:acetic acid (81:18:1, by volume) (Boberg 1966). The lipid fractions were visualized in UV light and scraped off separately. The lipid esters were trans methylated in warm, acidic environment overnight. The methylesters were extracted with petroleum ether and deionized water, and the solvent was evaporated under nitrogen. The fatty acid methyl esters were dissolved in hexane and separated by gas-liquid chromatography (GLC). The Hewlett Packard GLC system used for the analyses was consisted a GC 5890, automatic sampler 7671A, integrator 3392A, and 25 m Quadrex Fused Silica capillary column OV-351, with helium as the carrying gas. The temperature program used during the separation of the fatty acid methyl esters was 130-220°C. The fatty acids were identified by comparison of the retention times of separation was controlled by Nu Check Prep GLC reference standard GLC-68A.

Incident diabetes during follow-up was identified using the Swedish Hospital Discharge and Cause of Death registers and supplemented with ULSAM clinical assessments that occurred at throughout follow-up. All participants were followed regarding incidence of diabetes until December 31, 2011. Using registry data, diabetes was identified according to International Classification of Disease 9th (ICD-9) and 10th revision (ICD-10), codes 250 and E10-E14, respectively. Diabetes prevalence at baseline and subsequent ULSAM clinical assessments were determined as fasting blood glucose ≥6.1 mmol/L (corresponds to fasting plasma glucose ≥ 7.0 mmol/L) or fasting plasma glucose ≥7.0 mmol/L, or the use of glucose-lowering medication.

Women's Health Initiatives Memory Study (WHI), USA[41-43]

WHI was established to examine the effects of postmenopausal hormone therapy on cognitive function in women aged 65-80 years. Recruitment began in June 1995. Of 3200 eligible women free of probable dementia enrolled in the WHI, 2947 (92.1%) were enrolled in WHIMS. Diabetes status was last assessed in August 2009. Investigators of WHIMS can be found at http://www.whi.org/researchers/.

The fatty acid composition of RBC samples were analyzed by gas chromatography equipped with a SP 2560 capillary column after direct transesterification for 10 minutes in boron trifluoride/ methanol and hexane at 100 C as previously described. This technique generates fatty acids primarily from RBC glycerophospholipids. During the aliquoting phase, the RBC samples were stored improperly at -20°C for a period of approximately 2 weeks, causing oxidative degeneration of the PUFAs before measurement. The original FA levels were estimated with multiple imputations using independent data on fatty acid degradation and length of time the samples were exposed to -20°C.[41] All fatty acids present at >1% abundance had CVs of ≤6.5%. Genotyping was conducted using the Human Omni Express Exome-8v1_B, with imputation using the 1000 genomes reference panel.

Incident diabetes was defined as a positive answer to the question (asked annually) regarding "newly prescribed treatment for diabetes with pills or insulin shots." The date of diabetes onset was assigned as the midpoint between the dates between the survey when diabetes was self-reported and the previous survey.

SNPs and corresponding weights for the genetic risk score (GRS)

SNP_Effect Allele	Gene	Weight
rs340874_T	PROX1	wt1=0.1222
rs7578597_C	THADA	wt2= 0.0677
rs2943641_T	IRS1	wt3= 0.1398
rs780094_T	GCKR	wt4= 0.174
rs7593730_T	RBMS1	wt5= 0.077
rs4607103_T	ADAMTS9	wt6= 0.0583
rs1801282_G	PPARG	wt7= 0.1044
rs11708067_G	ADCY5	wt8= 0.0862
rs10010131_A	WFS1	wt9= 0.131
rs864745_C	JAZF1	wt10= 0.131
rs972283_A	KLF14	wt11=0.1133
rs2191349_G	DGKB	wt12=0.1044
rs13266634_T	SLC30A8	wt13= 0.077
rs10811661_C	CDKN2AB	wt14= 0.131
rs13292136_T	CHCHD9	wt15=0.0953
rs1111875_T	HHEX	wt16=0.0677
rs231362_A	KCNQ1	wt17=0.0677
rs1552224_C	CENTD2	wt18=0.0583
rs7957197_A	HNF1A	wt19=0.1398
rs11634397_A	ZFAND6	wt20=0.0583
rs10923931_T	NOTCH2	wt21=0.1823
rs243021_A	BCL11A	wt22=0.1044
rs4402960_T	IGF2BP2	wt23=0.1044
rs4457053_G	ZBED3	wt24=0.3148
rs10946398_C	CDKAL1	wt25=0.1398
rs4607517_A	GCK	wt26= 0.131
rs896854_T	TP53INP1	wt27= 0.077
rs12779790_G	CDC123	wt28= 0.131
rs7901695_C	TCF7L2	wt29=0.0862
rs5215_C	KCNJ11	wt30=0.0862
rs10830963_G	MTNR1B	wt31=0.0953
rs7961581_C	TSPAN8	wt32=0.0677
rs1531343_C	HMGA2	wt33=0.0583
rs8042680_A	PRC1	wt34=0.0677
rs4430796_A	HNF1B	wt35=0.0953

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Supplementary Table 1. Distribution of categorical covariates at baseline

Study	Race/ethnicity	Education	Occupation	Smoking	Treated or self-reported hypertension	Treated or self-reported hypercholesterolemia	Prevalent coronary heart disease	Fish oil use
AGES-R	White (100%)	<High school (21.8%), High school graduate (50.2%), College or higher (28.0%)	Clerical (64.3%), Other (35.7%)	Never (44.5%), Former (43.5%), Current (12.0%)	78.4%	-	23.9%	69.4%
AOC	White (98.33%), Black (0.39%), Asian (1.16%), Other (0.13%)	<High school (17.46%), High school graduate (68.55%), College or higher (13.22%)	-	Never (17.97%), Former (66.50%), Current (15.40%)	95.76%	96.02%	100%	0.0%
ARIC	White (88.66%), Black (11.34%)	<High school (16.62), High school graduate (41.7), College or higher (41.67)	Homemaking, not working outside the home (11.7%), Employed at a job for pay, either full or part-time (65.72%), Employed, but temporarily away from my regular job (0.89%), Unemployed, looking for work (0.82%), Unemployed, not looking for work (1.25%), Retired from my usual occupation and not working (14.39%), Retired from my usual occupation but working for pay (5.22%)	Never (31.53%), Former (30.49%), Current (37.98%)	24.69%	-	3.75%	-
CCCC	East Asian (100%)	<High school (95.6%), High school graduate (4.4%)	Clerical (10.5%), Labor (34.4%), Others (55.1%)	Never (55.7%), Former (6.3%), Current (38.0%)	33.75%	30.73%	2.0%	-
CHS	White (88.26%), Non-White (11.74%)	<High school (25.28%), High school graduate (27.58%), Some college (23.42%), College or higher (23.72%)	Professional/Technical/Managerial/Administrative (37.27%), Sales/Clerical Services (15.07%), Craftsman/Machine Operator/Laborer (13.64%), Farming/Forestry (1.66%), Housewife (22.63%), Others (9.72%)	Never (46.26%), Former (44.19%), Current (9.55%)	40.07%	6.29%	20.65%	3.97%
EPIC-InterAct	White (100%)	None (7.66%), Primary school completed (33.15%), Technical/profess school (23.18%), Secondary school (15.38%), Longer edu levels (coll) (20.62%)	-	Never (46.91%), Former (27.17%), Current (25.93%)	18.8%	-	17.0%	-

FDPS	White (100%)	<High school (37.4%), High school graduate (51.5%), College or higher (11.1%)	-	Never (59.8%), Former (31.3%), Current (8.9%)	71.0%	4.8%	3.3%	-
FHS	White (100%)	<High school (2.6%), High school graduate (45.2%), College or higher (51.7%)	Clerical (3.9%), Others (94.7%)	Never (90.6%), Current (9.1%)	40.4%	37.0%	8.0%	-
Hisayama	East Asian (100%)	-	-	Never (62.89%), Former (15.65%), Current (21.45%)	18.6	8.10%	3.0%	-
HPFS	White (93.88%), Black (0.13%), Asian (0.60%), Other (5.38%)	College or higher (100%)	Health professionals (100%)	Never (43.09%), Former (48.60%), Current (8.31%)	25.17%	27.25%	0.0%	3.9%
KIHD	White (100%)	<High school (52.5%), High school graduate (39.4%), College or higher (8.1%)	Clerical (47.6%), Others (52.4%)	Never (45.0%), Former (29.2%), Current (25.8%)	60.7%	54.0%	24.2%	0.1%
MCCS	White (100%)	<High school (53.8%), High school graduate (21.7%), College or higher (24.5%)	-	Never (57.5%),Former (31.3%),Current (11.2%)	21.4%	23.0%	4.9%	4.5%
MESA	White (30.35%), Chinese (24.00%), African American (21.90%), Hispanic (23.75%)	<High school (36.52%), High school graduate (22.47%), College or higher (41.01%)	Employed (53.59%), Others (46.41%)	Never (54.02%), Former (32.17%), Current (13.81%)	42.50%	36.40%	0.0%	-
METSIM	White (100%)	-	-	Never (43.9%), Former (38.0%), Current (18.1%)	12.5%	13.7%	0.2%	-
NHS	White (99.24%), Black (0.35%), Asian (0.35%), Other (0.07%)	College or higher (100%)	Health professionals (100%)	Never (42.02%), Former (39.46%), Current (18.52%)	22.77%	35.71%	0.0%	2.0%
PIVUS	White (100%)	<High school (55%), High school graduate (18%), College or higher (26%)	-	Neve (49%), Former (40%), Current (11%)	27.2%	13.7%	7.3%	-
3C	White (100%)	<High school (60.10%), High school graduate (22.09%), College or higher (17.82%)	Executives and intellectual profession (13.14%), Intermediate occupations (23.97%), Military, employee (18.23%), Housewives, workers (44.66%)	Never (65.11%), Former (29.97%), Current (4.93%)	77.83%	56.16%	9.28%	-
ULSAM-50	White (100%)	<High school (63%), High school graduate (26%), College or higher (10%)	Clerical (44%), Others (56%)	Never (25%), Former (23%), Current (51%)	3.90%	15.43%	0.32%	-

ULSAM-70	White (100%)	<High school (56%), High school graduate (31%), College or higher (13%)	Clerical (7%). Others (93%)	Never (30%), Former (49%), Current (20%)	31.7%	8.4%	7.3%	-
WHIMS	White (88.36%), Black (6.09%), Hispanic (2.06%), Asian (1.73%), Other (1.76%)	<High school (6.98%), High school graduate (22.37%), Some college/voc school (40.06%), College or higher (30.58%)	Manager (34.83%), Homemaker (12.19%), Technician (29.75%), Service/Laborer (8.75%), Missing/Other (14.48%)	Never (54.23%), Former (38.62%), Current (7.15%)	28.49%	17.0%	16.14%	-

AGES-R: Age, Gene/Environment Susceptibility Study (Reykjavik); AOC: Alpha Omega Cohort; ARIC: Atherosclerosis Risk in Communities; CCCC: Chin-Shan Community Cardiovascular Cohort Study; CHS: Cardiovascular Health Study; EPIC-InterAct: European Prospective Investigation into Cancer and Nutrition InterAct Consortium (France, Italy, Spain, UK, Netherlands, Germany, Sweden, and Denmark); FDPS: Finnish Diabetes Prevention Study; FHS: Framingham Heart Study; Hisayama: Hisayama Study; HPFS: Health Professionals Follow-up Study; KIHD: Kuopio Ischaemic Heart Disease Risk Factor Study; MCCS: Melbourne Collaborative Cohort Study; MESA: Multi-Ethnic Study of Atherosclerosis; METSIM: Metabolic Syndrome in Men Study; NHS: Nurses' Health Study; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; 3C: Three City Study; ULSAM-50: Uppsala Longitudinal Study of Adult Men-50; ULSAM-70: Uppsala Longitudinal Study of Adult Men-70; WHIMS: Women's Health Initiative Memory Study

Supplementary Table 2. Summary statistics of continuous covariates at baseline

Study	Alcohol intake, mean (SD)	Physical activity, mean (SD)	Waist circumference, mean (SD)	Triglycerides, mean (SD)	Fish/seafood consumption, mean (SD)
AGES-R	0.16 ± 0.36 servings/d	Never (18.7%), Rarely (16.2%), Occasionally (28.3%), Moderate (25.8%), High (11.1%)	99.5 ± 11.6 cm	101 ± 50.1 mg/dL	3.36 ± 1.39 servings/d
AOC	13.1 ± 14.8 g/d	38.2 ± 43.8 MET-hrs/wk	101.4 ± 10.3 cm	156 ± 84 mg/dL	16.7 ± 18.8 g/d
ARIC	1.54 ± 0.9 servings/d	2.55 ± 0.82 kcals/wk	94.3 ± 12.5 cm	128.1 ± 80.6 mg/dL	0.33 ± 0.33 servings/d
CCCC	Regular intake: 32.3%	Regular exercise: 17.24%	83.2 ± 10.1 cm	119.47 ± 81.73 mg/dL	-
CHS	2.75 ± 6.47 servings/d	1090.39 ± 1492.14 kcal/wk	95.72 ± 12.78 cm	136.91 ± 76.75 mg/dL	0.24 ± 0.20 servings/d
EPIC-InterAct	0.82 ± 1.15 servings/d	inactive (23.85%), moderately inactive (33.52%), moderately active (22.58 %), active (20.05%)	86.3 ± 12.7 cm	-	37.8 ± 33.6 g/d
FDPS	6.2 ± 13.6 g/d	7.3 ± 6.11 hours/wk	100.6 ± 11 cm	149.4 ± 63.1 mg/dL	42.6 ± 56.3 g/d
FHS	0.68 ± 1.00 servings/d	296.54 ± 41.5 kcals/wk	99.52 ± 13.76 cm	111.83 ± 61.03 mg/dL	1.97 ± 1.83 g/d
Hisayama	0.90 servings/d	Regular physical activity: 33.98%	81.54 cm	113.82 mg/dL	86.53 g/d
HPFS	11.82 ± 15.86 g/d	36.28 ± 38.89 MET-hrs/wk	36.36 ± 10.21 in	113.71 ± 109.56 mg/dL	0.27 ± 0.26 servings/d
KIHD	59.7 ± 116.3 ml/d	151.7 ± 184.4 kcals/d	89.8 ± 10.5 cm	1.27 ± 0.72 mmol/L	43.6 ± 51.5 g/d
MCCS	11.7 ± 18.6 g/d	Physical activity score: 0 (21.2%), >0 & <4 (20.5%), >=4 & <6 (34.5%), >=6 (23.8%)	85.3 ± 12.6 cm	110.3 ± 63.5 mg/dL	0.3 ± 0.3 servings/d
MESA	4.47 ± 10.03 g/d	5786.22 ± 6042.49 METs/wk	95.77 ± 13.99 cm	131.62 ± 80.90 mg/dL	0.32 ± 0.37 servings/d
METSIM	14.29 ± 16.85 g/d	-	95.9 ± 9.7 cm	119.6 ± 73.21 mg/dL	-
NHS	5.44 ± 10.10 g/d	15.76 ± 18.03 MET-hrs/wk	25.72 ± 12.50 in	130.31 ± 84.49 mg/dL	0.30 ± 0.30 servings/d
PIVUS	6.80 ± 7.88 g/d	258.71 ± 4.85 METs/wk	90.31 ± 11.25 cm	1.25 ± 0.56 mmol/L	43.8 ± 31.4 g/d
3C	13.54 ± 15.64 g/d	Regularly engage in moderate physical activity: 28.08%	90.70 ± 11.86 cm	1.22 ± 0.57 mmol/L	2.83 ± 1.71 g/d
ULSAM-50	-	Sedentary (14%), Moderate (35%), Regular (41%), Athletic (5%)	87.56 ± 8.62 cm	1.88 ± 1.00 mmol/L	-
ULSAM-70	6.48 ± 7.08 g/d	Sedentary (2%), Moderate (31%), Regular (54%), Athletic (6%)	94.24 ± 9.05 cm	1.40 ± 0.69 mmol/L	28.6 ± 21.6 g/d
WHIMS	0.52 ± 0.87 servings/d	2.52 ± 1.13 METs/wk	87.39 ± 12.82 cm	138.19 ± 74.28 mg/dL	Long-chain omega-3s: 1.37 ± 0.8 g/d

AGES-R: Age, Gene/Environment Susceptibility Study (Reykjavik); AOC: Alpha Omega Cohort; ARIC: Atherosclerosis Risk in Communities; CCCC: Chin-Shan Community Cardiovascular Cohort Study; CHS: Cardiovascular Health Study; EPIC-InterAct: European Prospective Investigation into Cancer and Nutrition InterAct Consortium (France, Italy, Spain, UK, Netherlands, Germany, Sweden, and Denmark); FDPS: Finnish Diabetes Prevention Study; FHS: Framingham Heart Study; Hisayama: Hisayama Study; HPFS: Health Professionals Follow-up Study; KIHD: Kuopio Ischaemic Heart Disease Risk Factor Study; MCCS: Melbourne Collaborative Cohort Study; MESA: Multi-Ethnic Study of Atherosclerosis; METSIM: Metabolic Syndrome in Men Study; NHS: Nurses' Health Study; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; 3C: Three City Study; ULSAM-50: Uppsala Longitudinal Study of Adult Men-50; ULSAM-70: Uppsala Longitudinal Study of Adult Men-70; WHIMS: Women's Health Initiative Memory Study

Supplementary Table 3. Pearson correlations between omega-3 fatty acids

Study	Number of participants	Biomarker compartment	Pearson correlation coefficients between select fatty acids									
			ALA and EPA	ALA and DPA	ALA and DHA	ALA and Sum	EPA and DPA	EPA and DHA	EPA and Sum	DPA and DHA	DPA and Sum	DHA and Sum
AGES-R	753	Plasma phospholipids	0.01	0.05	-0.14	-0.06	0.43	0.76	0.94	0.54	0.56	0.94
AOC	779	Plasma phospholipids	0.08	0.05	-0.13	-0.05	0.39	0.64	0.85	0.28	0.45	0.94
ARIC	3273	Plasma phospholipids	0.16	-0.002	-0.09	-0.03	0.39	0.41	0.67	0.16	0.39	0.94
CCCC	1443	Total plasma	0.26	-	0.17	0.22	-	0.46	0.70	-	-	0.96
CHS	3077	Plasma phospholipids	0.16	0.06	-0.002	0.06	0.44	0.54	0.76	0.22	0.43	0.95
EPIC-InterAct	27296	Plasma phospholipids	0.02	0.0002	-0.07	-0.04	0.42	0.58	0.83	0.42	0.55	0.93
FDPS	396	Total serum	-0.01	0.04	0.03	0.02	0.72	0.84	0.95	0.63	0.74	0.96
FHS	1872	Erythrocyte phospholipids	0.14	0.06	-0.01	0.40	0.62	0.66	0.83	0.40	0.65	0.94
Hisayama	2172	Total serum	-0.09	0.05	-0.01	-0.05	0.67	0.77	0.94	0.82	0.82	0.95
HPFS	1491	Total plasma	0.16	0.14	0.10	0.13	0.64	0.67	0.83	0.53	0.69	0.95
HPFS	1491	Erythrocyte phospholipids	0.19	0.00	0.04	0.06	0.56	0.71	0.8	0.44	0.66	0.96
KIHD	3389	Total serum	-0.13	0.21	-0.05	-0.07	0.43	0.73	0.93	0.52	0.57	0.92
MCCS	4034	Plasma phospholipids	0.28	0.10	-0.12	0.02	0.35	0.42	0.73	0.02	0.30	0.91
MESA	2099	Plasma phospholipids	0.09	0.11	-0.02	0.03	0.49	0.61	0.84	0.42	0.57	0.94
METSIM	1302	Plasma phospholipids	-0.06	-0.09	-0.20	-0.15	0.48	0.65	0.89	0.40	0.54	0.92
METSIM	1302	Erythrocyte phospholipids	-0.005	0.08	-0.18	-0.10	0.43	0.68	0.87	0.24	0.51	0.92
METSIM	1302	Cholesterol esters	-0.02	-	-0.12	-0.04	-	0.73	0.99	-	-	0.83
METSIM	1302	Triglycerides	0.16	0.28	0.15	0.17	0.80	0.90	0.95	0.79	0.85	0.99
NHS	1446	Total plasma	0.14	0.18	0.09	0.13	0.60	0.53	0.75	0.47	0.67	0.93
NHS	1446	Erythrocyte phospholipids	0.35	0.23	0.19	0.24	0.63	0.60	0.74	0.51	0.73	0.95
PIVUS	872	Plasma phospholipids	-0.15	-0.16	-0.25	-0.23	0.39	0.63	0.88	0.45	0.55	0.91
PIVUS	872	Cholesterol esters	-0.04	-	-0.17	-0.07	-	0.68	0.99	-	-	0.79
3C	1218	Total plasma	0.11	0.09	0.15	0.16	0.27	0.54	0.82	0.37	0.49	0.91
ULSAM-50	1899	Cholesterol ester	0.11	-	-0.08	0.07	-	0.60	0.98	-	-	0.76
ULSAM-70	738	Adipose tissue	-0.07	0.05	0.07	0.04	0.45	0.65	0.75	0.79	0.88	0.96
WHIMS	5668	Erythrocyte phospholipids	0.07	0.05	-0.04	-0.00002	0.37	0.52	0.70	0.26	0.51	0.94

AGES-R: Age, Gene/Environment Susceptibility Study (Reykjavik); AOC: Alpha Omega Cohort; ARIC: Atherosclerosis Risk in Communities; CCCC: Chin-Shan Community Cardiovascular Cohort Study; CHS: Cardiovascular Health Study; EPIC-InterAct: European Prospective Investigation into Cancer and Nutrition InterAct Consortium (France, Italy, Spain, UK, Netherlands, Germany, Sweden, and Denmark); FDPS: Finnish Diabetes Prevention Study; FHS: Framingham Heart Study; Hisayama: Hisayama Study; HPFS: Health Professionals Follow-up Study; KIHD: Kuopio Ischaemic Heart Disease Risk Factor Study; MCCS: Melbourne Collaborative Cohort Study; MESA: Multi-Ethnic Study of Atherosclerosis; METSIM: Metabolic Syndrome in Men Study; NHS: Nurses' Health Study; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; 3C: Three City Study; ULSAM-50: Uppsala Longitudinal Study of Adult Men-50; ULSAM-70: Uppsala Longitudinal Study of Adult Men-70; WHIMS: Women's Health Initiative Memory Study

Supplementary Table 4. Sensitivity analysis of omega-3 fatty acid biomarkers and T2D

	ALA	EPA	DPA	DHA	EPA + DPA + DHA
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Overall estimate	**0.97 (0.92, 1.02)**	**0.92 (0.87, 0.96)**	**0.79 (0.73, 0.85)**	**0.82 (0.76, 0.89)**	**0.81 (0.75, 0.88)**
Exclude diabetes cases diagnosed in the first two years of follow-up	0.98 (0.93, 1.03)	0.90 (0.86, 0.95)	0.79 (0.73, 0.85)	0.81 (0.74, 0.88)	0.80 (0.74, 0.87)
Restrict to the first six years of follow-up	1.01 (0.93, 1.09)	0.89 (0.83, 0.95)	0.73 (0.65, 0.82)	0.82 (0.74, 0.92)	0.79 (0.71, 0.88)
Excluding EPIC-InterAct	1.01 (0.95, 1.08)	0.94 (0.89, 1.00)	0.85 (0.77, 0.93)	0.86 (0.78, 0.93)	0.85 (0.78, 0.92)

ALA: alpha linolenic acid; DHA: docosahexaneoic acid; DPA: docosapentaenoic acid; EPA: eicosapentaenoic acid

Notes:

[1] Multiple lipid fractions were available for some studies, but only one lipid fraction was used for the overall analysis.

[2] Effect estimates were pooled using inverse-variance weighted fixed-effect meta-analysis.

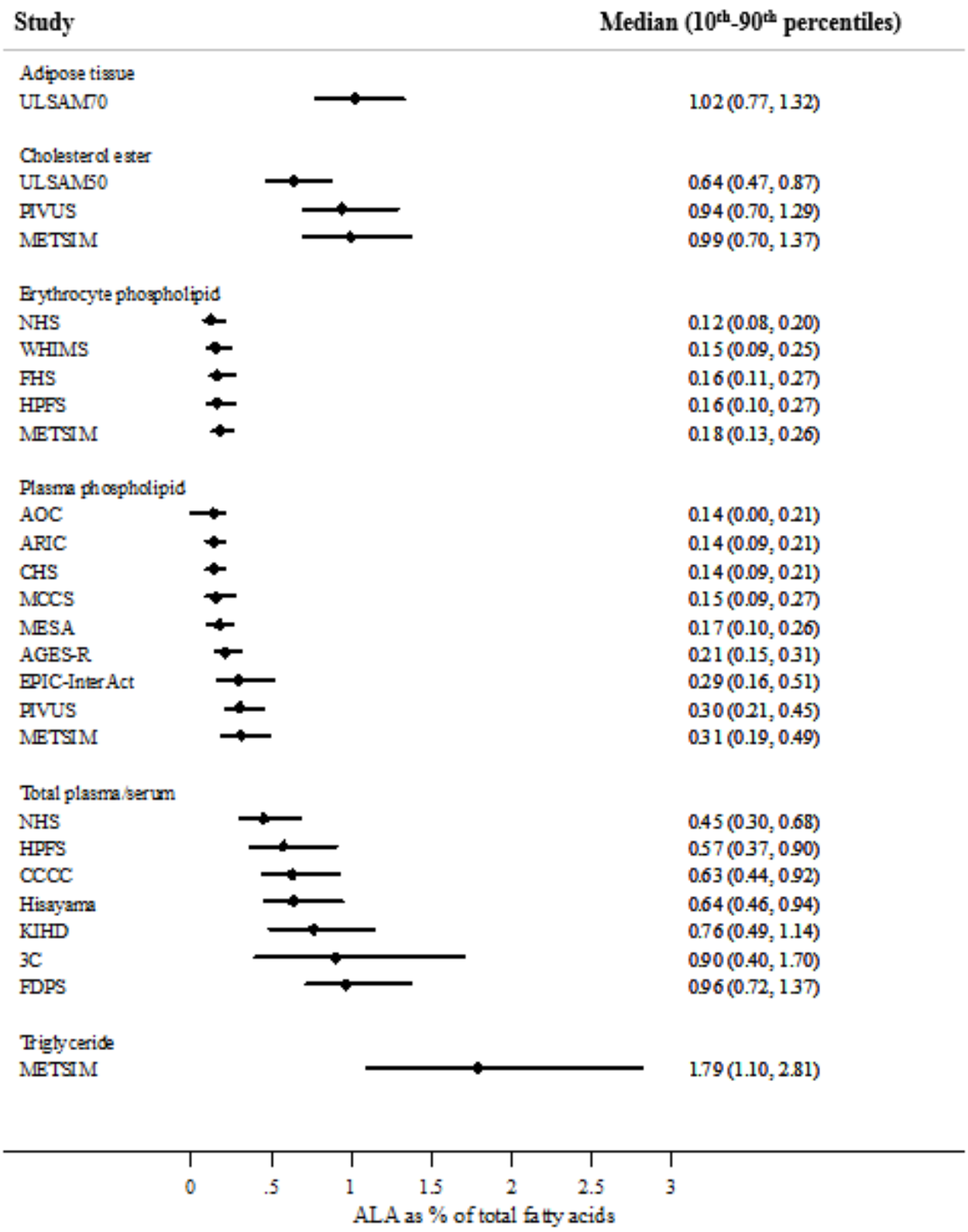
Supplementary Table 5. Interaction between omega-3 fatty acid biomarkers and a 35-SNP weighted genetic risk score for type 2 diabetes

	ALA	EPA	DPA	DHA	EPA + DPA + DHA
	RR (95% CI)[1,2]	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	0.87 (0.66, 1.14)	0.86 (0.68, 1.09)	0.74 (0.57, 0.94)	0.86 (0.65, 1.14)	0.88 (0.66, 1.17)
Q3	0.92 (0.70, 1.21)	0.76 (0.57, 1.01)	0.79 (0.62, 1.01)	0.88 (0.66, 1.19)	0.75 (0.56, 1.00)
Q4	0.92 (0.699, 1.22)	0.70 (0.53, 0.92)	0.75 (0.57, 0.98)	0.71 (0.52, 0.97)	0.71 (0.53, 0.96)
Q5	0.88 (0.68, 1.15)	0.80 (0.62, 1.03)	0.75 (0.57, 0.98)	0.81 (0.60, 1.08)	0.79 (0.60, 1.05)
$P_{interaction}$	0.98	0.72	0.98	0.76	0.76

ALA: alpha linolenic acid; DHA: docosahexaneoic acid; DPA: docosapentaenoic acid; EPA: eicosapentaenoic acid

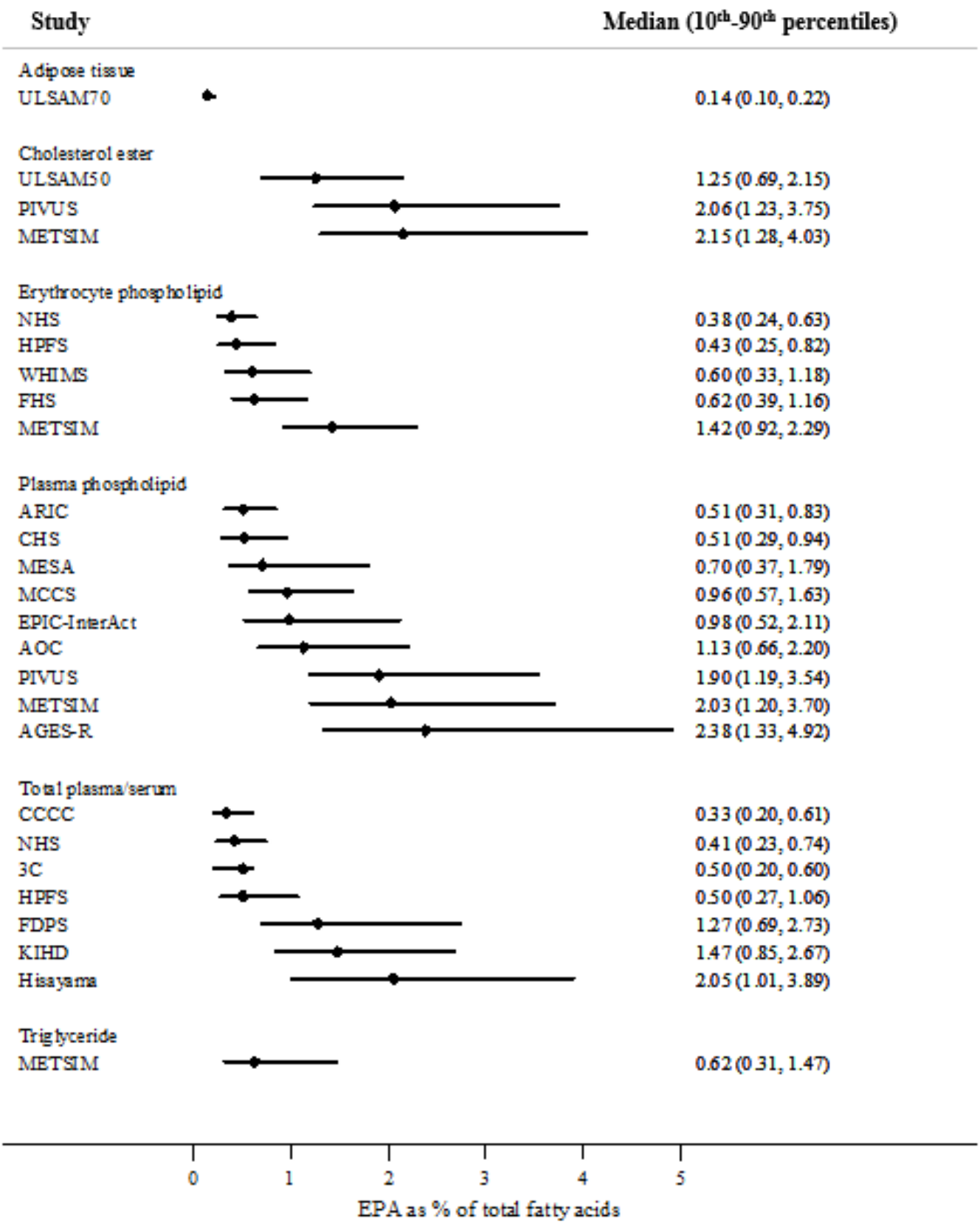
Notes:

[1] Association per 1-standardard deviation increment in a 35-SNP weighted genetic risk score

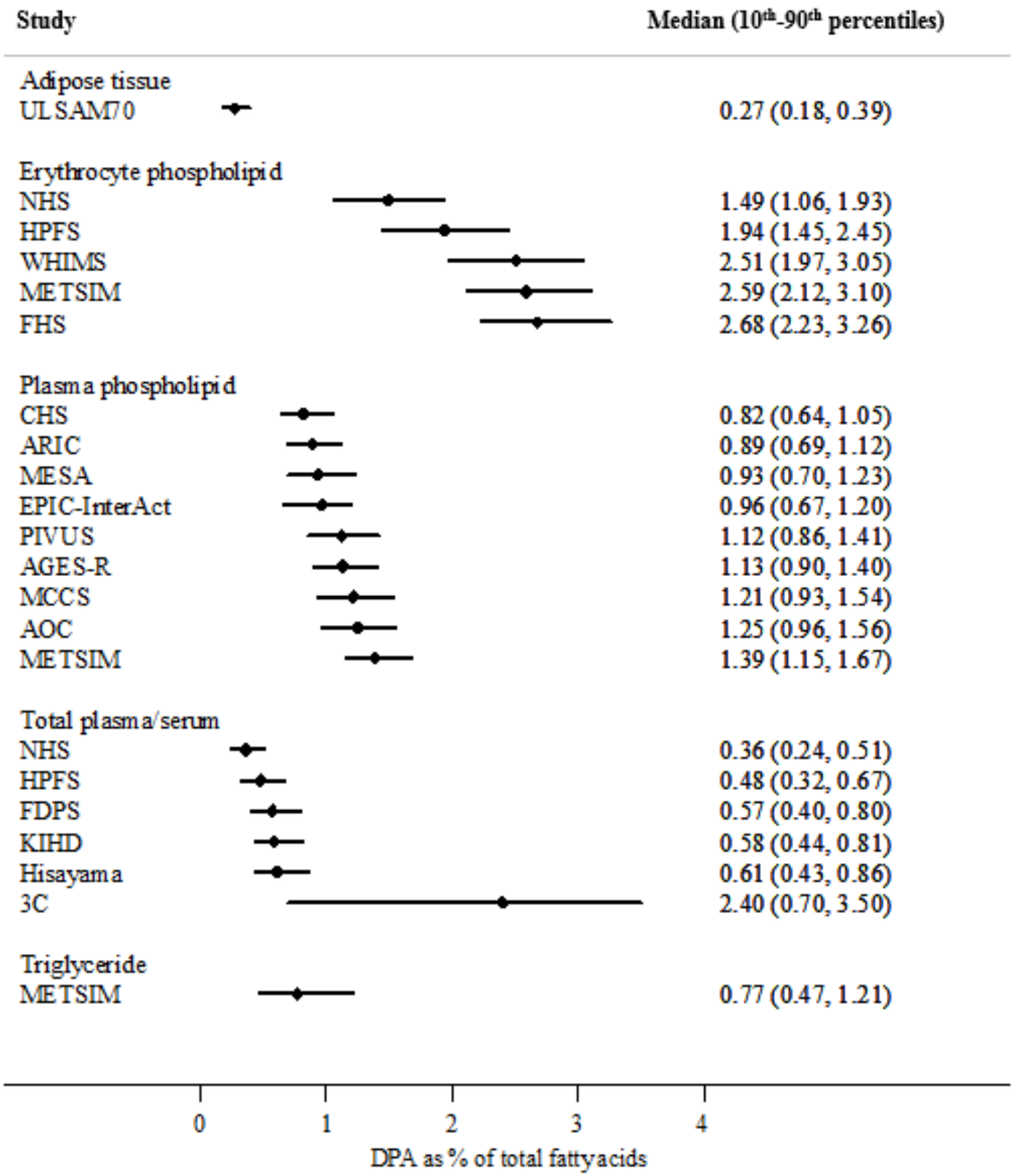


Supplementary Figure 1.

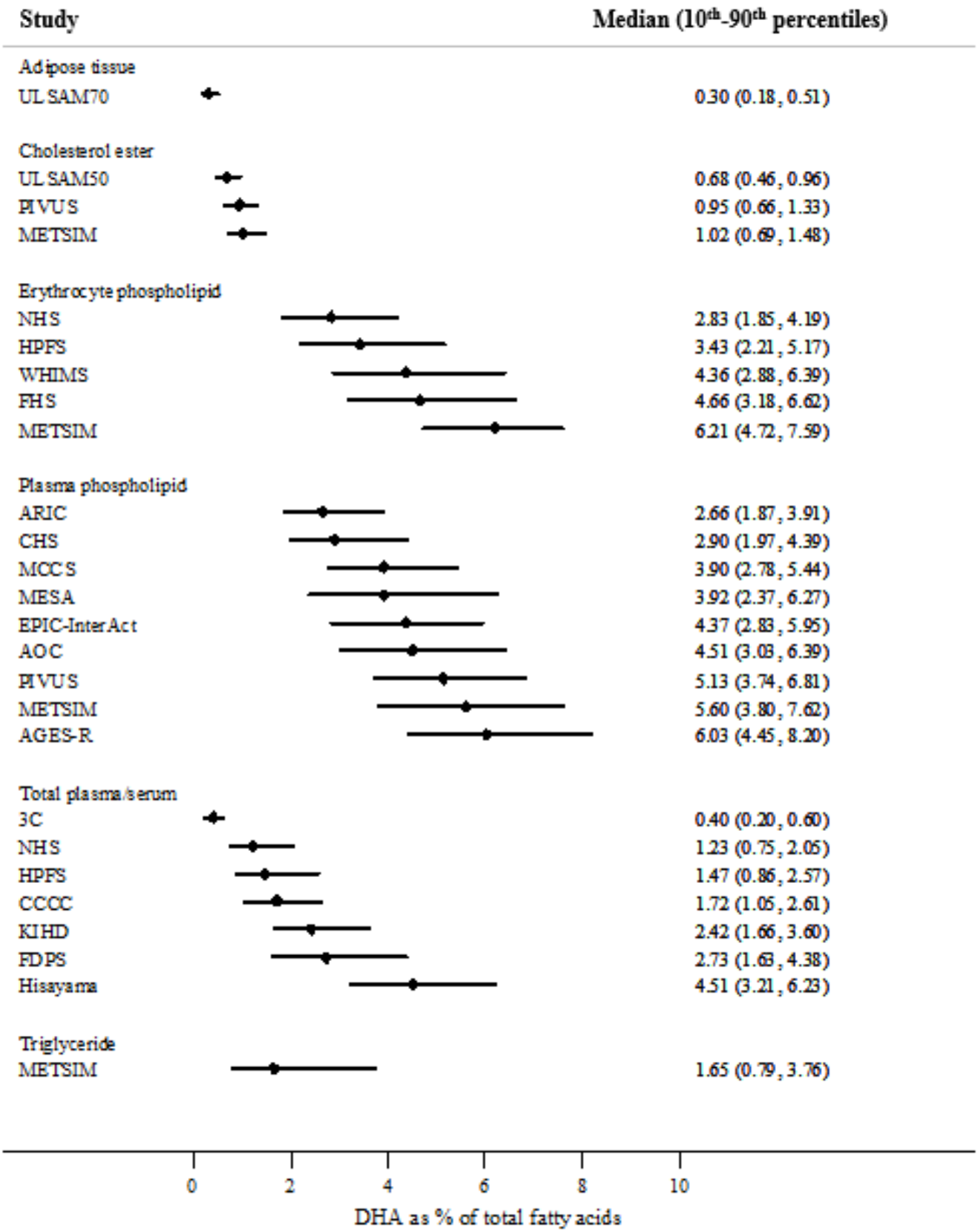
(A) Relative concentration of ALA in different lipid fractions for all 20 participating cohorts. Values in the graph represent median (point) and 10^{th}-90^{th} percentile ranges.



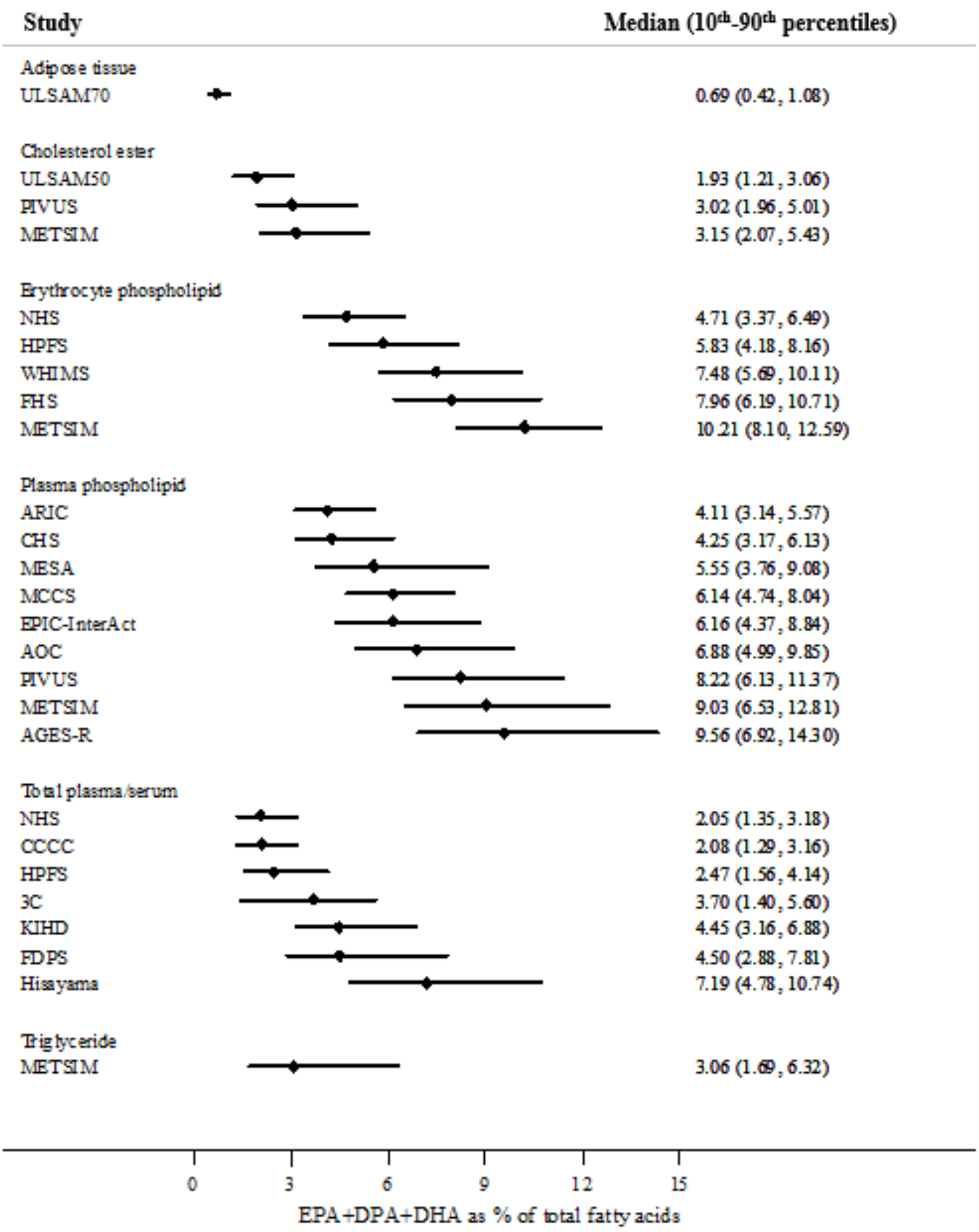
(B) Relative concentration of EPA in different lipid fractions for all 20 participating cohorts. Values in the graph represent median (point) and 10^{th}-90^{th} percentile ranges.



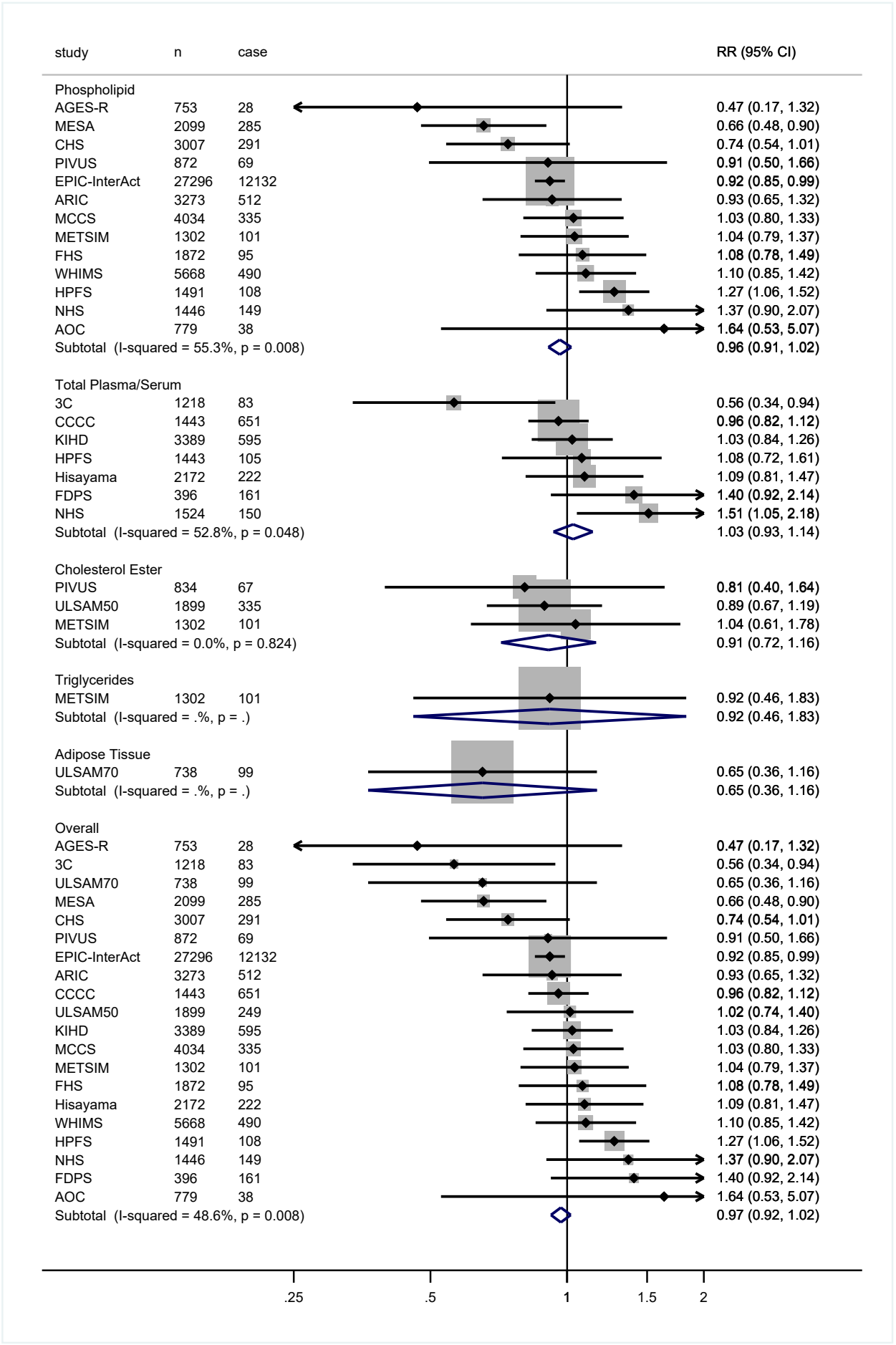
(C) Relative concentration of DPA in different lipid fractions for all 20 participating cohorts. Values in the graph represent median (point) and 10^{th}-90^{th} percentile ranges.



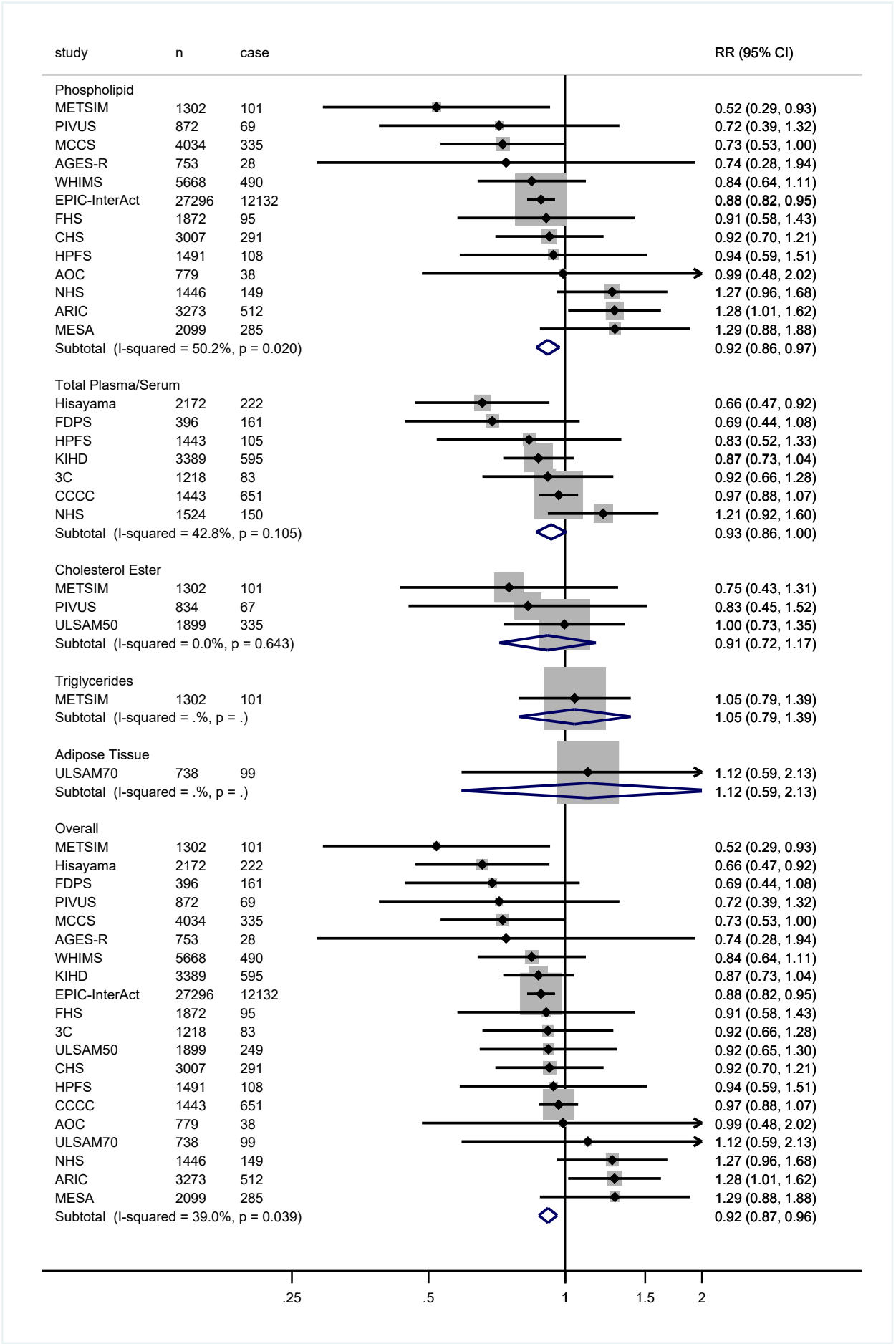
(D) Relative concentration of DHA in different lipid fractions for all 20 participating cohorts. Values in the graph represent median (point) and 10^{th}-90^{th} percentile ranges.



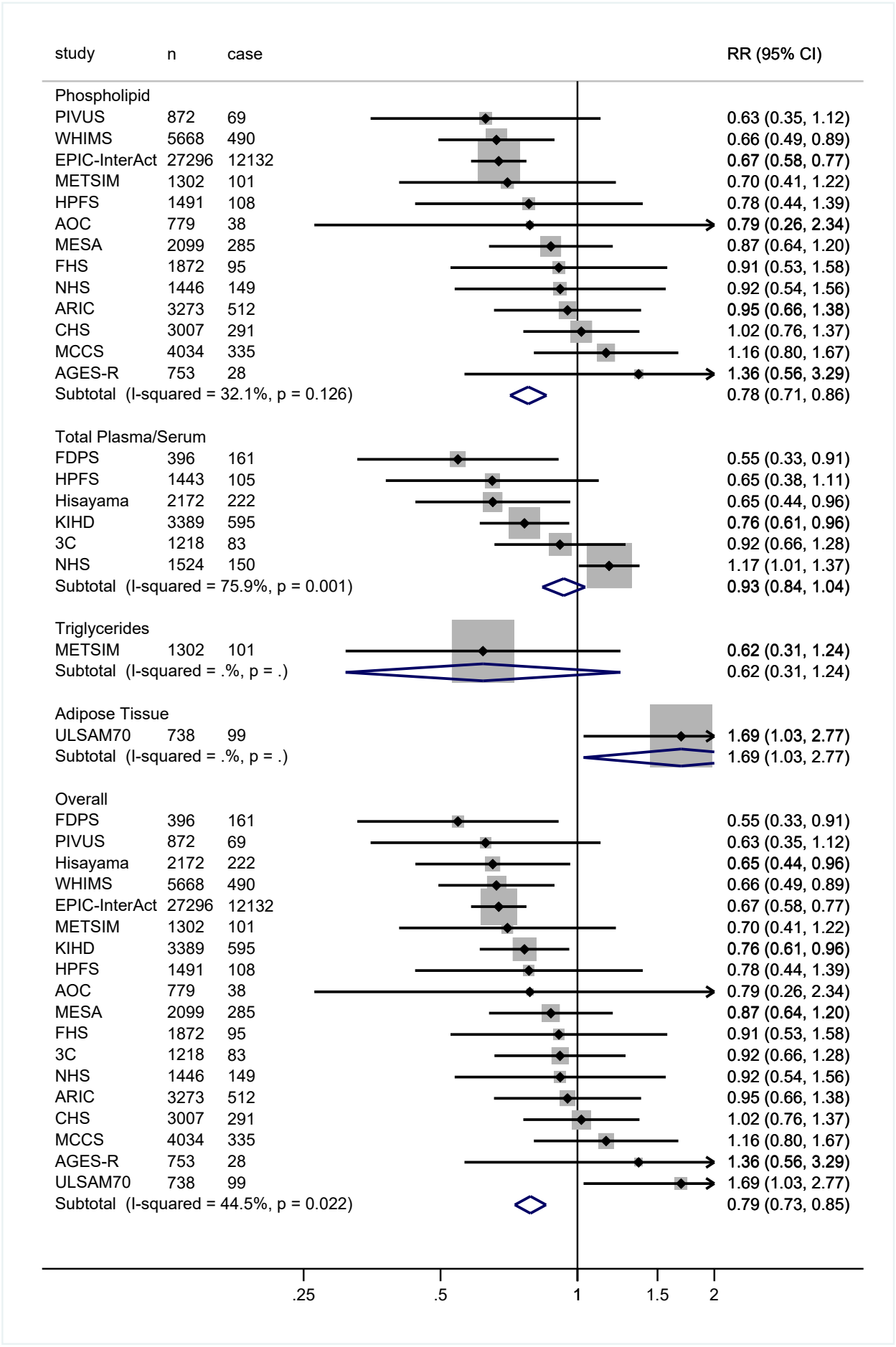
(E) Relative concentration of EPA + DPA + DHA in different lipid fractions for all 20 participating cohorts. Values in the graph represent median (point) and 10th-90th percentile ranges.


study
n
case
RR (95% CI)
Phospholipid
AGES-R 753 28 0.47 (0.17, 1.32)
MESA 2099 285 0.66 (0.48, 0.90)
CHS 3007 291 0.74 (0.54, 1.01)
PIVUS 872 69 0.91 (0.50, 1.66)
EPIC-InterAct 27296 12132 0.92 (0.85, 0.99)
ARIC 3273 512 0.93 (0.65, 1.32)
MCCS 4034 335 1.03 (0.80, 1.33)
METSIM 1302 101 1.04 (0.79, 1.37)
FHS 1872 95 1.08 (0.78, 1.49)
WHIMS 5668 490 1.10 (0.85, 1.42)
HPFS 1491 108 1.27 (1.06, 1.52)
NHS 1446 149 1.37 (0.90, 2.07)
AOC 779 38 1.64 (0.53, 5.07)
Subtotal (I-squared = 55.3%, p = 0.008) 0.96 (0.91, 1.02)
Total Plasma/Serum
3C 1218 83 0.56 (0.34, 0.94)
CCCC 1443 651 0.96 (0.82, 1.12)
KIHD 3389 595 1.03 (0.84, 1.26)
HPFS 1443 105 1.08 (0.72, 1.61)
Hisayama 2172 222 1.09 (0.81, 1.47)
FDPS 396 161 1.40 (0.92, 2.14)
NHS 1524 150 1.51 (1.05, 2.18)
Subtotal (I-squared = 52.8%, p = 0.048) 1.03 (0.93, 1.14)
Cholesterol Ester
PIVUS 834 67 0.81 (0.40, 1.64)
ULSAM50 1899 335 0.89 (0.67, 1.19)
METSIM 1302 101 1.04 (0.61, 1.78)
Subtotal (I-squared = 0.0%, p = 0.824) 0.91 (0.72, 1.16)
Triglycerides
METSIM 1302 101 0.92 (0.46, 1.83)
Subtotal (I-squared = .%, p = .) 0.92 (0.46, 1.83)
Adipose Tissue
ULSAM70 738 99 0.65 (0.36, 1.16)
Subtotal (I-squared = .%, p = .) 0.65 (0.36, 1.16)
Overall
AGES-R 753 28 0.47 (0.17, 1.32)
3C 1218 83 0.56 (0.34, 0.94)
ULSAM70 738 99 0.65 (0.36, 1.16)
MESA 2099 285 0.66 (0.48, 0.90)
CHS 3007 291 0.74 (0.54, 1.01)
PIVUS 872 69 0.91 (0.50, 1.66)
EPIC-InterAct 27296 12132 0.92 (0.85, 0.99)
ARIC 3273 512 0.93 (0.65, 1.32)
CCCC 1443 651 0.96 (0.82, 1.12)
ULSAM50 1899 249 1.02 (0.74, 1.40)
KIHD 3389 595 1.03 (0.84, 1.26)
MCCS 4034 335 1.03 (0.80, 1.33)
METSIM 1302 101 1.04 (0.79, 1.37)
FHS 1872 95 1.08 (0.78, 1.49)
Hisayama 2172 222 1.09 (0.81, 1.47)
WHIMS 5668 490 1.10 (0.85, 1.42)
HPFS 1491 108 1.27 (1.06, 1.52)
NHS 1446 149 1.37 (0.90, 2.07)
FDPS 396 161 1.40 (0.92, 2.14)
AOC 779 38 1.64 (0.53, 5.07)
Subtotal (I-squared = 48.6%, p = 0.008) 0.97 (0.92, 1.02)
.25
.5
1
1.5
2

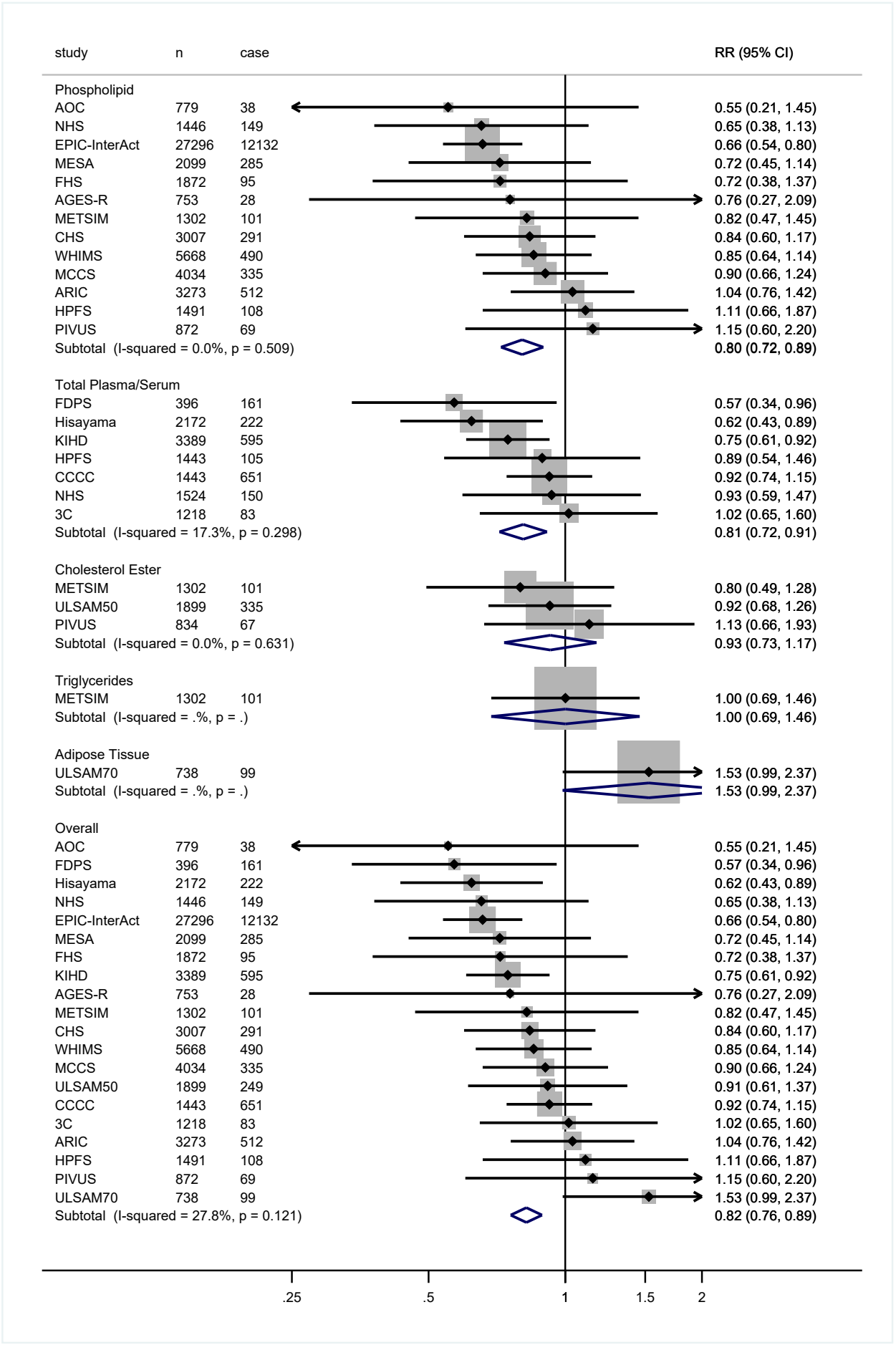
Supplementary Figure 2A. Pooled relative risks of type 2 diabetes according to interquintile range (difference between 90th and 10th percentiles) of alpha linolenic acid (ALA) biomarker. The association between ALA and type 2 diabetes was assessed in multivariable models for each cohort, and the results were pooled using inverse-variance weighted fixed effects meta-analysis. In each cohort, multivariate RR was assessed adjusting for sex, age, field site (if appropriate), race, socioeconomic status (education, occupation), smoking status, physical activity, alcohol consumption, treatment for hypertension, treatment for hypercholesterolemia, prevalent coronary heart disease, body mass index, waist circumference, and biomarkers of linoleic acid (18:2n-6) and trans fatty acids (total *t*-18:1 and *t*-18:2). If multiple biomarkers were available for a study, only one was used for the overall analysis based on the best ability to reflect long-term dietary intake (in the following order of preference): adipose tissue, erythrocyte phospholipids, plasma phospholipids, total plasma/serum, cholesterol esters, and triglycerides.


study
n
case
RR (95% CI)
Phospholipid
METSIM 1302 101 0.52 (0.29, 0.93)
PIVUS 872 69 0.72 (0.39, 1.32)
MCCS 4034 335 0.73 (0.53, 1.00)
AGES-R 753 28 0.74 (0.28, 1.94)
WHIMS 5668 490 0.84 (0.64, 1.11)
EPIC-InterAct 27296 12132 0.88 (0.82, 0.95)
FHS 1872 95 0.91 (0.58, 1.43)
CHS 3007 291 0.92 (0.70, 1.21)
HPFS 1491 108 0.94 (0.59, 1.51)
AOC 779 38 0.99 (0.48, 2.02)
NHS 1446 149 1.27 (0.96, 1.68)
ARIC 3273 512 1.28 (1.01, 1.62)
MESA 2099 285 1.29 (0.88, 1.88)
Subtotal (I-squared = 50.2%, p = 0.020) 0.92 (0.86, 0.97)
Total Plasma/Serum
Hisayama 2172 222 0.66 (0.47, 0.92)
FDPS 396 161 0.69 (0.44, 1.08)
HPFS 1443 105 0.83 (0.52, 1.33)
KIHD 3389 595 0.87 (0.73, 1.04)
3C 1218 83 0.92 (0.66, 1.28)
CCCC 1443 651 0.97 (0.88, 1.07)
NHS 1524 150 1.21 (0.92, 1.60)
Subtotal (I-squared = 42.8%, p = 0.105) 0.93 (0.86, 1.00)
Cholesterol Ester
METSIM 1302 101 0.75 (0.43, 1.31)
PIVUS 834 67 0.83 (0.45, 1.52)
ULSAM50 1899 335 1.00 (0.73, 1.35)
Subtotal (I-squared = 0.0%, p = 0.643) 0.91 (0.72, 1.17)
Triglycerides
METSIM 1302 101 1.05 (0.79, 1.39)
Subtotal (I-squared = .%, p = .) 1.05 (0.79, 1.39)
Adipose Tissue
ULSAM70 738 99 1.12 (0.59, 2.13)
Subtotal (I-squared = .%, p = .) 1.12 (0.59, 2.13)
Overall
METSIM 1302 101 0.52 (0.29, 0.93)
Hisayama 2172 222 0.66 (0.47, 0.92)
FDPS 396 161 0.69 (0.44, 1.08)
PIVUS 872 69 0.72 (0.39, 1.32)
MCCS 4034 335 0.73 (0.53, 1.00)
AGES-R 753 28 0.74 (0.28, 1.94)
WHIMS 5668 490 0.84 (0.64, 1.11)
KIHD 3389 595 0.87 (0.73, 1.04)
EPIC-InterAct 27296 12132 0.88 (0.82, 0.95)
FHS 1872 95 0.91 (0.58, 1.43)
3C 1218 83 0.92 (0.66, 1.28)
ULSAM50 1899 249 0.92 (0.65, 1.30)
CHS 3007 291 0.92 (0.70, 1.21)
HPFS 1491 108 0.94 (0.59, 1.51)
CCCC 1443 651 0.97 (0.88, 1.07)
AOC 779 38 0.99 (0.48, 2.02)
ULSAM70 738 99 1.12 (0.59, 2.13)
NHS 1446 149 1.27 (0.96, 1.68)
ARIC 3273 512 1.28 (1.01, 1.62)
MESA 2099 285 1.29 (0.88, 1.88)
Subtotal (I-squared = 39.0%, p = 0.039) 0.92 (0.87, 0.96)
.25
.5
1
1.5
2

Supplementary Figure 2B. Pooled relative risks of type 2 diabetes according to interquintile range (difference between 90th and 10th percentiles) of eicosapentaenoic acid (EPA) biomarker. The association between EPA and type 2 diabetes was assessed in multivariable models for each cohort, and the results were pooled using inverse-variance weighted fixed effects meta-analysis. In each cohort, multivariate RR was assessed adjusting for sex, age, field site (if appropriate), race, socioeconomic status (education, occupation), smoking status, physical activity, alcohol consumption, treatment for hypertension, treatment for hypercholesterolemia, prevalent coronary heart disease, body mass index, waist circumference, and biomarkers of linoleic acid (18:2n-6) and trans fatty acids (total *t*-18:1 and *t*-18:2). If multiple biomarkers were available for a study, only one was used for the overall analysis based on the best ability to reflect long-term dietary intake (in the following order of preference): adipose tissue, erythrocyte phospholipids, plasma phospholipids, total plasma/serum, cholesterol esters, and triglycerides.


study
n
case
RR (95% CI)
Phospholipid
PIVUS 872 69 0.63 (0.35, 1.12)
WHIMS 5668 490 0.66 (0.49, 0.89)
EPIC-InterAct 27296 12132 0.67 (0.58, 0.77)
METSIM 1302 101 0.70 (0.41, 1.22)
HPFS 1491 108 0.78 (0.44, 1.39)
AOC 779 38 0.79 (0.26, 2.34)
MESA 2099 285 0.87 (0.64, 1.20)
FHS 1872 95 0.91 (0.53, 1.58)
NHS 1446 149 0.92 (0.54, 1.56)
ARIC 3273 512 0.95 (0.66, 1.38)
CHS 3007 291 1.02 (0.76, 1.37)
MCCS 4034 335 1.16 (0.80, 1.67)
AGES-R 753 28 1.36 (0.56, 3.29)
Subtotal (I-squared = 32.1%, p = 0.126) 0.78 (0.71, 0.86)
Total Plasma/Serum
FDPS 396 161 0.55 (0.33, 0.91)
HPFS 1443 105 0.65 (0.38, 1.11)
Hisayama 2172 222 0.65 (0.44, 0.96)
KIHD 3389 595 0.76 (0.61, 0.96)
3C 1218 83 0.92 (0.66, 1.28)
NHS 1524 150 1.17 (1.01, 1.37)
Subtotal (I-squared = 75.9%, p = 0.001) 0.93 (0.84, 1.04)
Triglycerides
METSIM 1302 101 0.62 (0.31, 1.24)
Subtotal (I-squared = .%, p = .) 0.62 (0.31, 1.24)
Adipose Tissue
ULSAM70 738 99 1.69 (1.03, 2.77)
Subtotal (I-squared = .%, p = .) 1.69 (1.03, 2.77)
Overall
FDPS 396 161 0.55 (0.33, 0.91)
PIVUS 872 69 0.63 (0.35, 1.12)
Hisayama 2172 222 0.65 (0.44, 0.96)
WHIMS 5668 490 0.66 (0.49, 0.89)
EPIC-InterAct 27296 12132 0.67 (0.58, 0.77)
METSIM 1302 101 0.70 (0.41, 1.22)
KIHD 3389 595 0.76 (0.61, 0.96)
HPFS 1491 108 0.78 (0.44, 1.39)
AOC 779 38 0.79 (0.26, 2.34)
MESA 2099 285 0.87 (0.64, 1.20)
FHS 1872 95 0.91 (0.53, 1.58)
3C 1218 83 0.92 (0.66, 1.28)
NHS 1446 149 0.92 (0.54, 1.56)
ARIC 3273 512 0.95 (0.66, 1.38)
CHS 3007 291 1.02 (0.76, 1.37)
MCCS 4034 335 1.16 (0.80, 1.67)
AGES-R 753 28 1.36 (0.56, 3.29)
ULSAM70 738 99 1.69 (1.03, 2.77)
Subtotal (I-squared = 44.5%, p = 0.022) 0.79 (0.73, 0.85)
.25
.5
1
1.5
2

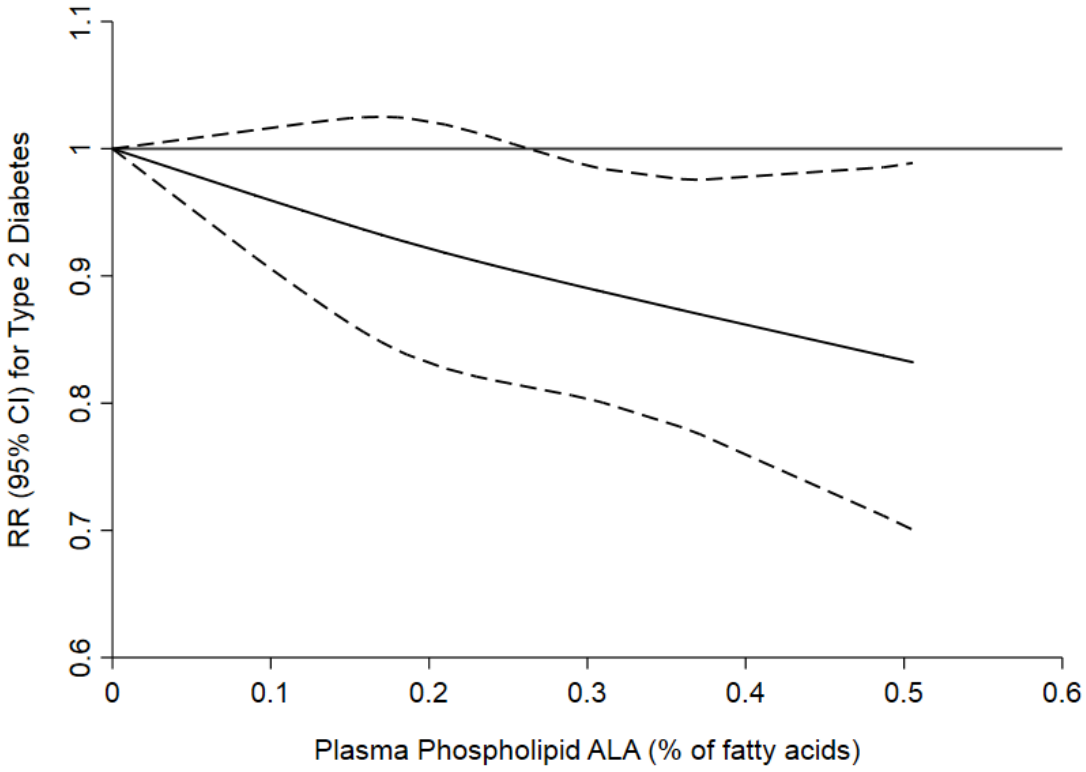
Supplementary Figure 2C. Pooled relative risks of type 2 diabetes according to interquintile range (difference between 90th and 10th percentiles) of docosapentaenoic acid (DPA) biomarker. The association between DPA and type 2 diabetes was assessed in multivariable models for each cohort, and the results were pooled using inverse-variance weighted fixed effects meta-analysis. In each cohort, multivariate RR was assessed adjusting for sex, age, field site (if appropriate), race, socioeconomic status (education, occupation), smoking status, physical activity, alcohol consumption, treatment for hypertension, treatment for hypercholesterolemia, prevalent coronary heart disease, body mass index, waist circumference, and biomarkers of linoleic acid (18:2n-6) and trans fatty acids (total *t*-18:1 and *t*-18:2). If multiple biomarkers were available for a study, only one was used for the overall analysis based on the best ability to reflect long-term dietary intake (in the following order of preference): adipose tissue, erythrocyte phospholipids, plasma phospholipids, total plasma/serum, cholesterol esters, and triglycerides.


study
n
case
RR (95% CI)
Phospholipid
AOC 779 38 0.55 (0.21, 1.45)
NHS 1446 149 0.65 (0.38, 1.13)
EPIC-InterAct 27296 12132 0.66 (0.54, 0.80)
MESA 2099 285 0.72 (0.45, 1.14)
FHS 1872 95 0.72 (0.38, 1.37)
AGES-R 753 28 0.76 (0.27, 2.09)
METSIM 1302 101 0.82 (0.47, 1.45)
CHS 3007 291 0.84 (0.60, 1.17)
WHIMS 5668 490 0.85 (0.64, 1.14)
MCCS 4034 335 0.90 (0.66, 1.24)
ARIC 3273 512 1.04 (0.76, 1.42)
HPFS 1491 108 1.11 (0.66, 1.87)
PIVUS 872 69 1.15 (0.60, 2.20)
Subtotal (I-squared = 0.0%, p = 0.509) 0.80 (0.72, 0.89)
Total Plasma/Serum
FDPS 396 161 0.57 (0.34, 0.96)
Hisayama 2172 222 0.62 (0.43, 0.89)
KIHD 3389 595 0.75 (0.61, 0.92)
HPFS 1443 105 0.89 (0.54, 1.46)
CCCC 1443 651 0.92 (0.74, 1.15)
NHS 1524 150 0.93 (0.59, 1.47)
3C 1218 83 1.02 (0.65, 1.60)
Subtotal (I-squared = 17.3%, p = 0.298) 0.81 (0.72, 0.91)
Cholesterol Ester
METSIM 1302 101 0.80 (0.49, 1.28)
ULSAM50 1899 335 0.92 (0.68, 1.26)
PIVUS 834 67 1.13 (0.66, 1.93)
Subtotal (I-squared = 0.0%, p = 0.631) 0.93 (0.73, 1.17)
Triglycerides
METSIM 1302 101 1.00 (0.69, 1.46)
Subtotal (I-squared = .%, p = .) 1.00 (0.69, 1.46)
Adipose Tissue
ULSAM70 738 99 1.53 (0.99, 2.37)
Subtotal (I-squared = .%, p = .) 1.53 (0.99, 2.37)
Overall
AOC 779 38 0.55 (0.21, 1.45)
FDPS 396 161 0.57 (0.34, 0.96)
Hisayama 2172 222 0.62 (0.43, 0.89)
NHS 1446 149 0.65 (0.38, 1.13)
EPIC-InterAct 27296 12132 0.66 (0.54, 0.80)
MESA 2099 285 0.72 (0.45, 1.14)
FHS 1872 95 0.72 (0.38, 1.37)
KIHD 3389 595 0.75 (0.61, 0.92)
AGES-R 753 28 0.76 (0.27, 2.09)
METSIM 1302 101 0.82 (0.47, 1.45)
CHS 3007 291 0.84 (0.60, 1.17)
WHIMS 5668 490 0.85 (0.64, 1.14)
MCCS 4034 335 0.90 (0.66, 1.24)
ULSAM50 1899 249 0.91 (0.61, 1.37)
CCCC 1443 651 0.92 (0.74, 1.15)
3C 1218 83 1.02 (0.65, 1.60)
ARIC 3273 512 1.04 (0.76, 1.42)
HPFS 1491 108 1.11 (0.66, 1.87)
PIVUS 872 69 1.15 (0.60, 2.20)
ULSAM70 738 99 1.53 (0.99, 2.37)
Subtotal (I-squared = 27.8%, p = 0.121) 0.82 (0.76, 0.89)
.25
.5
1
1.5
2

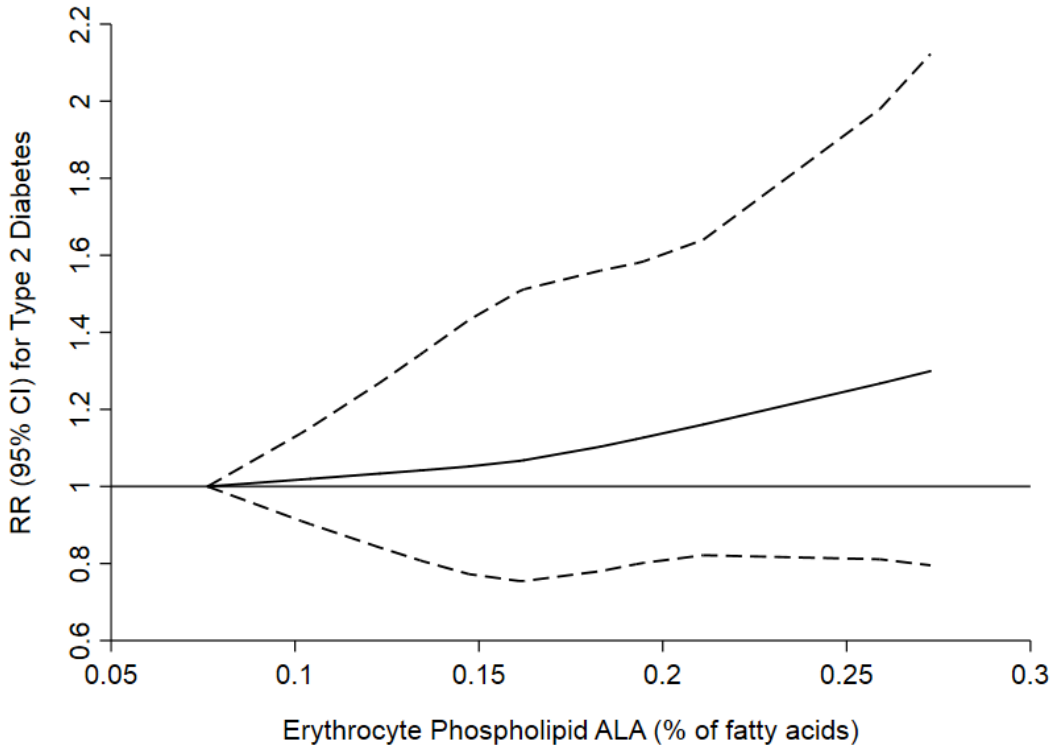
Supplementary Figure 2D. Pooled relative risks of type 2 diabetes according to interquintile range (difference between 90th and 10th percentiles) of docosahexaenoic acid (DHA) biomarker. The association between DHA and type 2 diabetes was assessed in multivariable models for each cohort, and the results were pooled using inverse-variance weighted fixed effects meta-analysis. In each cohort, multivariate RR was assessed adjusting for sex, age, field site (if appropriate), race, socioeconomic status (education, occupation), smoking status, physical activity, alcohol consumption, treatment for hypertension, treatment for hypercholesterolemia, prevalent coronary heart disease, body mass index, waist circumference, and biomarkers of linoleic acid (18:2n-6) and trans fatty acids (total *t*-18:1 and *t*-18:2). If multiple biomarkers were available for a study, only one was used for the overall analysis based on the best ability to reflect long-term dietary intake (in the following order of preference): adipose tissue, erythrocyte phospholipids, plasma phospholipids, total plasma/serum, cholesterol esters, and triglycerides.

Supplementary Figure 3. Restricted cubic splines for individual omega-3 fatty acid biomarkers and incidence of T2D by lipid compartment.

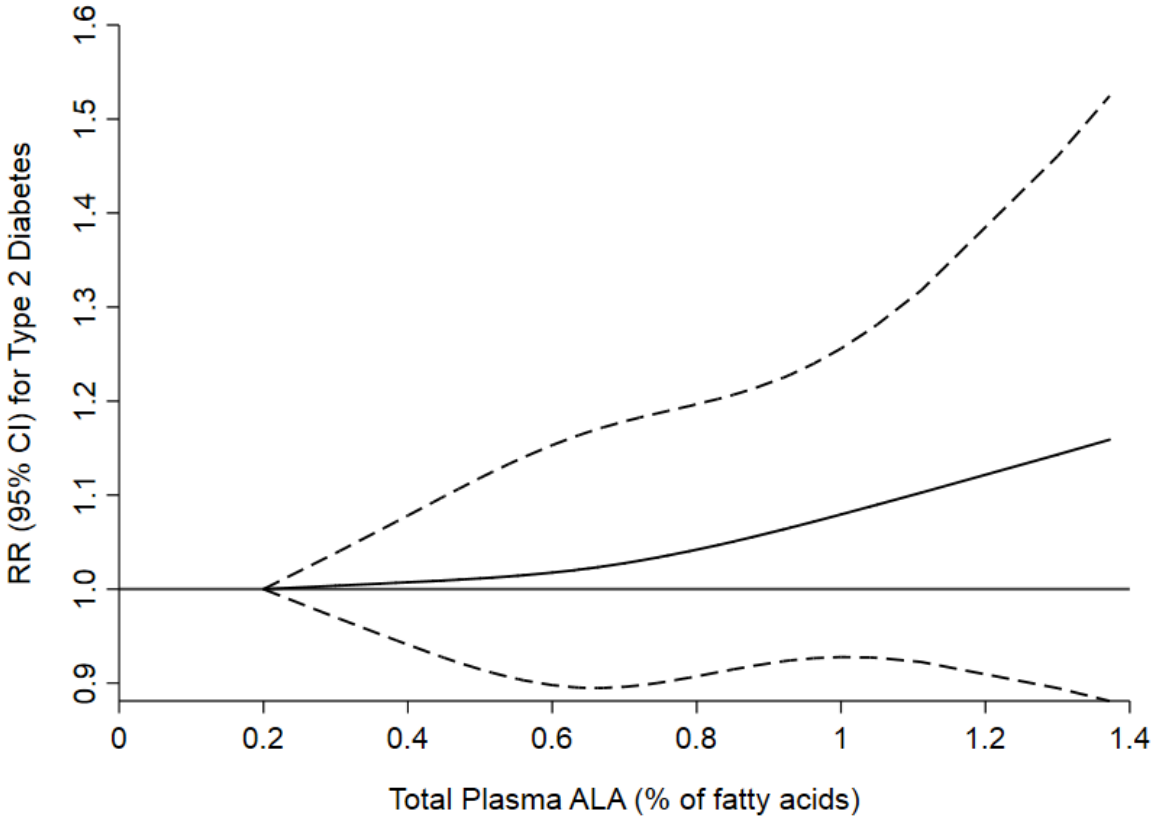
(A) ALA – Plasma Phospholipids (P_{linear} = 0.01, $P_{non\text{-}linear}$ = 0.87)



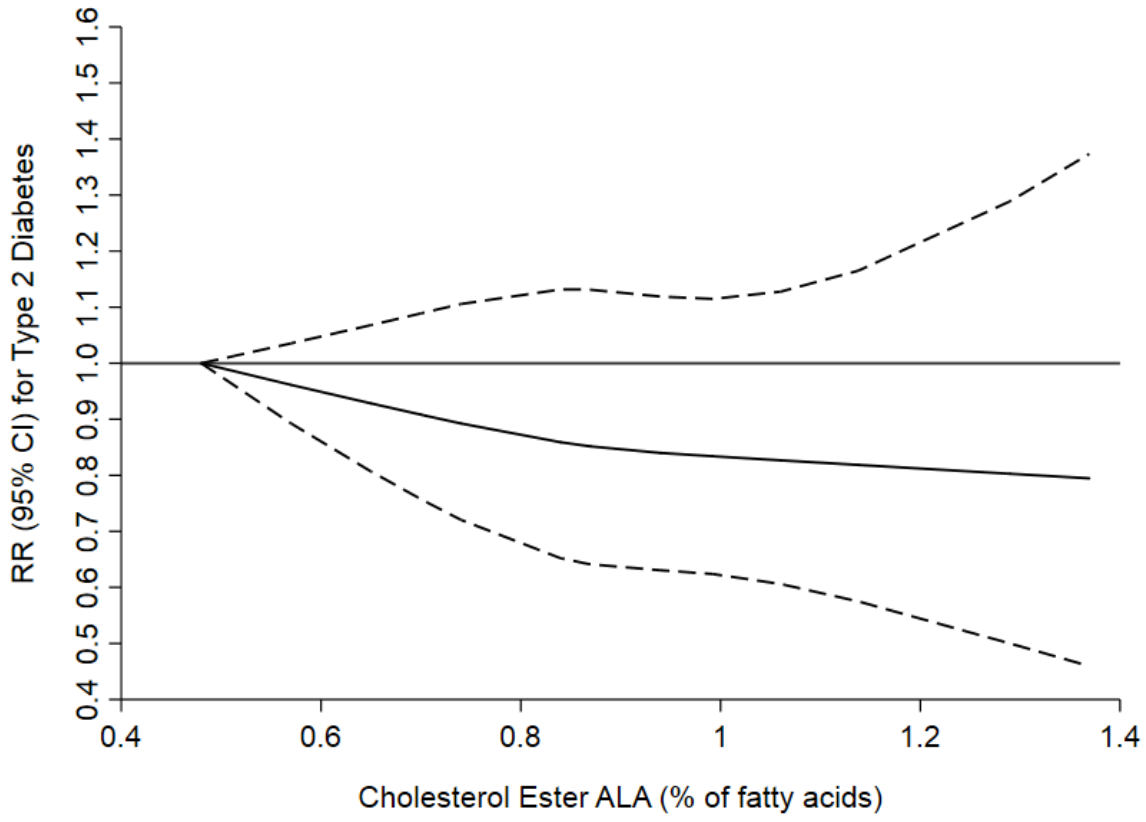
(B) ALA – Erythrocyte Phospholipids (P_{linear} = 0.26, $P_{non\text{-}linear}$ = 0.75)



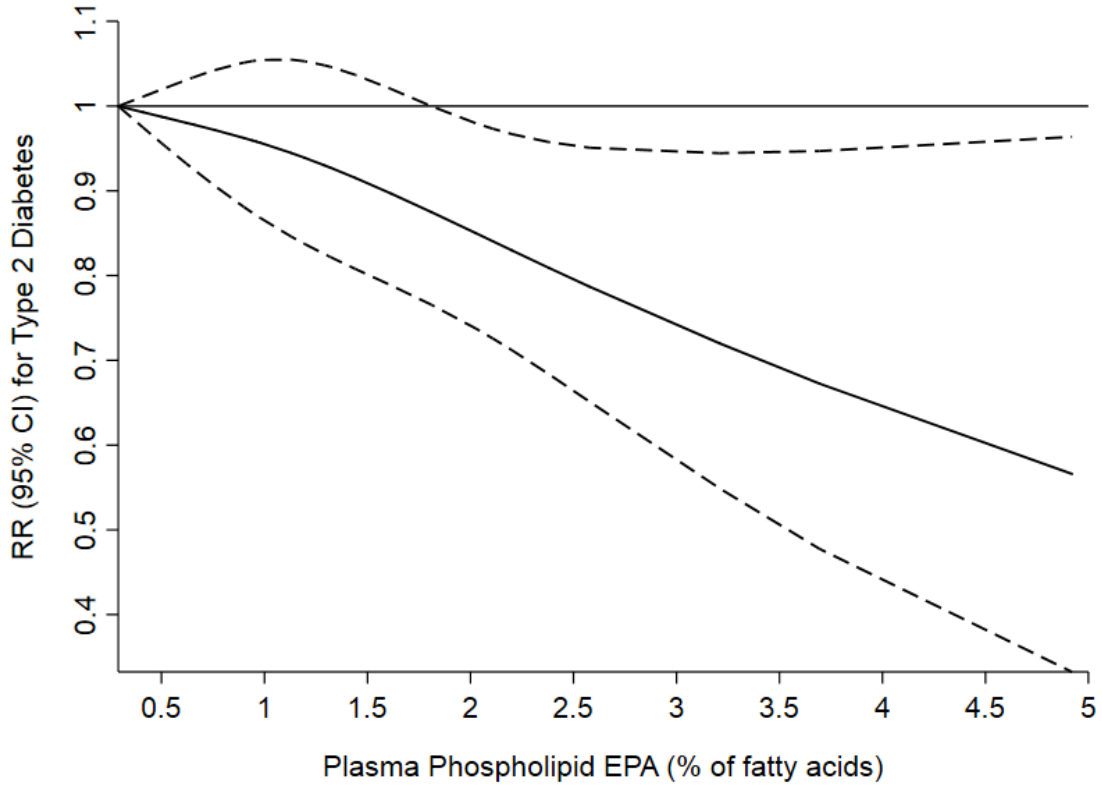
(C) ALA – Total Plasma/Serum (P_{linear} = 0.30, $P_{non\text{-}linear}$ = 0.67)



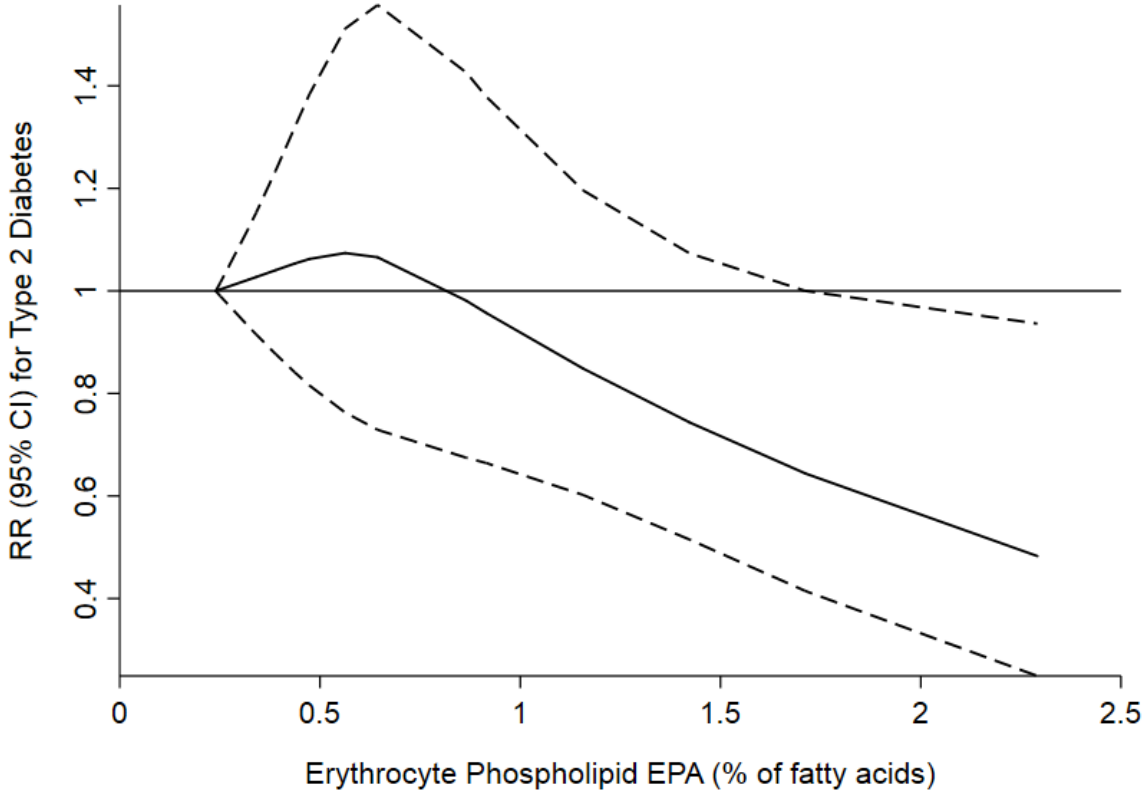
(D) ALA – Cholesterol Esters (P_{linear} = 0.26, $P_{non\text{-}linear}$ = 0.75)



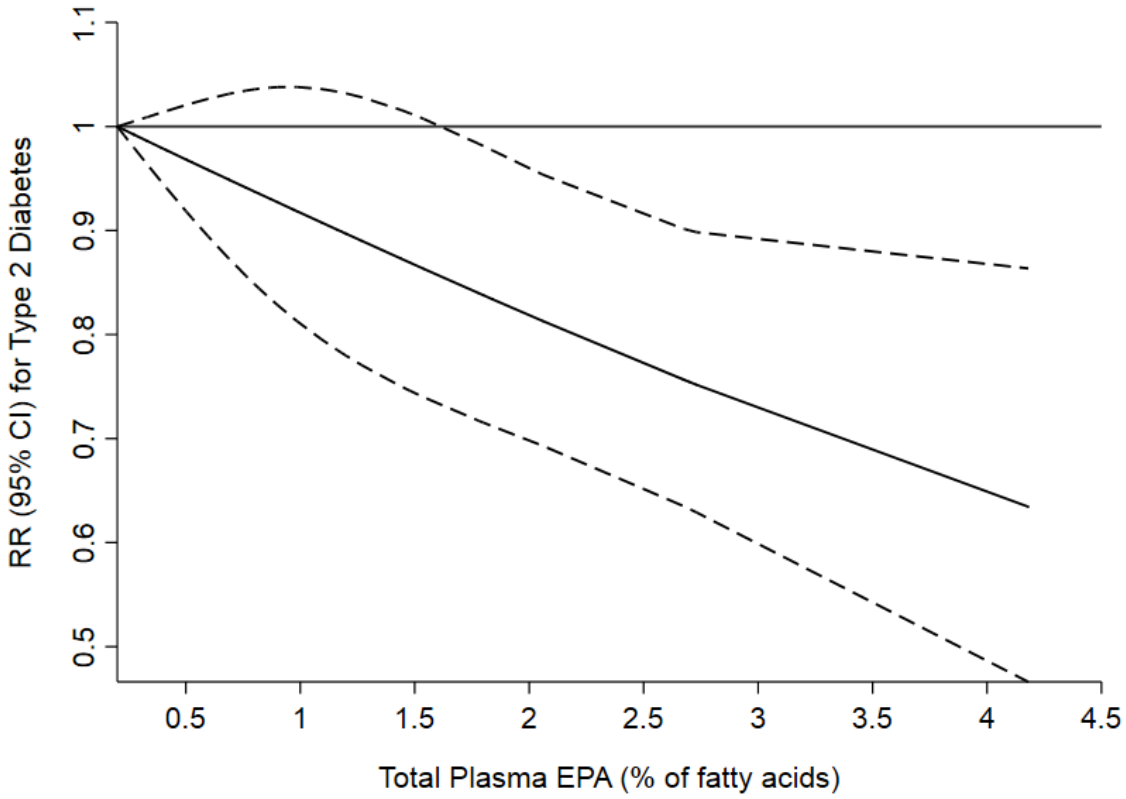
(E) EPA, Plasma Phospholipids (P_{linear} = 0.01, $P_{non\text{-}linear}$ = 0.54)



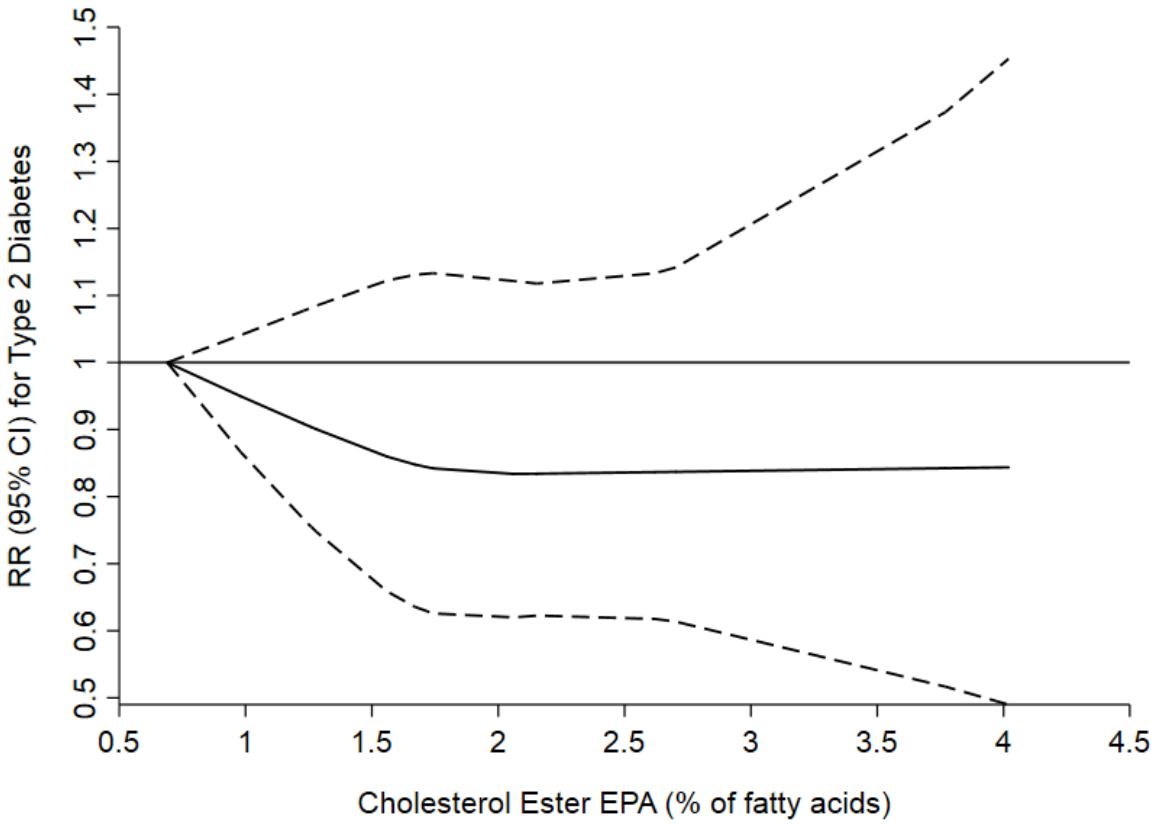
(F) EPA, Erythrocyte Phospholipids (P_{linear} = 0.03, $P_{non\text{-}linear}$ = 0.27)



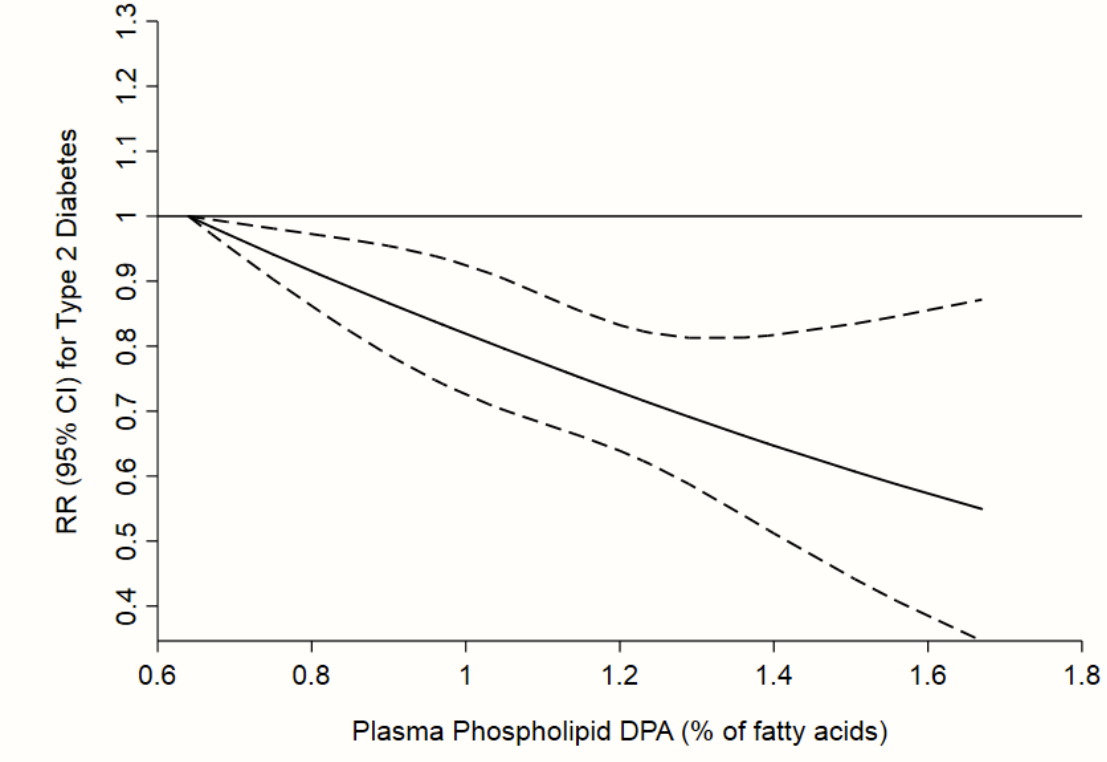
(G)EPA, Total Plasma/Serum (P_{linear} = 0.001, $P_{non\text{-}linear}$ = 0.94)



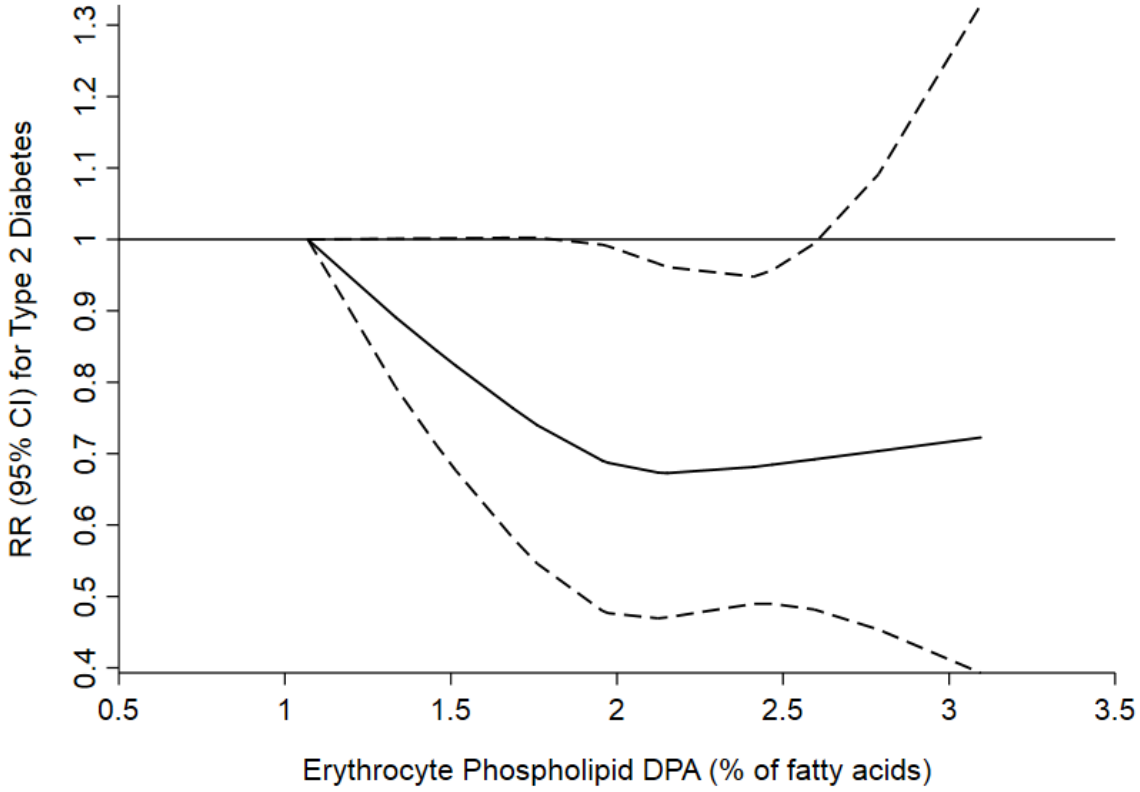
(H)EPA, Cholesterol Esters (P_{linear} = 0.28, $P_{non\text{-}linear}$ = 0.42)



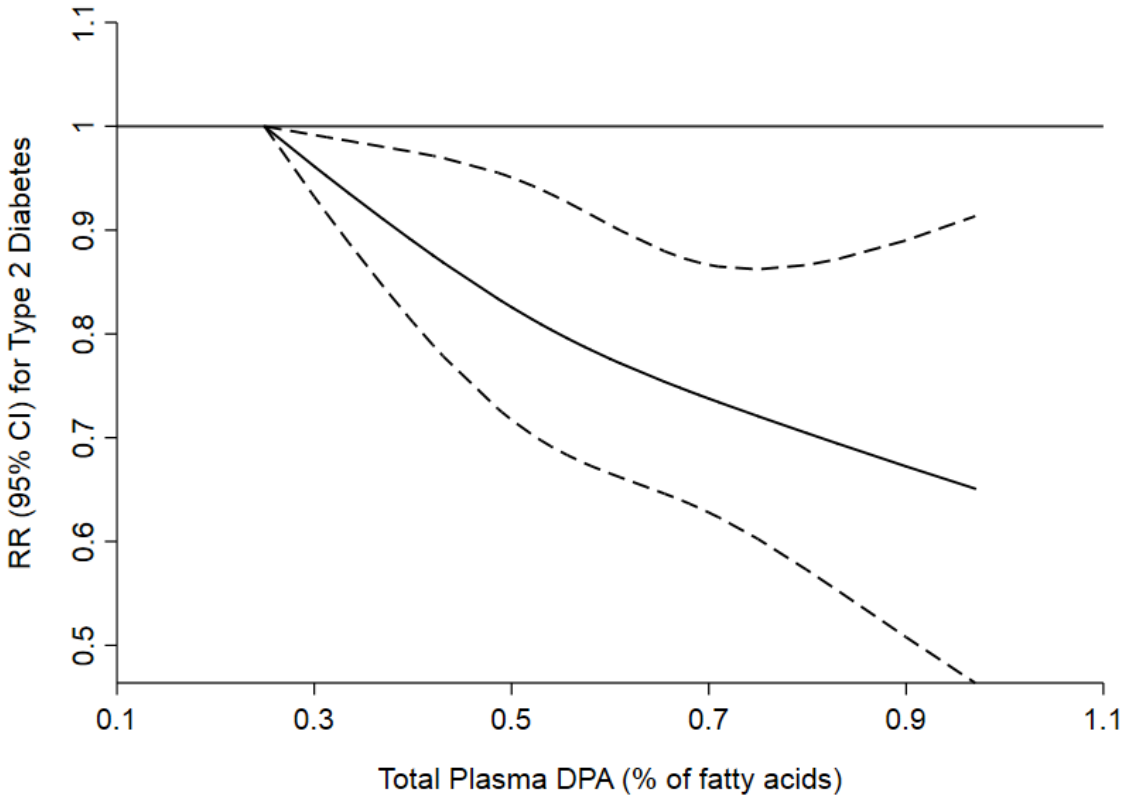
(I) DPA, Plasma Phospholipids ($P_{linear} < 0.001$, $P_{non\text{-}linear} = 0.93$)



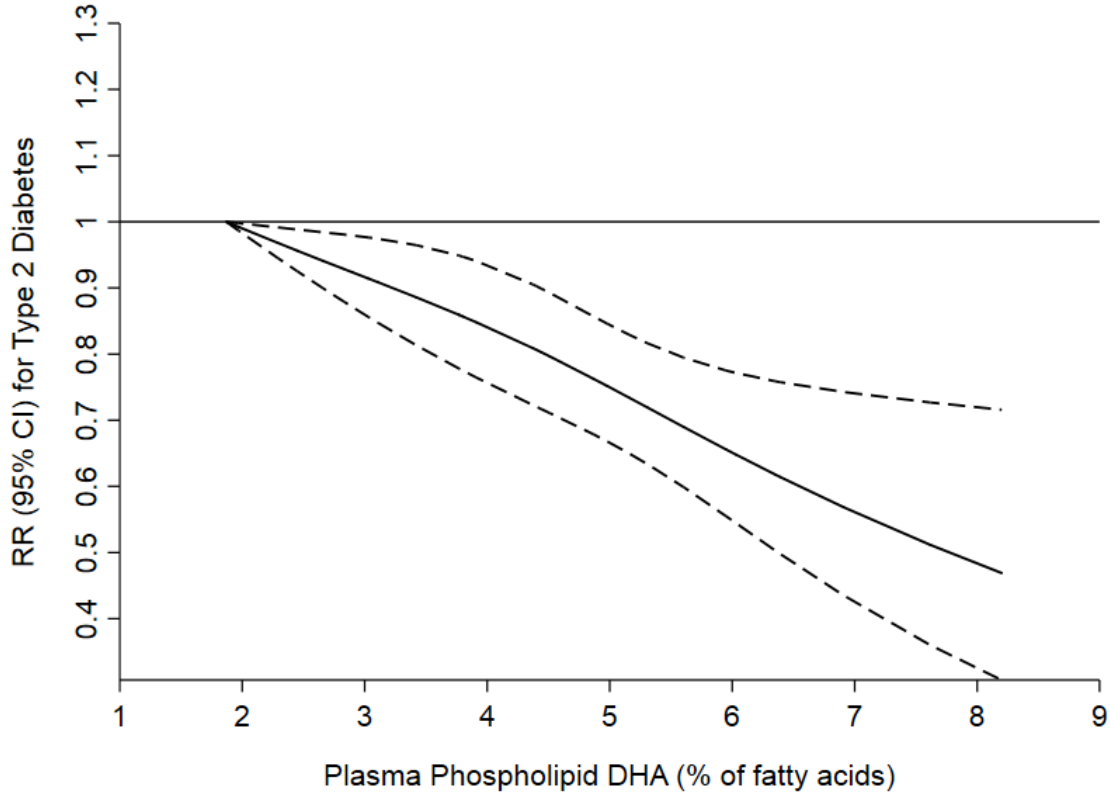
(J) DPA, Erythrocyte Phospholipids ($P_{linear} = 0.02$, $P_{non\text{-}linear} = 0.28$)



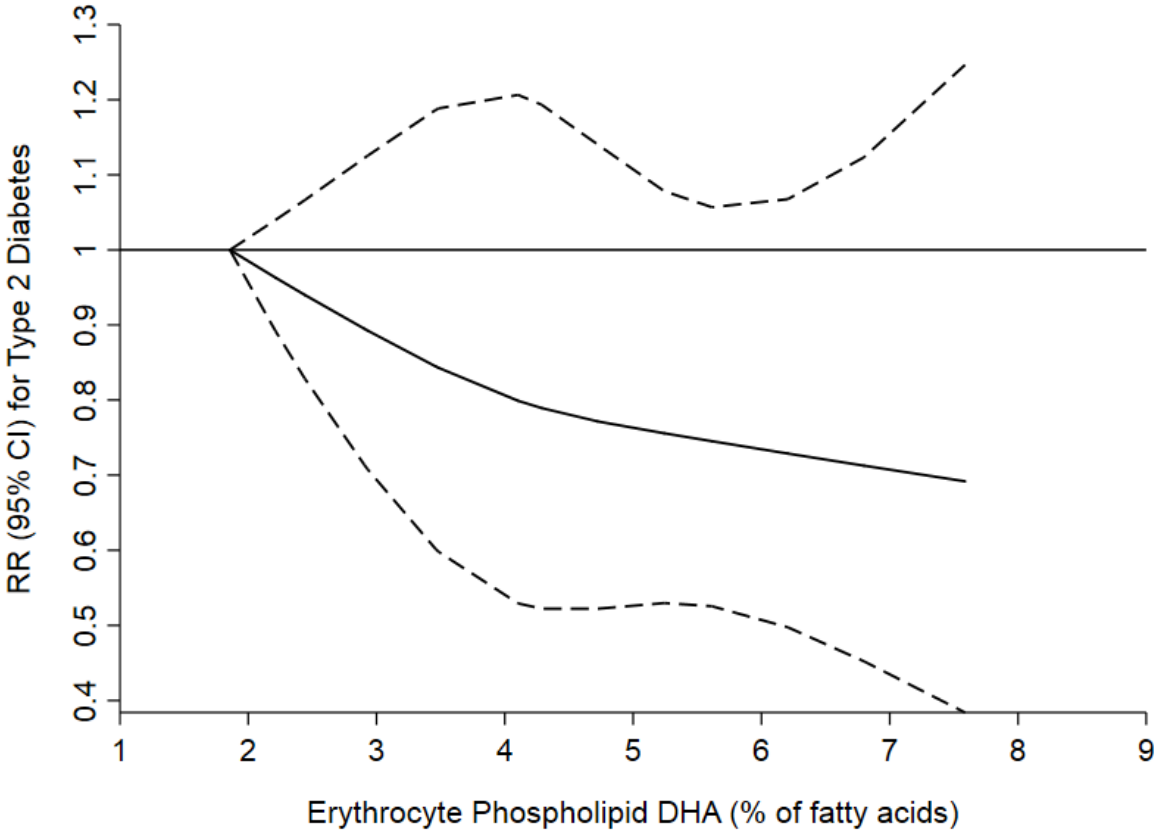
(K) DPA, Total Plasma/Serum ($P_{linear} < 0.001$, $P_{non\text{-}linear} = 0.65$)



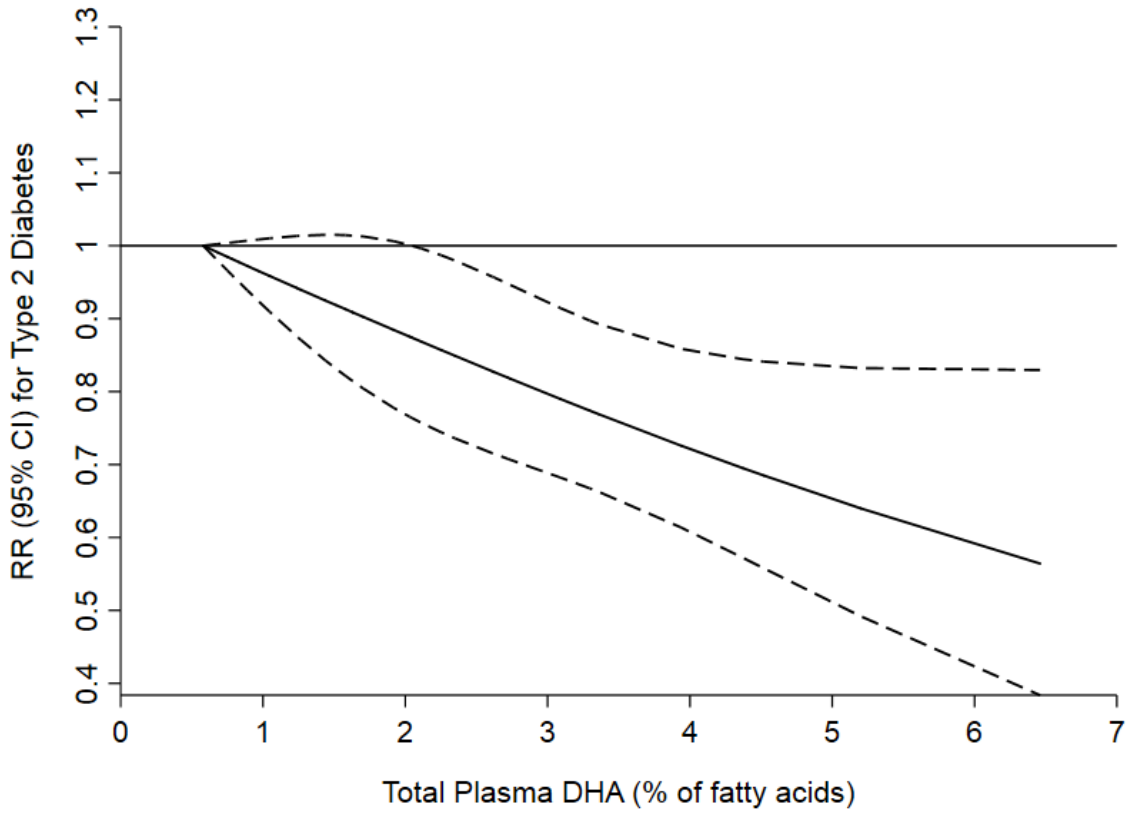
(L) DHA, Plasma Phospholipids ($P_{linear} < 0.001$, $P_{non\text{-}linear} = 0.38$)



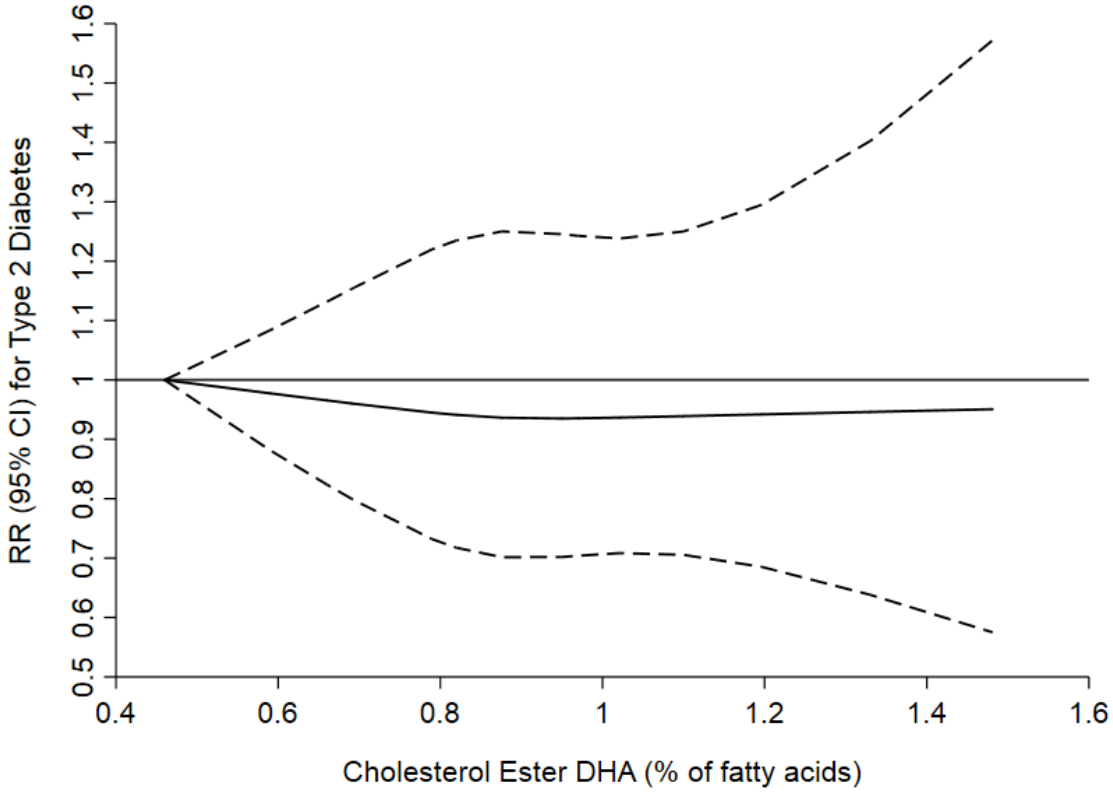
(M) DHA, Erythrocyte Phospholipids (P_{linear} = 0.07, $P_{non\text{-}linear}$ = 0.72)



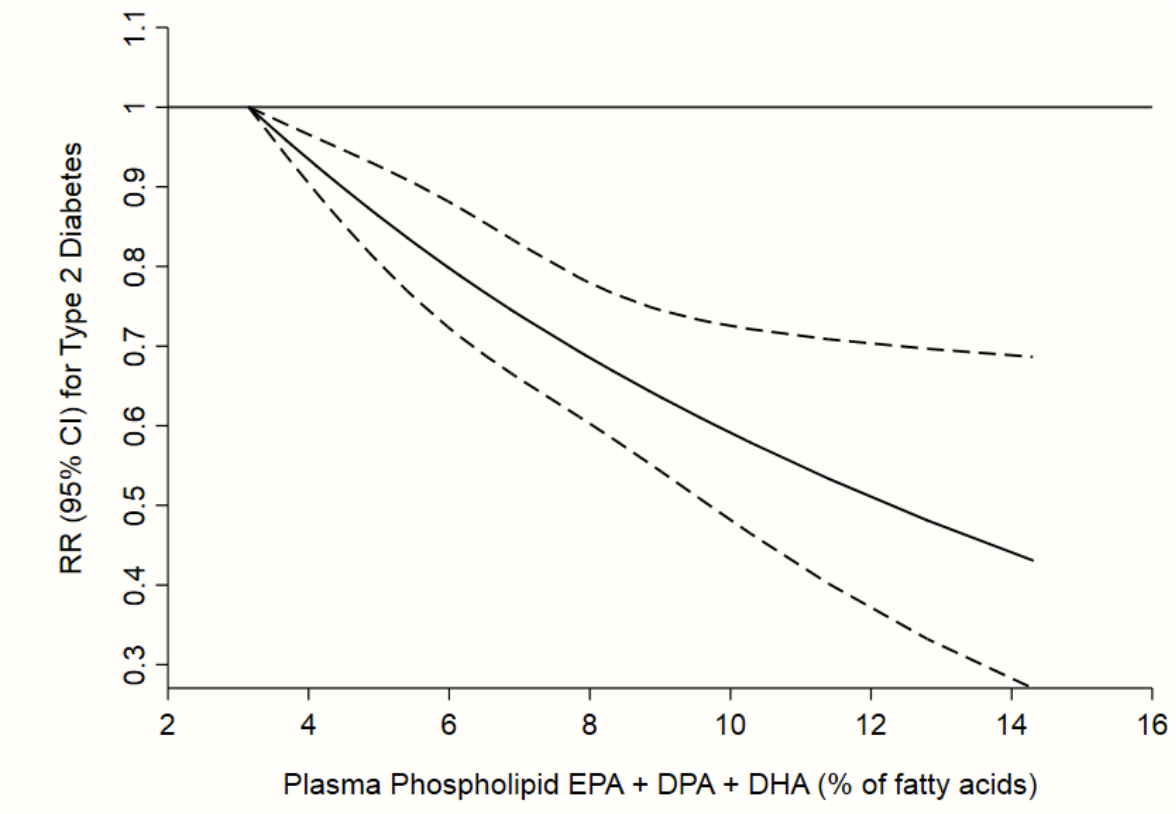
(N) DHA, Total Plasma (P_{linear} < 0.001, $P_{non\text{-}linear}$ = 0.93)



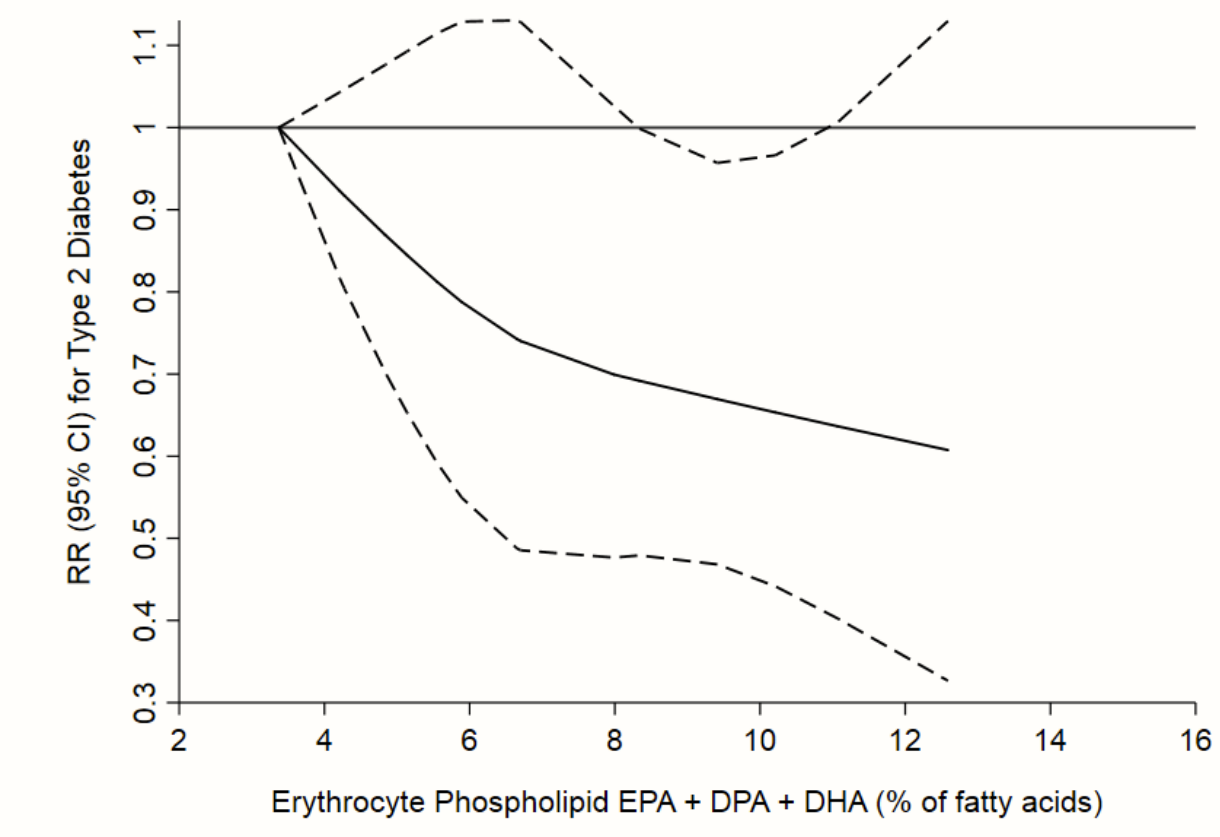
(O)DHA, Cholesterol Esters (P_{linear} = 0.68, $P_{non\text{-}linear}$ = 0.76)



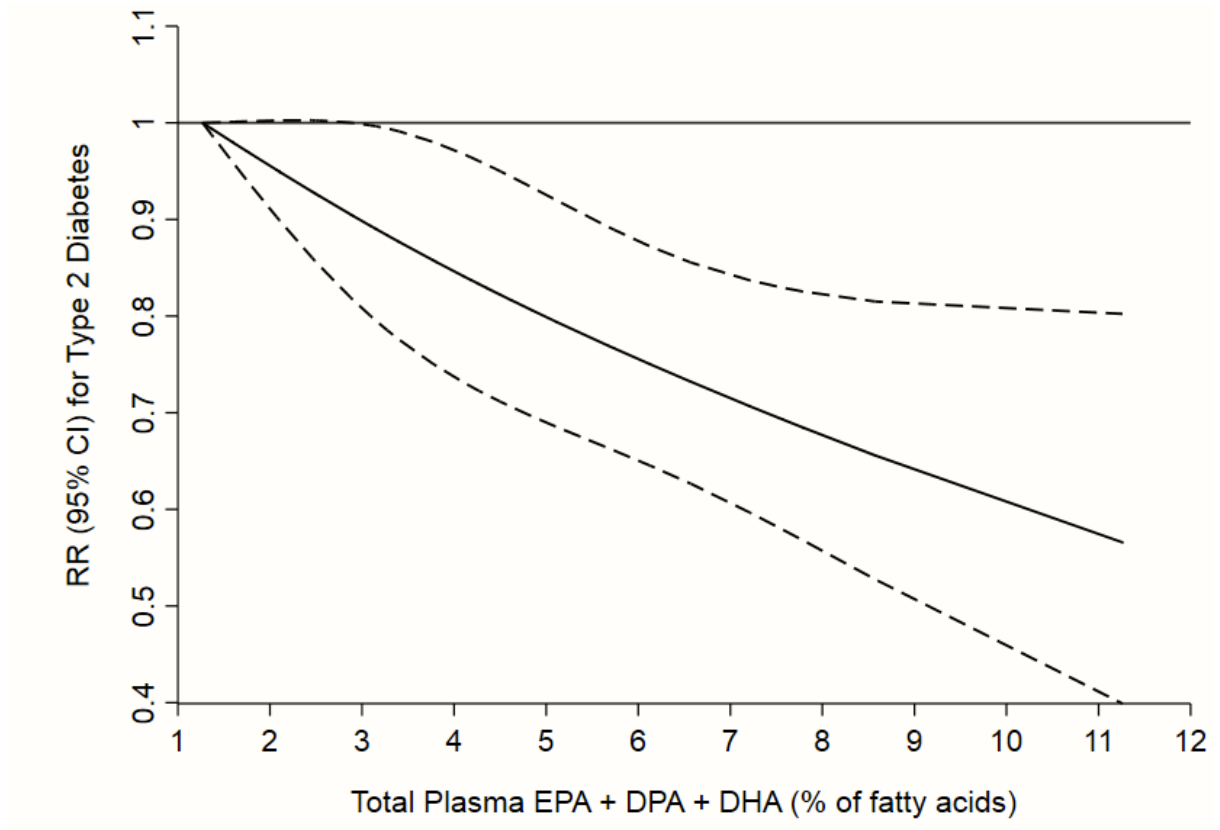
(P) EPA + DPA + DHA, Plasma Phospholipids (P_{linear} < 0.001, $P_{non\text{-}linear}$ = 0.89)



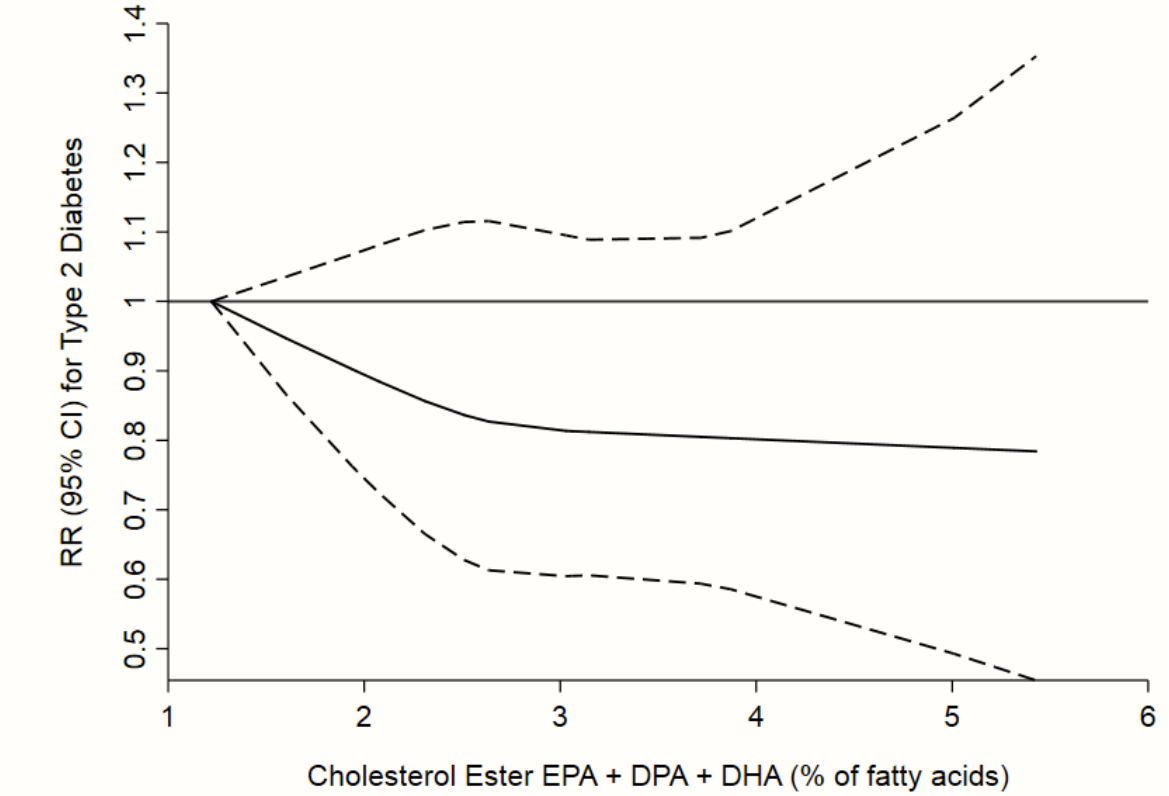
(Q) EPA + DPA + DHA, Erythrocyte Phospholipids (P_{linear} = 0.02, $P_{non\text{-}linear}$ = 0.59)

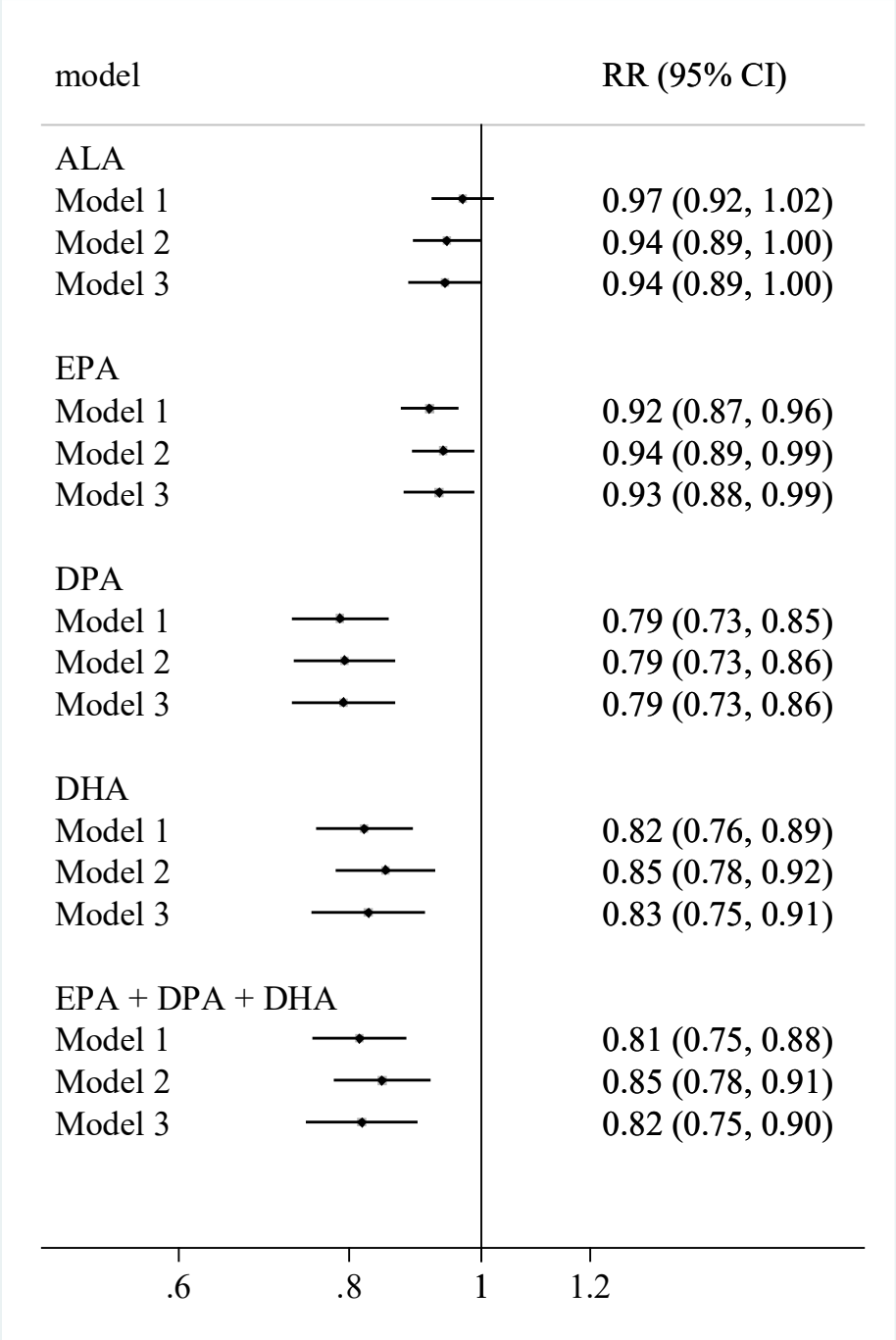


(R) EPA + DPA + DHA, Total Plasma/Serum (P_{linear} < 0.001, $P_{non\text{-}linear}$ = 0.89)



(S) EPA + DPA + DHA, Cholesterol Esters (P_{linear} = 0.16, $P_{non\text{-}linear}$ = 0.47)





Supplementary Figure 4. Pooled relative risks of type 2 diabetes according to interquintile range (difference between 90th and 10th percentiles). The association between each omega-3 fatty acid and type 2 diabetes was assessed in multivariable models for each cohort, and the results were pooled using inverse-variance weighted fixed effects meta-analysis. In each cohort, multivariate RR was assessed adjusting for – Model 1: sex, age, field site (if appropriate), race, socioeconomic status (education, occupation), smoking status, physical activity, alcohol consumption, treatment for hypertension, treatment for hypercholesterolemia, prevalent coronary heart disease, body mass index, waist circumference, and biomarkers of linoleic acid (18:2n-6) and trans fatty acids (total *t*-18:1 and *t*-18:2). Model 2 additionally adjusted for circulating triglycerides. Model 3 additionally adjusted for total fish/seafood intake.

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