Supplemental Material

Expanded Methods

Online Note I: Study populations

The PREDIMED Study and the nested heart failure case-control study

The PREDIMED trial was a multicenter randomized primary prevention study designed to assess the effect of the Mediterranean diet on cardiovascular disease (CVD) risk. Between 2003 and 2009, 7447 participants (3165 men, aged 55 to 80 years; 4282 women, aged 60 to 80 years) were recruited, without prior CVD but at high risk (either prevalent T2D or at least three of the following CVD-risk factors: current smoking, overweight/obesity, high LDL-cholesterol, low HDL-cholesterol, family history of early CAD, or hypertension). The present analysis used the PREDIMED-trial as an observational cohort, with an extended follow-up until December 31st, 2017. At study inception, 7403 participants were free of HF. In the study course, 362 incident HF cases were registered (Online Figure I), 331 with available blood samples. From this source population, we constructed a nested HF-case-control study, applying incidence density sampling. For each case, between 1 and 3 controls were randomly selected from all participants at risk at the date of HF-diagnosis, matched by recruitment center, year of birth (± 5 years), and sex. The analytical sample comprised the 331 incident HF cases and 507 matched controls.

The EPIC-Potsdam cohort and the HF-replication sample

The prospective EPIC-Potsdam cohort study included 27,548 participants (16,644 women and 10,904 men), recruited between 1994 and 1998 from the general population within the age range of 35-65 years. During the follow-up period, participants were actively contacted every 2-3 years with response rates between 90% and 96% per follow-up round. Nested case-cohorts were constructed by drawing a representative, random sample (subcohort, n=1,262) from all participants who provided blood at baseline (n=26,437), and all incident CVD- and T2D-cases that occurred in the full cohort until case-specific censoring dates. The replication sample was based on nested case-cohorts for CVD and T2D, including a random subsample (subcohort, n=1,262), all participants with incident type 2 diabetes (n = 820) and all participants with incident primary CVD (n = 583). Censoring dates were 31st of August 2005 for T2D, and 31st of November 2006 for CVD. Assuming the oversampling of future CVD and T2D cases fairly resembled the high cardiometabolic risk profile in PREDIMED, we analyzed all participants with available lipidomics profiles. After exclusion of participants with missing follow-up information or insufficient blood specimens or prevalent HF, the replication cohort comprised 2414 at-risk-participants, of whom 87 developed incident HF over the study course.

Online Note II: Lipidomics - analytical chemistry and data preparation

The plasma polar and nonpolar lipids were profiled using a Nexera X2 U-HPLC system (Shimadzu Scientific Instruments; Marlborough, MA) coupled to an Exactive Plus orbitrap mass spectrometer (Thermo Fisher Scientific; Waltham, MA). Lipids were extracted from plasma (10 µL) using 190 µL of isopropanol containing 1,2-didodecanoyl-sn-glycero-3-phosphocholine as an internal standard (Avanti Polar Lipids; Alabaster, AL). After centrifugation (10 min, 9,000 x g, ambient temperature), supernatants (10 µL) were injected directly onto a 100 x 2.1 mm ACQUITY BEH C8 column (1.7 µm; Waters; Milford, MA). The column was eluted at a flow rate of 450 µL/min isocratically for 1 minute at 80% mobile phase A (95:5:0.1 vol/vol/vol 10 mM ammonium acetate/methanol/acetic acid), followed by a linear gradient to 80% mobile-phase B (99.9:0.1 vol/vol methanol/acetic acid) over 2 minutes, a linear gradient to 100% mobile phase B over 7 minutes, and then 3 minutes at 100% mobile-phase B. MS analyses were carried out using electrospray ionization in the positive ion mode using full scan analysis over m/z 200-1100 at 70,000 resolution and 3 Hz data acquisition rate. Additional MS settings were ion spray voltage, 3.0 kV; capillary temperature, 300°C; probe heater temperature, 300 °C; sheath gas, 50; auxiliary gas, 15; and S-lens RF level 60. Raw data were processed using Progenesis QI software (NonLinear Dynamics) for feature alignment, nontargeted signal detection, and signal integration. Targeted processing of a subset of lipids was conducted using TraceFinder software (version 3.2, Thermo Fisher Scientific; Waltham, MA). Lipids are denoted by headgroup and total acyl carbon content and total acyl double bond content.

In PREDIMED, targeted processing of a subset of 216 known lipids was conducted using the TraceFinder software (version 3.2, Thermo Fisher Scientific; Waltham, MA), generating information on the lipid class and the total content of carbon atoms and double bonds across of all contained acyl chains. Therefore, lipids are reported at the level of lipid class, total acyl carbon content, and total double bond content. Based on the assumption that missing values reflect true metabolite concentration under the limit of detection, we imputed missing data with half the minimal measured value, adding random noise unrelated to the case-status. Then, we applied inverse normal transformation, which produces a rank-based smooth normal distribution [mean=0, standard deviation (SD)=1].

In EPIC-Potsdam, per participant, 30 mL of venous blood was collected in a standardized procedure and subsequently fractioned and citrate plasma was stored in tanks of liquid nitrogen (approximately -196°C) or deep freezers (-80°C). The lipid profiling data was generated with Metabolon (Morrisville, US) using the Metabolon® Complex Lipid Panel. The platform generates the molecular species concentration and complete fatty acid composition of each covered lipid class. From plasma samples, lipids were extracted in methanol:dichloromethane, concentrated under nitrogen and reconstituted in ammonium acetate dichloromethane:methanol (50:50). The extracts were directly infused into the ionization source of a Sciex SelexION® -5500 QTRAP mass spectrometer. After ionization, the lipids passed through SelexIon differential mobility spectrometry (DMS), in which voltages are applied that selectively allow the passage of only a specific lipid class at any given time. After the DMS filtering, lipids entered the Multiple Reaction Monitoring (MRM), where the lipid mass and its characteristic fragment were measured. The Metabolon® Complex Lipid Panel included more than 50 isotopically labeled internal standards, which were introduced in the biological sample early in the process and permitted accurate quantitation of lipids across and within classes.

In EPIC-Potsdam, measurements for 1043 distinct lipid species were retrieved. Like the data preparation in PREDIMED, missing values were imputed below the lowest measured value, and inverse normal transformation was applied (see above). Lipids with >30% missing data were excluded.

Online Note III: Heart failure ascertainment

In the PREDIMED trial, heart failure was a pre-specified secondary outcome (9). All HF events were assigned according to the 2005 (time of study design) guidelines on the diagnosis and treatment of acute and chronic HF of the European Society of Cardiology (10,11). At each recruitment center, incident HF cases were detected by study the physicians through review of the medical records of all participants and consultation of the National Death Index. Then, for the final adjudication of HF incidence, anonymized patient information was reviewed by the independent central Event Ascertainment Committee. For the present analysis, all HF cases up to December 31st 2017 –except for one recruitment center with available follow-up information until December 31st 2014– were included.

In EPIC-Potsdam, potential HF cases were identified by self-report, death certificates, and linkage to hospital records. Additionally, participants have been actively enquired for HF if they reported an incident myocardial infarction or usage of drugs typical for HF treatment. Potential cases were validated by the attending physicians using a standard validation form, including assessment of the exact date of diagnosis. Only participants with a physician-verified HF-diagnosis (I50 of International Classification of Diseases, 10th revision) after the recruitment were considered confirmed incident HF cases.

Online Note IV: Matching the lipids from PREDIMED to EPIC-Potsdam

In PREDIMED, information on lipid metabolites was restricted to the sum of carbon atoms and double bonds across all acyl chains. In EPIC-Potsdam, metabolites with two FA-residues were resolved to the number of carbon atoms and double bonds within each acyl chain; TAG-measurements contained the sum of carbon atoms and double bonds across the three acyl chains and also the carbon atoms and double bonds of the FA-residue in the sn-3 position. Therefore, matching was unambiguous for lipids with a single acyl chain (SLs, LPLs, MAGs, and CEs), but several measurements in EPIC-Potsdam potentially matched the PREDIMED measurements in classes with two or three acyl chains (two: PCs, PEs, DAGs, PEPLGs, and PCPLGs; three: TAGs). For replication of PREDIMED-findings, we selected all the isomers of a lipid metabolite in EPIC-Potsdam that had the same sum formula. Then, we summed all the absolute concentrations of these lipids in EPIC-Potsdam. We also ran models that simultaneously included all the matched isomers and selected the most significant predictors using a backwards procedure.

Online Tables

Online Table I: Baseline-characteristics of the HF-cohort within the EPIC-Potsdam study

	Full sample	Non-incident HF	Incident HF
n	2414	2327	87
Women	1220 (50.5%)*	1156 (49.7%)	64 (73.6%)
Age [years]	54 (45, 60)†	54 (45, 60)	59 (53, 62)
BMI [kg/sqm]	27.0 (24.3, 30.2)	27.0 (24.3, 30.2)	27.8 (25.8, 31.1)
Highest education			
Primary school	992 (41.1%)	959 (41.2%)	33 (37.9%)
Sec./high school	573 (23.7%)	552 (23.7%)	21 (24.1%)
College/higher	849 (35.2%)	816 (35.1%)	33 (37.9%)
Smoker			
Never	984 (40.8%)	966 (41.5%)	18 (20.7%)
Former	866 (35.9%)	835 (35.9%)	31 (35.6%)
Current smoker (<20 U/day)	368 (15.2%)	348 (15.0%)	20 (23.0%)
Current smoker (≥20 U/day)	196 (8.1%)	178 (7.6%)	18 (20.7%)
Prevalent HT	1516 (62.8%)	1450 (62.3%)	66 (75.9%)
Prevalent T2D	49 (2.0%)	44 (1.9%)	5 (5.7%)
Follow-up time	8.4 (7.6, 9.2)	8.4 (7.6, 9.3)	5.9 (3.2, 7.4)
Incident HF	87 (3.6%)	0 (0.0%)	87 (100.0%)
First incident disease			
T2D	775 (32.1%)	758 (32.6%)	17 (19.5%)

HF	50 (2.1%)	0 (0.0%)	50 (57.5%)
MI	250 (10.4%)	230 (9.9%)	20 (23.0%)
Stroke	4 (0.2%)	4 (0.2%)	0 (0.0%)
None	1335 (55.3%)	1335 (57.4%)	0 (0.0%)

Baseline-characteristics of the subsample for assessment of HF risk, nested within the EPIC-Potsdam cohort.

*Number of observations (column percentage), all such values.

†Median (25th, 75thpercentile), all such values.

Online Table II: All single-lipid HF-associations in PREDIMED

lipid	RR_M1	p-val.	Adj-P	RR_M2	p-val.	FDR
EA18:1	1.38 (1.21, 1.57)	1.6E-06	3.6E-04	1.26 (1.09, 1.46)	0.002	0.066
PI38_4	0.82 (0.73, 0.93)	0.001	0.122	0.79 (0.68, 0.91)	0.001	0.056
PC32_0	1.21 (1.07, 1.36)	0.002	0.122	1.23 (1.08, 1.41)	0.002	0.066
CER16:0	1.2 (1.07, 1.34)	0.002	0.122	1.28 (1.13, 1.47)	1.7E-04	0.036
DAG36_0	0.83 (0.73, 0.94)	0.004	0.153	0.81 (0.71, 0.93)	0.003	0.08
Q10	0.84 (0.74, 0.95)	0.004	0.153	0.83 (0.72, 0.95)	0.006	0.11
DAG34_0	0.84 (0.73, 0.95)	0.007	0.219	0.76 (0.65, 0.88)	3.3E-04	0.036
DAG34_2	1.16 (1.04, 1.31)	0.009	0.232	1.05 (0.93, 1.2)	0.42	0.858
PC40_10	0.86 (0.76, 0.97)	0.011	0.232	0.94 (0.82, 1.07)	0.335	0.804
PIPERINE	1.19 (1.04, 1.35)	0.011	0.232	1.09 (0.94, 1.27)	0.228	0.721
TAG51_1	1.15 (1.03, 1.29)	0.012	0.232	1.03 (0.9, 1.17)	0.671	0.937
SPHINGOSINE	1.17 (1.03, 1.32)	0.013	0.232	1.14 (1, 1.31)	0.053	0.395
PC-PLGA36_5	0.86 (0.77, 0.97)	0.015	0.246	0.91 (0.81, 1.04)	0.188	0.655
PS34_0	0.87 (0.77, 0.97)	0.017	0.251	0.91 (0.81, 1.04)	0.17	0.642
DAG34_3	1.15 (1.03, 1.3)	0.017	0.251	1.04 (0.91, 1.19)	0.52	0.906
PC40_6	0.87 (0.78, 0.98)	0.02	0.275	0.9 (0.78, 1.02)	0.09	0.439
EA16:1	1.16 (1.02, 1.32)	0.023	0.281	1.11 (0.96, 1.27)	0.156	0.637
CE22:5	0.88 (0.79, 0.98)	0.023	0.281	0.98 (0.87, 1.11)	0.79	0.944
TAG50_0	1.13 (1.01, 1.26)	0.026	0.299	1.01 (0.89, 1.15)	0.839	0.979
PE34_2	1.13 (1.01, 1.27)	0.031	0.34	1.07 (0.95, 1.22)	0.261	0.752
PC40_9	0.88 (0.78, 0.99)	0.034	0.349	0.95 (0.84, 1.09)	0.489	0.873

SM16:1	1.15 (1.01, 1.32)	0.041	0.385	1.3 (1.1, 1.54)	0.002	0.066
DAG34_1	1.13 (1, 1.26)	0.041	0.385	1.01 (0.89, 1.15)	0.89	0.979
DAG36_4	1.13 (1, 1.26)	0.043	0.391	1.11 (0.98, 1.25)	0.118	0.51
TAG52_4	1.12 (1, 1.25)	0.046	0.392	1.09 (0.97, 1.23)	0.164	0.642
TAG54_3	0.9 (0.8, 1)	0.047	0.392	0.9 (0.8, 1.02)	0.091	0.439
CE20:4	0.9 (0.8, 1)	0.05	0.401	0.95 (0.84, 1.07)	0.393	0.858
OH36_4	1.15 (1, 1.32)	0.052	0.401	1.19 (1.01, 1.4)	0.038	0.34
TAG50_1	1.12 (1, 1.24)	0.057	0.405	0.98 (0.86, 1.11)	0.725	0.937
TAG48_0	1.11 (1, 1.23)	0.061	0.405	0.99 (0.87, 1.12)	0.887	0.979
CE22:6	0.9 (0.8, 1.01)	0.063	0.405	1 (0.88, 1.14)	0.966	0.984
PC36_1	0.9 (0.79, 1.01)	0.064	0.405	0.9 (0.78, 1.04)	0.149	0.621
TAG56_3	0.9 (0.81, 1.01)	0.065	0.405	0.89 (0.79, 1)	0.041	0.354
DAG32_0	0.88 (0.76, 1.01)	0.066	0.405	0.83 (0.7, 0.97)	0.021	0.267
DAG32_1	1.12 (0.99, 1.25)	0.069	0.405	0.98 (0.86, 1.12)	0.79	0.944
TAG58_8	0.9 (0.79, 1.01)	0.071	0.405	0.91 (0.8, 1.04)	0.179	0.642
LPE16:0	1.12 (0.99, 1.25)	0.073	0.405	1.17 (1.02, 1.34)	0.024	0.267
LPE18:2	1.11 (0.99, 1.24)	0.075	0.405	1.2 (1.05, 1.37)	0.008	0.133
PC38_4	0.9 (0.8, 1.01)	0.077	0.405	0.89 (0.78, 1.01)	0.07	0.4
SM14:0	1.11 (0.99, 1.24)	0.077	0.405	1.16 (1.02, 1.32)	0.026	0.267
PC34_2	1.11 (0.99, 1.24)	0.079	0.405	1.13 (0.99, 1.28)	0.064	0.4
PC38_6	0.9 (0.8, 1.01)	0.08	0.405	0.97 (0.85, 1.1)	0.614	0.928
DAG30_0	1.11 (0.99, 1.24)	0.081	0.405	1.01 (0.88, 1.16)	0.871	0.979
TAG58_7	0.9 (0.8, 1.01)	0.083	0.406	0.89 (0.78, 1.01)	0.07	0.4
PE36_0	1.11 (0.99, 1.25)	0.086	0.413	1.09 (0.96, 1.24)	0.176	0.642

PE36_3	1.11 (0.99, 1.23)	0.088	0.413	1.09 (0.96, 1.24)	0.175	0.642
LPC16:1	1.11 (0.98, 1.24)	0.091	0.419	1.09 (0.95, 1.26)	0.193	0.656
PE-PLG34_3	1.09 (0.98, 1.22)	0.095	0.421	1.11 (0.98, 1.25)	0.106	0.489
SM24:0	0.9 (0.81, 1.02)	0.095	0.421	0.94 (0.82, 1.09)	0.427	0.858
TAG52_1	1.09 (0.98, 1.23)	0.098	0.422	0.97 (0.85, 1.11)	0.675	0.937
PC-PLG36_2	0.91 (0.82, 1.02)	0.105	0.447	1.03 (0.9, 1.17)	0.694	0.937
DAG36_1	0.9 (0.81, 1.02)	0.109	0.449	0.79 (0.69, 0.9)	0.001	0.036
LPC16:0	1.11 (0.98, 1.25)	0.11	0.449	1.19 (1.02, 1.38)	0.024	0.267
PC38_2	0.9 (0.8, 1.02)	0.114	0.455	0.91 (0.79, 1.06)	0.23	0.721
TAG51_0	1.09 (0.98, 1.23)	0.118	0.463	1.01 (0.88, 1.15)	0.906	0.979
PE-PLG40_7	0.9 (0.81, 1.03)	0.12	0.463	0.96 (0.84, 1.1)	0.582	0.922
PE36_4	1.09 (0.97, 1.23)	0.125	0.467	1.02 (0.9, 1.16)	0.741	0.937
CER22:0	1.09 (0.98, 1.23)	0.125	0.467	1.11 (0.97, 1.26)	0.12	0.51
DAG32_2	1.09 (0.97, 1.22)	0.132	0.472	1 (0.88, 1.14)	0.985	0.985
DAG36_3	1.09 (0.97, 1.22)	0.139	0.472	1.06 (0.94, 1.2)	0.329	0.804
CE20:5	0.91 (0.81, 1.03)	0.141	0.472	1 (0.87, 1.14)	0.958	0.984
MAG16:1	0.9 (0.78, 1.04)	0.144	0.472	0.83 (0.7, 0.98)	0.024	0.267
LPE22:6	1.08 (0.97, 1.22)	0.145	0.472	1.13 (0.99, 1.28)	0.069	0.4
TAG54_1	1.08 (0.97, 1.21)	0.15	0.472	0.97 (0.86, 1.11)	0.686	0.937
TAG49_0	1.08 (0.97, 1.21)	0.152	0.472	0.99 (0.87, 1.13)	0.897	0.979
PE34_0	1.08 (0.97, 1.22)	0.153	0.472	1.09 (0.96, 1.24)	0.18	0.642
SM18:2	1.11 (0.96, 1.26)	0.155	0.472	1.26 (1.06, 1.49)	0.008	0.133
PC38_3	0.91 (0.82, 1.03)	0.157	0.472	0.85 (0.74, 0.97)	0.019	0.267
PC-PLG40_7	0.91 (0.81, 1.03)	0.157	0.472	0.99 (0.87, 1.14)	0.916	0.98

PE38_6	1.08 (0.97, 1.22)	0.157	0.472	1.04 (0.93, 1.18)	0.477	0.873
CE16:1	1.08 (0.97, 1.2)	0.157	0.472	1.02 (0.91, 1.15)	0.732	0.937
SM16:0	1.08 (0.97, 1.22)	0.159	0.472	1.28 (1.11, 1.49)	0.001	0.036
TAG50_2	1.08 (0.97, 1.21)	0.159	0.472	0.95 (0.84, 1.09)	0.495	0.873
TAG52_5	1.08 (0.97, 1.21)	0.164	0.479	1.05 (0.93, 1.19)	0.448	0.873
LPE20:4	1.08 (0.96, 1.22)	0.173	0.498	1.13 (0.98, 1.3)	0.09	0.439
TAG56_2	0.92 (0.83, 1.03)	0.176	0.499	0.86 (0.76, 0.97)	0.017	0.257
LPC18:2	1.07 (0.97, 1.2)	0.183	0.505	1.22 (1.06, 1.39)	0.005	0.11
PC34_0	1.08 (0.96, 1.21)	0.184	0.505	1.14 (1, 1.29)	0.045	0.363
TAG46_3	1.08 (0.96, 1.22)	0.185	0.505	1.02 (0.89, 1.17)	0.769	0.944
PE36_2	1.08 (0.96, 1.21)	0.188	0.508	1.02 (0.9, 1.16)	0.719	0.937
LPC14:0	1.08 (0.96, 1.22)	0.21	0.555	1.04 (0.9, 1.19)	0.591	0.922
LPC20:4	1.07 (0.96, 1.2)	0.211	0.555	1.12 (0.97, 1.28)	0.11	0.497
PE-PLG36_4	1.07 (0.96, 1.19)	0.217	0.566	1.12 (0.98, 1.26)	0.091	0.439
SM18:0	1.07 (0.96, 1.21)	0.228	0.586	1.15 (1, 1.32)	0.045	0.363
TAG56_5	1.07 (0.96, 1.21)	0.233	0.592	1.02 (0.9, 1.16)	0.713	0.937
TAG44_2	1.07 (0.95, 1.2)	0.239	0.6	1.01 (0.88, 1.16)	0.877	0.979
PE-PLG34_2	1.06 (0.96, 1.19)	0.243	0.603	1.12 (0.99, 1.26)	0.069	0.4
TAG50_3	1.07 (0.95, 1.2)	0.246	0.604	0.96 (0.84, 1.1)	0.561	0.918
PC30_0	1.07 (0.96, 1.19)	0.249	0.604	1.02 (0.9, 1.17)	0.709	0.937
PE-PLG36_1	1.06 (0.96, 1.19)	0.254	0.609	1.08 (0.96, 1.21)	0.181	0.642
TAG46_2	1.07 (0.95, 1.2)	0.258	0.609	0.99 (0.86, 1.13)	0.874	0.979
PC34_1	0.93 (0.83, 1.05)	0.262	0.609	0.95 (0.83, 1.08)	0.429	0.858
PE-PLG36_3	1.07 (0.95, 1.2)	0.262	0.609	1.13 (1, 1.28)	0.053	0.395

PC-PLG34_2	0.94 (0.84, 1.05)	0.267	0.61	1.04 (0.92, 1.19)	0.497	0.873
LPC18:3	1.07 (0.95, 1.21)	0.272	0.61	1.15 (0.99, 1.33)	0.064	0.4
LPE18:0	1.07 (0.95, 1.21)	0.274	0.61	1.12 (0.97, 1.29)	0.114	0.503
TAG47_0	1.06 (0.95, 1.19)	0.274	0.61	0.98 (0.86, 1.11)	0.723	0.937
SM18:1	1.07 (0.94, 1.22)	0.279	0.616	1.2 (1.02, 1.4)	0.032	0.313
CE20:3	0.94 (0.84, 1.05)	0.295	0.641	0.93 (0.82, 1.06)	0.27	0.752
TAG56_7	0.94 (0.83, 1.06)	0.297	0.641	0.95 (0.84, 1.08)	0.427	0.858
TAG49_2	1.06 (0.95, 1.18)	0.302	0.641	0.97 (0.85, 1.1)	0.642	0.937
TAG48_2	1.06 (0.95, 1.19)	0.303	0.641	0.94 (0.83, 1.08)	0.4	0.858
TAG44_1	1.06 (0.95, 1.19)	0.31	0.65	0.99 (0.87, 1.14)	0.915	0.98
PE32_0	1.06 (0.95, 1.18)	0.313	0.65	1.05 (0.92, 1.19)	0.478	0.873
SM24:1	0.94 (0.84, 1.06)	0.321	0.661	1.06 (0.92, 1.23)	0.386	0.851
TAG50_4	1.06 (0.94, 1.19)	0.327	0.667	0.99 (0.87, 1.13)	0.895	0.979
TAG45_2	1.05 (0.95, 1.18)	0.339	0.685	0.98 (0.86, 1.11)	0.737	0.937
TAG46_4	1.06 (0.94, 1.19)	0.349	0.694	1.02 (0.89, 1.16)	0.81	0.961
TAG48_3	1.06 (0.94, 1.19)	0.35	0.694	0.97 (0.85, 1.11)	0.676	0.937
TAG49_1	1.05 (0.94, 1.17)	0.362	0.707	0.97 (0.85, 1.1)	0.609	0.928
PC-PLG34_4	0.95 (0.85, 1.06)	0.364	0.707	0.97 (0.86, 1.1)	0.627	0.934
TAG52_0	1.05 (0.94, 1.18)	0.369	0.707	0.95 (0.83, 1.09)	0.458	0.873
TAG46_1	1.05 (0.94, 1.18)	0.37	0.707	0.95 (0.83, 1.09)	0.48	0.873
PC-PLG38_7	0.95 (0.85, 1.07)	0.384	0.725	0.97 (0.86, 1.1)	0.649	0.937
TAG48_4	1.05 (0.94, 1.19)	0.386	0.725	1 (0.87, 1.14)	0.971	0.984
TAG43_0	1.05 (0.94, 1.18)	0.389	0.725	1.01 (0.89, 1.16)	0.857	0.979
PC32_2	1.05 (0.93, 1.19)	0.394	0.728	1.03 (0.9, 1.17)	0.693	0.937

TAG45_3	1.05 (0.94, 1.18)	0.399	0.73	0.97 (0.85, 1.11)	0.687	0.937
CE18:0	0.95 (0.86, 1.07)	0.419	0.761	1.01 (0.9, 1.15)	0.817	0.964
TAG51_3	1.05 (0.94, 1.17)	0.424	0.763	0.99 (0.88, 1.13)	0.922	0.981
TAG54_5	1.05 (0.93, 1.18)	0.431	0.769	0.97 (0.85, 1.11)	0.676	0.937
LPC18:0	1.05 (0.93, 1.18)	0.442	0.769	1.15 (0.99, 1.33)	0.063	0.4
PE40_6	0.96 (0.85, 1.07)	0.442	0.769	0.93 (0.82, 1.06)	0.273	0.752
TAG41_0	1.05 (0.93, 1.18)	0.446	0.769	1.04 (0.91, 1.2)	0.555	0.918
TAG54_4	0.96 (0.86, 1.07)	0.447	0.769	1 (0.89, 1.13)	0.942	0.984
TAG58_9	0.95 (0.85, 1.08)	0.451	0.769	1 (0.88, 1.14)	0.979	0.984
TAG48_1	1.04 (0.93, 1.16)	0.452	0.769	0.92 (0.81, 1.06)	0.26	0.752
LPC20:5	1.04 (0.93, 1.16)	0.461	0.771	1.16 (1.02, 1.33)	0.026	0.267
LPC22:6	1.04 (0.93, 1.16)	0.464	0.771	1.12 (0.99, 1.28)	0.083	0.439
TAG54_10	0.96 (0.85, 1.08)	0.464	0.771	1 (0.87, 1.15)	0.975	0.984
PC36_0	0.96 (0.86, 1.07)	0.476	0.772	1.05 (0.92, 1.2)	0.451	0.873
TAG54_6	1.04 (0.93, 1.16)	0.48	0.772	1.07 (0.95, 1.21)	0.259	0.752
PC-PLG34_1	0.96 (0.85, 1.08)	0.481	0.772	1.08 (0.94, 1.24)	0.275	0.752
PE-PLG38_7	0.96 (0.85, 1.08)	0.482	0.772	1 (0.88, 1.14)	0.95	0.984
DAG38_5	1.04 (0.93, 1.18)	0.483	0.772	0.96 (0.85, 1.1)	0.591	0.922
PC-PLG38_6	0.96 (0.85, 1.08)	0.49	0.776	0.97 (0.85, 1.11)	0.657	0.937
TAG47_2	1.04 (0.93, 1.16)	0.492	0.776	0.95 (0.83, 1.08)	0.418	0.858
TAG49_3	1.04 (0.93, 1.16)	0.498	0.779	0.93 (0.82, 1.06)	0.273	0.752
PC36_2	0.96 (0.86, 1.08)	0.515	0.8	1 (0.88, 1.14)	0.975	0.984
CAMPESTEROL	0.96 (0.86, 1.08)	0.528	0.815	1.04 (0.91, 1.2)	0.554	0.918
TAG58_11	0.96 (0.86, 1.08)	0.539	0.821	0.97 (0.86, 1.09)	0.582	0.922

TAG46_0	1.03 (0.93, 1.15)	0.543	0.821	0.93 (0.83, 1.06)	0.302	0.787
PC-PLG36_3	0.96 (0.86, 1.08)	0.544	0.821	1.06 (0.94, 1.21)	0.338	0.804
LPE22:0	0.97 (0.87, 1.08)	0.574	0.859	1.15 (1, 1.31)	0.055	0.395
PC36_4	1.03 (0.92, 1.15)	0.579	0.859	1.13 (0.99, 1.29)	0.073	0.405
PC-PLG36_1	0.97 (0.87, 1.08)	0.581	0.859	1.06 (0.94, 1.2)	0.337	0.804
TAG54_2	0.97 (0.87, 1.08)	0.585	0.859	0.9 (0.79, 1.02)	0.091	0.439
TAG53_3	0.97 (0.87, 1.08)	0.591	0.863	0.97 (0.86, 1.09)	0.584	0.922
TAG51_2	1.03 (0.92, 1.15)	0.6	0.864	0.94 (0.82, 1.07)	0.346	0.808
TAG50_5	1.03 (0.92, 1.16)	0.602	0.864	0.98 (0.86, 1.11)	0.718	0.937
TAG43_1	1.03 (0.92, 1.15)	0.609	0.864	0.96 (0.84, 1.1)	0.596	0.922
TAG60_12	0.97 (0.86, 1.09)	0.615	0.864	0.97 (0.86, 1.09)	0.597	0.922
TAG48_5	1.03 (0.91, 1.16)	0.619	0.864	0.99 (0.87, 1.13)	0.853	0.979
TAG56_10	0.97 (0.87, 1.09)	0.619	0.864	0.97 (0.86, 1.09)	0.619	0.928
TAG56_4	0.97 (0.87, 1.09)	0.625	0.864	0.97 (0.86, 1.09)	0.577	0.922
TAG56_8	1.03 (0.92, 1.16)	0.631	0.864	1.03 (0.91, 1.16)	0.672	0.937
TAG47_1	1.03 (0.92, 1.14)	0.642	0.864	0.94 (0.82, 1.07)	0.348	0.808
PC32_1	1.03 (0.92, 1.15)	0.651	0.864	0.95 (0.84, 1.08)	0.42	0.858
PE38_4	1.03 (0.91, 1.16)	0.658	0.864	0.96 (0.84, 1.1)	0.557	0.918
SM20:0	0.97 (0.86, 1.1)	0.658	0.864	1.08 (0.94, 1.25)	0.282	0.76
TAG43_2	1.03 (0.92, 1.15)	0.659	0.864	0.95 (0.83, 1.08)	0.421	0.858
PC36_3	0.97 (0.86, 1.1)	0.66	0.864	0.98 (0.85, 1.13)	0.78	0.944
PE38_2	0.98 (0.87, 1.09)	0.66	0.864	1.06 (0.94, 1.2)	0.338	0.804
PC34_4	0.97 (0.86, 1.1)	0.663	0.864	0.94 (0.82, 1.08)	0.413	0.858
PE-PLG38_5	0.97 (0.87, 1.1)	0.669	0.864	0.98 (0.86, 1.11)	0.728	0.937

PC-PLGB36_5	1.02 (0.92, 1.15)	0.673	0.864	1.01 (0.89, 1.14)	0.904	0.979
TAG54_8	0.98 (0.87, 1.09)	0.68	0.864	0.97 (0.86, 1.1)	0.654	0.937
CE18:1	0.98 (0.87, 1.09)	0.681	0.864	1.09 (0.96, 1.24)	0.178	0.642
TAG42_0	1.02 (0.91, 1.15)	0.685	0.864	0.98 (0.86, 1.12)	0.767	0.944
TAG52_3	1.02 (0.91, 1.15)	0.685	0.864	0.96 (0.85, 1.09)	0.554	0.918
SM22:0	0.98 (0.87, 1.1)	0.687	0.864	1.03 (0.89, 1.18)	0.702	0.937
CHOLESTEROL	0.98 (0.87, 1.1)	0.688	0.864	1.05 (0.92, 1.21)	0.457	0.873
TAG52_2	1.02 (0.91, 1.15)	0.696	0.869	0.93 (0.82, 1.06)	0.285	0.76
TAG44_0	1.02 (0.92, 1.14)	0.7	0.869	0.94 (0.83, 1.07)	0.366	0.831
TAG52_6	1.02 (0.91, 1.15)	0.718	0.878	0.99 (0.88, 1.11)	0.85	0.979
CE16:0	1.02 (0.91, 1.14)	0.72	0.878	1.15 (1.01, 1.31)	0.033	0.313
PE-PLG38_6	0.98 (0.87, 1.1)	0.722	0.878	1.02 (0.9, 1.16)	0.707	0.937
CER24:0	1.02 (0.91, 1.14)	0.726	0.878	1.04 (0.92, 1.18)	0.528	0.909
CE18:2	0.98 (0.88, 1.1)	0.732	0.878	1.08 (0.96, 1.23)	0.207	0.679
TAG55_3	0.98 (0.88, 1.09)	0.732	0.878	1 (0.89, 1.12)	0.971	0.984
DAG36_2	0.98 (0.88, 1.1)	0.747	0.891	0.93 (0.82, 1.05)	0.237	0.725
TAG56_9	0.98 (0.88, 1.1)	0.754	0.894	0.99 (0.88, 1.11)	0.848	0.979
TAG50_6	1.02 (0.9, 1.15)	0.762	0.894	0.98 (0.86, 1.12)	0.78	0.944
TAG45_1	1.02 (0.91, 1.13)	0.763	0.894	0.94 (0.83, 1.07)	0.377	0.84
TAG54_7	1.02 (0.91, 1.14)	0.766	0.894	1.01 (0.9, 1.13)	0.875	0.979
LPE20:0	1.02 (0.91, 1.14)	0.774	0.899	1.09 (0.96, 1.25)	0.194	0.656
TAG54_9	0.98 (0.88, 1.11)	0.783	0.905	0.98 (0.87, 1.11)	0.788	0.944
CE18:3	0.99 (0.88, 1.1)	0.792	0.908	1 (0.88, 1.13)	0.944	0.984
PE36_1	0.99 (0.88, 1.1)	0.799	0.908	0.92 (0.81, 1.05)	0.238	0.725

PE-PLG36_5	1.01 (0.91, 1.14)	0.801	0.908	1 (0.88, 1.13)	0.964	0.984
LPC18:1	1.01 (0.91, 1.13)	0.803	0.908	1.14 (0.99, 1.3)	0.066	0.4
PC-PLG34_3	0.99 (0.89, 1.1)	0.81	0.911	1.04 (0.92, 1.18)	0.489	0.873
TAG58_6	1.01 (0.9, 1.14)	0.816	0.912	0.96 (0.85, 1.08)	0.481	0.873
PE-PLG42_11	0.99 (0.87, 1.11)	0.819	0.912	1.06 (0.93, 1.23)	0.369	0.831
DAG38_4	0.99 (0.88, 1.11)	0.827	0.916	0.92 (0.82, 1.05)	0.221	0.711
TAG52_7	0.99 (0.88, 1.11)	0.847	0.919	0.96 (0.85, 1.09)	0.53	0.909
LPE18:1	0.99 (0.89, 1.1)	0.848	0.919	1.05 (0.92, 1.19)	0.449	0.873
MAG18:0	0.99 (0.85, 1.14)	0.849	0.919	0.92 (0.79, 1.09)	0.367	0.831
TAG58_10	1.01 (0.9, 1.13)	0.85	0.919	1.02 (0.91, 1.15)	0.754	0.944
PC-PLG34_5	1.01 (0.91, 1.13)	0.851	0.919	1.02 (0.9, 1.14)	0.791	0.944
PE-PLG38_3	0.99 (0.89, 1.11)	0.877	0.942	1.03 (0.92, 1.16)	0.619	0.928
TAG55_2	1.01 (0.9, 1.13)	0.888	0.95	0.94 (0.83, 1.07)	0.339	0.804
TAG56_6	0.99 (0.88, 1.12)	0.901	0.958	0.96 (0.85, 1.09)	0.552	0.918
CE14:0	1.01 (0.91, 1.12)	0.907	0.958	0.99 (0.88, 1.12)	0.929	0.983
PC30_1	1.01 (0.9, 1.12)	0.911	0.958	0.93 (0.82, 1.06)	0.293	0.771
TAG45_0	1.01 (0.9, 1.13)	0.914	0.958	0.95 (0.84, 1.09)	0.467	0.873
TAG53_2	0.99 (0.89, 1.11)	0.92	0.958	0.93 (0.82, 1.06)	0.314	0.804
PC-PLG38_4	0.99 (0.89, 1.11)	0.922	0.958	0.99 (0.88, 1.12)	0.907	0.979
PE38_5	1.01 (0.89, 1.13)	0.928	0.959	1.02 (0.9, 1.16)	0.78	0.944
PE-PLG36_2	1 (0.9, 1.12)	0.936	0.959	1.05 (0.92, 1.19)	0.478	0.873
PS40_6	1 (0.89, 1.12)	0.937	0.959	0.98 (0.86, 1.12)	0.742	0.937
PC34_3	1 (0.89, 1.13)	0.949	0.962	1.01 (0.88, 1.15)	0.906	0.979
TAG56_1	1 (0.9, 1.12)	0.949	0.962	0.92 (0.81, 1.04)	0.201	0.668

SM22:1	1 (0.88, 1.14)	0.983	0.989	1.15 (0.97, 1.35)	0.101	0.476
CE22:4	1 (0.89, 1.12)	0.984	0.989	1.07 (0.95, 1.21)	0.244	0.733
CER24:1	1 (0.89, 1.12)	0.99	0.99	1.06 (0.94, 1.21)	0.322	0.804

The relative risks (RRs) correspond to OR from a conditional logistic regression model. FDR: false discovery rate-controlled p-value.

M1: controlled for age, sex, and study center (if applicable).

M2: additionally adjusted for T2D- and hypertension prevalence, BMI, smoking status, educational attainment, family history of early CAD, and intervention group.

Online Table III: Single lipid-HF associations for all lipids that were nominally significantly associated with HF risk in PREDIMED and available in EPIC-Potsdam

	PREDIMED			EPIC-Potsdam			
Model	Lipid	RR (95% CI)*	p-value†	Matched lipid‡	RR (95% CI)	p-value‖	FDR#
Significant in PREDIMED, replicated in EPIC-Potsdam & robust against adjustment for other risk factors							
M1	PC32_0	1.21 (1.07, 1.36)	0.00180	PC 16:0/16:0	1.49 (1.19, 1.86)	0.00024	0.0018
M2		1.23 (1.08, 1.41)	0.00224		1.43 (1.14, 1.80)	0.00101	0.0076
M1	CER16:0	1.20 (1.07, 1.34)	0. 00226	CER 16:0	1.60 (1.29, 1.99)	1.2E-05	0.0002
M2		1.28 (1.13, 1.47)	0.00017		1.48 (1.17, 1.87)	0.00048	0.0072
Significant in PREDIMED, replicated in EPIC-Potsdam, but NOT robust against further adjustment							
M1	DAG34_2	1.16 (1.04, 1.31)	0.009	DAG16:1/18:1	1.24 (0.99, 1.54)	0.029	0.062
M2		1.05 (0.93, 1.20)	0.42		1.12 (0.88, 1.42)	0.177	0.332
M1	TAG51_1	1.15 (1.03, 1.29)	0.012	TAG51_1-fa16:0	1.32 (1.06, 1.64)	0.006	0.018
M2		1.03 (0.90, 1.17)	0.671		1.21 (0.95, 1.53)	0.058	0.174
M1	TAG50_0	1.13 (1.01, 1.26)	0.026	TAG50_0-fa16:0	1.33 (1.06, 1.65)	0.006	0.018
M2		1.01 (0.89, 1.15)	0.839		1.20 (0.94, 1.52)	0.075	0.188

M1	PE34_2	1.13 (1.01, 1.27)	0.031	PE18:1/16:1	1.26 (1.02, 1.56)	0.015	0.038
M2		1.07 (0.95, 1.22)	0.261		1.20 (0.97, 1.49)	0.048	0.174
M1	DAG34_1	1.13 (1.00, 1.26)	0.041	DAG16:1/18:0	1.35 (1.08, 1.68)	0.004	0.018
M2		1.01 (0.89, 1.15)	0.89		1.25 (0.99, 1.58)	0.031	0.155
M1	TAG52_4	1.12 (1.00, 1.25)	0.046	TAG52_4-fa22:1	1.21 (0.98, 1.51)	0.041	0.077
M2		1.09 (0.97, 1.23)	0.164		1.13 (0.91, 1.42)	0.137	0.294
Significant association in PREDIMED, NOT replicated							
M1	PI38_4	0.82 (0.73, 0.93)	0.001	PI18:0/20:4	1.08 (0.88, 1.33)	d.i.	1
M2		0.79 (0.68, 0.91)	0.001		1.02 (0.83, 1.27)	d.i.	1
M1	DAG34_0	0.84 (0.73, 0.95)	0.007	DAG14:0/20:0	1.07 (0.87, 1.33)	d.i.	1
M2		0.76 (0.65, 0.88)	<0.001		1.00 (0.80, 1.24)	d.i.	1
M1	DAG34_3	1.15 (1.03, 1.30)	0.017	DAG16:0/18:3	1.19 (0.96, 1.48)	0.059	0.098
M2		1.04 (0.91, 1.19)	0.52		1.10 (0.87, 1.41)	0.211	0.352
M1	PC40_6	0.87 (0.78, 0.98)	0.02	PC18:1/22:5	1.12 (0.90, 1.38)	d.i.	1
M2		0.90 (0.78, 1.02)	0.09		1.10 (0.89, 1.38)	d.i.	1
M1	CE22:5	0.88 (0.79, 0.98)	0.023	CE22:5	1.07 (0.86, 1.33)	d.i.	1
		0.98 (0.87, 1.11)	0.79		1.06 (0.85, 1.33)	d.i.	1

M1	DAG36_4	1.13 (1.00, 1.26)	0.043	DAG16:0/20:4	1.15 (0.92, 1.43)	0.106	0.159
M2		1.11 (0.98, 1.25)	0.118		1.04 (0.81, 1.33)	0.382	0.573
M1	TAG54_3	0.90 (0.80, 1.00)	0.047	TAG53_4-fa18:0	1.31 (1.05, 1.63)	d.i.	1
M2		0.90 (0.80, 1.02)	0.091		1.20 (0.95, 1.52)	d.i.	1

Heart failure risk associations of the 15 of 26 marginally significant (p-value<0.05) lipids in PREDIMED, which were available for replication in EPIC-Potsdam.

*In PREDIMED, the relative risk (RR) correspond to OR from a conditional logistic regression model.

†Two-tailed p-value in PREDIMED.

[‡] For isomeric lipids with multiple matches in EPIC-Potsdam, the best predictor among these lipids was selected according the lowest p-value (backwards selection).

[§] In EPIC-Potsdam, RRs correspond to hazard ratios from a Cox model.

[||] One-tailed p-value in EPIC-Potsdam (testing for directionally consistent estimates only).

*FDR: false discovery rate, controlled for the 15 intended replications (for M1 and M2 separately).

d.i.: directionally inconsistent risk estimate, one-tailed p-value not meaningful.

M1: controlled for age, sex, and study center (if applicable).

M2: additionally adjusted for T2D- and hypertension prevalence, BMI, smoking status, educational attainment, family history of early CAD, and intervention group (if applicable).

Online Table IV: Single lipid-HF associations: additional adjustment for standard blood lipid markers

PREDIMED			EPIC-Potsdam		
Lipid	RR (95% CI)*	p-value	Matched lipid	RR (95% CI)†	p-value
PC 32_0	1.23 (1.07, 1.41)	0.003	PC 16:0/16:0	1.45 (1.13, 1.88)	0.004
CER 16:0	1.28 (1.13, 1.46)	<0.001	CER 16:0	1.57 (1.17,2.09)	0.002

The association with the relative risk (RR) of heart failure was controlled for age, sex, study center (PREDIMED only), T2D- and hypertension prevalence, BMI, smoking status, educational attainment, family history of early CAD, and intervention group, AND standard blood lipid markers (prevalence of dyslipidemia in PREDIMED and plasma concentrations of HDL-cholesterol, total cholesterol and total triglycerides in EPIC-Potsdam).

Online Table V: Lipid clusters and heart failure incidence

	PREDIMED			EPIC-Potsdam		
Model	Lipid	RR (95% CI)*	p-value†	Matched lipid‡	RR (95% CI)§	p-value‖
Cluster 1: MAGs & EA16:1						
M1	EA16:1	1.27 (1.09, 1.47)	0.002			
M2		1.24 (1.06, 1.46)	0.008			
M1	MAG16:1	0.8 (0.67, 0.95)	0.010	MAG16:1	1.09 (0.87, 1.37)	d.i.
M2		0.74 (0.62, 0.89)	0.002		1.05 (0.83, 1.33)	d.i.
Cluster 2: Sphingolipids						
M1	CER16:0	1.24 (1.06, 1.46)	0.008	CER16:0	1.81 (1.24, 2.63)	0.001
M2		1.27 (1.06, 1.51)	0.009		1.72 (1.14, 2.6)	0.005
M1	CER24:1	0.81 (0.7, 0.94)	0.006	CER24:1	0.92 (0.63, 1.35)	0.337
M2		0.86 (0.73, 1)	0.048		0.92 (0.62, 1.38)	0.345
M1	SM16:1	2.02 (1.47, 2.76)	<0.001			
M2		1.85 (1.32, 2.6)	<0.001			
M1	SM18:0	1.61 (1.16, 2.24)	0.005	SM18:0	1.71 (0.93, 3.16)	0.043
M2		1.43 (1.01, 2.02)	0.042		1.54 (0.82, 2.9)	0.091
M1	SM18:1	0.57 (0.39, 0.85)	0.006	SM18:1	0.53 (0.3, 0.96)	0.017
M2		0.66 (0.43, 1.02)	0.059		0.63 (0.34, 1.15)	0.066
M1	SM24:0	0.69 (0.58, 0.83)	<0.001	SM24:0	1.16 (0.81, 1.67)	d.i.
M2		0.7 (0.57, 0.85)	<0.001		1.27 (0.88, 1.83)	d.i.
M1	SM24:1	0.75 (0.61, 0.92)	0.005	SM24:1	0.8 (0.53, 1.21)	0.147
M2		0.88 (0.71, 1.09)	0.234		0.68 (0.44, 1.04)	0.037
Cluster 3: lc-SFA PCs						

M1	PC32_0	1.27 (1.12, 1.45)	<0.001	PC16:0/16:0	1.31 (0.99, 1.73)	0.030
M2		1.25 (1.08, 1.44)	0.002		1.34 (1.01, 1.79)	0.022
M1	PC36_0	0.88 (0.77, 0.99)	0.032	PC18:0/18:0	1.23 (0.95, 1.61)	d.i.
M2		0.96 (0.84, 1.11)	0.600		1.11 (0.84, 1.47)	d.i.
Cluster 4: Phospholipids						
M1	LPC16:1	1.24 (1.07, 1.44)	0.004	LPC16:1	0.71 (0.51, 0.98)	d.i.
M2		1.32 (1.11, 1.56)	0.002		0.75 (0.53, 1.05)	d.i.
M1	PC30_1	0.68 (0.56, 0.81)	<0.001	PC14:0/16:1	0.96 (0.71, 1.31)	0.402
M2		0.66 (0.53, 0.81)	<0.001		0.89 (0.65, 1.22)	0.241
M1	PC34_2	1.66 (1.38, 2)	<0.001	PC18:1/16:1	1.82 (1.25, 2.63)	0.00097
M2		1.54 (1.25, 1.89)	<0.001		1.82 (1.24, 2.67)	0.00141
M1	PE36_0	1.73 (1.38, 2.16)	<0.001	PE18:0/18:0	0.95 (0.73, 1.24)	d.i.
M2		1.51 (1.19, 1.92)	<0.001		0.95 (0.73, 1.24)	d.i.
M1	PE38_2	0.57 (0.45, 0.72)	<0.001	PE18:0/20:2	1.07 (0.83, 1.39)	d.i.
M2		0.7 (0.54, 0.9)	0.006		1.04 (0.79, 1.35)	d.i.
M1	PI38_4	0.78 (0.68, 0.88)	<0.001	PI18:0/20:4	0.96 (0.76, 1.21)	0.371
M2		0.75 (0.64, 0.87)	<0.001		0.92 (0.72, 1.17)	0.242
Cluster 5: SFA-DAGs						
M1	DAG36_0	0.83 (0.73, 0.94)	0.004			
M2		0.81 (0.71, 0.93)	0.003			
Cluster 6: Plasmalogens						
M1	PC-PLG36_2	0.79 (0.68, 0.91)	0.002			
M2		0.9 (0.76, 1.06)	0.202			
M1	PE-PLG34_3	1.28 (1.11, 1.49)	<0.001			

M2		1.2 (1.01, 1.41)	0.036			
M1	PE-PLG36_1	1.16 (1.03, 1.32)	0.018	PE-PLG18:0/18:1	1.48 (1.17, 1.86)	0.00052
M2		1.12 (0.98, 1.28)	0.089		1.39 (1.1, 1.76)	0.00336
M1	PE-PLG40_7	0.65 (0.51, 0.82)	<0.001	PE-PLG18:1/22:6	0.76 (0.6, 0.97)	0.01178
M2		0.68 (0.53, 0.87)	0.002		0.79 (0.62, 1)	0.02319
M1	PE-PLG42_11	1.33 (1.07, 1.67)	0.011			
M2		1.36 (1.07, 1.72)	0.011			
Cluster 7: Unsaturated FA-DAGs						
M1	DAG34_1	1.63 (1.3, 2.03)	<0.001	DAG16:1/18:0	1.45 (1.02, 2.06)	0.020
M2		1.31 (1.03, 1.67)	0.028		1.35 (0.94, 1.93)	0.050
M1	DAG36_2	0.65 (0.53, 0.81)	<0.001	DAG18:0/18:2	0.92 (0.65, 1.29)	0.306
M2		0.74 (0.59, 0.93)	0.011		0.91 (0.64, 1.28)	0.289
Cluster 8: TAGs						
M1	TAG55_2	1.16 (1, 1.34)	0.049	TAG55_2-fa18:1	1.42 (0.99, 2.03)	0.029
M2		1.13 (0.96, 1.33)	0.132		1.43 (0.95, 2.17)	0.044
M1	TAG56_5	1.26 (1.09, 1.45)	0.002	TAG56_5-fa16:0	3.06 (1.69, 5.55)	0.00011
M2		1.2 (1.03, 1.41)	0.022		2.6 (1.41, 4.78)	0.00107
M1	TAG58_7	0.55 (0.4, 0.76)	<0.001	TAG58_7-fa16:0	0.38 (0.23, 0.63)	8.40E-05
M2		0.49 (0.35, 0.7)	<0.001		0.38 (0.23, 0.65)	0.00017
M1	TAG58_9	1.44 (1.09, 1.89)	0.009	TAG58_9-fa22:5	0.7 (0.51, 0.97)	d.i.
M2		1.69 (1.23, 2.32)	0.001		0.76 (0.55, 1.06)	d.i.

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*PREDIMED: relative risks (RRs) based on OR from a conditional logistic regression model.

†Two-tailed p-value in PREDIMED.

‡For isomeric lipids with multiple matches in EPIC-Potsdam, the best predictor among these lipids was

selected according the lowest p-value.

[§] In EPIC-Potsdam, RRs correspond to HRs from a Cox model.

[||] One-tailed p-value.

[#] d.i., directionally inconsistent

M1: controlled for age, sex, and study center (if applicable).

M2: additionally adjusted for T2D- and hypertension prevalence, BMI, smoking status, educational attainment, family history of early CAD, and intervention group (if applicable).

Online Table VI: Replication with the sum of all isomeric lipids in EPIC-Potsdam that match a PREDIMED-hit

EPIC-Potsdam SUM of ALL MATCHES	Model	RR	p-value
Replicated & robust against adjustment for other risk factors			
PC 32_0	M1	1.46 (1.18, 1.8)	0.00033
	M2	1.41 (1.14, 1.74)	0.00140
Replicated, but NOT robust against further adjustment			
DAG 34_2	M1	1.23 (0.99, 1.53)	0.0331
	M2	1.12 (0.88, 1.43)	0.1701
TAG 51_1	M1	1.3 (1.05, 1.61)	0.0085
	M2	1.19 (0.94, 1.5)	0.0715
TAG 50_0	M1	1.32 (1.06, 1.64)	0.0065
	M2	1.19 (0.94, 1.52)	0.0731
PE 34_2	M1	1.29 (1.05, 1.59)	0.0077
	M2	1.2 (0.97, 1.49)	0.0483
DAG 34_1	M1	1.32 (1.06, 1.65)	0.0063
	M2	1.21 (0.96, 1.54)	0.0554
TAG 52_4	M1	1.2 (0.97, 1.49)	0.0478
	M2	1.12 (0.89, 1.4)	0.1742
NOT replicated			
PI 38_4	M1	1.12 (0.91, 1.38)	0.1382
	M2	1.07 (0.86, 1.32)	0.2688

DAG 34_0	M1	1.19 (0.96, 1.48)	0.0546
	M2	1.08 (0.86, 1.36)	0.2509
DAG 34_3	M1	1.19 (0.96, 1.48)	0.0593
	M2	1.1 (0.87, 1.4)	0.2139
PC 40_6	M1	1.05 (0.85, 1.31)	0.3228
	M2	1.01 (0.82, 1.25)	0.4524
DAG 36_4	M1	1.15 (0.92, 1.43)	0.1062
	M2	1.04 (0.81, 1.33)	0.3821
TAG 54_3	M1	1.33 (1.08, 1.65)	0.0088
	M2	1.23 (0.97, 1.55)	0.086

M1: controlled for age, sex

M2: additionally adjusted for T2D- and hypertension prevalence, BMI, smoking status, educational attainment, family history of early CAD, and intervention group

For isomeric lipids with multiple matches in EPIC-Potsdam, the absolute concentrations of all lipids were summed. For each constructed summary-measure, the matched lipids that were summed in EPIC-Potsdam are listed below:

PC 32_0: PC 18:0/14:0+PC 16:0/16:0

DAG 34_2: DAG 16:0/18:2+DAG 16:1/18:1

TAG 51_1: TAG 51_1-fa15:0+TAG 51_1-fa16:0+TAG 51_1-fa17:0+TAG 51_1-fa18:0+TAG 51_1-fa18:1

TAG 50_0: TAG 50_0-fa14:0+TAG 50_0-fa16:0+TAG 50_0-fa18:0 DAG 34_0

PE 34_2: PE 18:1/16:1+PE 16:0/18:2

DAG 34_1: DAG 16:0/18:1+DAG 16:1/18:0

TAG 52_4: TAG 52_4-fa14:0 + TAG 52_4_fa16:0 + TAG 52_4-fa16:1 +TAG 52_4-fa18:0 + TAG 52_4_fa18:1 + TAG 52_4-fa18:2 +TAG 52_4-fa18:3 + TAG 52_4-fa20:0 + TAG 52_4-fa20:2 +TAG 52_4-fa20:3 + TAG

52_4-fa20:4 + TAG 52_4-fa22:1 +TAG 52_4-fa22:4

PI 38_4: PI 18:1/20:3+PI 18:0/20:4

DAG 34_0: DAG 14:0/20:0+DAG 16:0/18:0

DAG 34_3: DAG 16:0/18:3+DAG 16:1/18:2

PC 40_6: PC 18:0/22:6+PC 18:1/22:5

DAG 36_4: DAG 16:0/20:4

TAG 54_3: TAG54_3-fa16:0 + TAG54_3-fa16:1 + TAG54:3-fa18:0 + TAG54_3-fa18:1 + TAG54_3-fa18:2 + TAG54_3-fa18:3 + TAG54_3-fa20:1 + TAG54_3-fa20:2 + TAG54_3-fa20:3

Online Table VII: Lipid score-HF associations: additional adjustment for standard blood lipid markers

PREDIMED			EPIC-Potsdam		
Lipid	RR (95% CI)	p-value	Matched lipid	RR (95% CI)	p-value
Score 1	2.32 (1.92, 2.80)	<2E-16			
Score 2	1.29 (1.13, 1.46)	0.0001	Score 2	1.49 (1.15, 1.93)	0.002

Controlled for age, sex, study center (PREDIMED only), T2D- and hypertension prevalence, BMI, smoking status, educational attainment, family history of early CAD, and intervention group, AND standard blood lipid markers (prevalence of dyslipidemia in PREDIMED and plasma concentrations of HDL-cholesterol, total cholesterol and total triglycerides in EPIC-Potsdam).

Online Table VIII: Lipid marker-HF associations, stratified by intervention group.

lipid	Intervention group	Model	RR		P(IA)
CER16:0	Low-fat (control)	M1	1.14 (0.94, 1.38)		ref.
		M2	1.17 (0.98, 1.41)		
	MedDiet+EVOO	M1	1.19 (0.98, 1.44)		0.82
		M2	1.23 (1.01, 1.5)		
	MedDiet+nuts	M1	1.11 (0.92, 1.34)		0.915
		M2	1.16 (0.95, 1.42)		
PC32_0	Low-fat (control)	M1	1.16 (0.94, 1.43)		ref.
		M2	1.19 (0.97, 1.47)		
	MedDiet+EVOO	M1	1.14 (0.93, 1.41)		0.626
		M2	1.1 (0.91, 1.34)		
	MedDiet+nuts	M1	1.22 (0.99, 1.49)		0.789
		M2	1.25 (1.02, 1.54)		
Score 1 (cross- validated)	Low-fat (control)	M1	1.68 (1.41, 1.99)		ref.
		M2	1.62 (1.37, 1.91)		
	MedDiet+EVOO	M1	1.72 (1.45, 2.04)		0.66
		M2	1.63 (1.37, 1.93)		
	MedDiet+nuts	M1	1.52 (1.31, 1.77)		0.367
		M2	1.5 (1.27, 1.77)		
Score 2 (replicated)	Low-fat (control)	M1	1.19 (0.98, 1.44)		ref.
		M2	1.13 (0.93, 1.38)		
	MedDiet+EVOO	M1	1.29 (1.08, 1.56)		0.447
		M2	1.2 (0.99, 1.45)		
	MedDiet+nuts	M1	1.31 (1.09, 1.58)		0.663
		M2	1.25 (1.03, 1.52)		

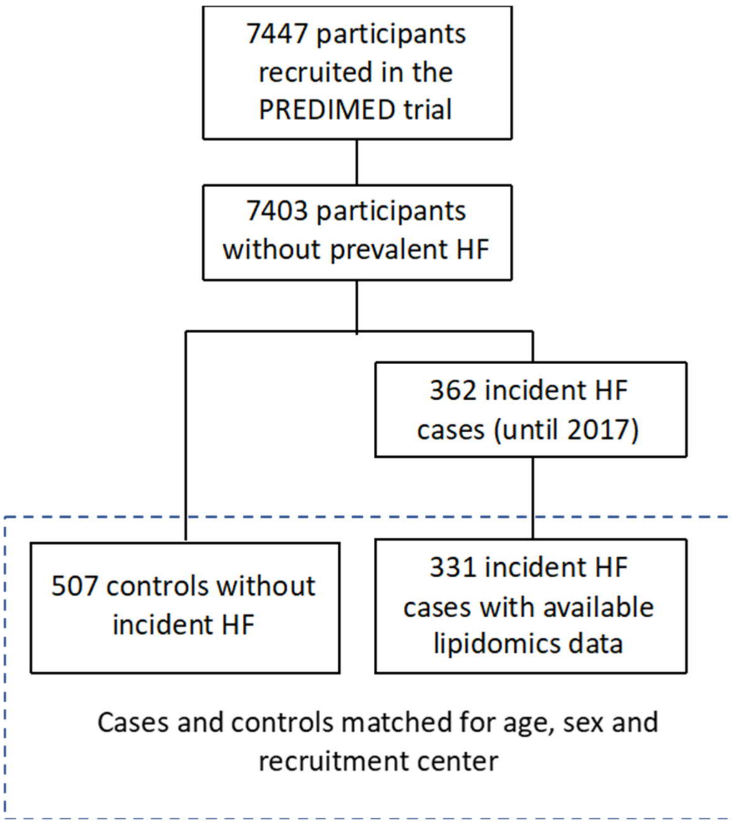
Lipid marker-HF risk associations stratified by intervention group. The three long-term intervention diet include: low-fat (control), Mediterranean Diet (MedDiet) enriched with extra-virgin olive oil (+EVOO) or with nuts (+nuts).Unmatched logistic regression models were used to estimate effects of each lipid-exposure in each stratum.

M1 corresponds to the age- and sex-adjusted model.

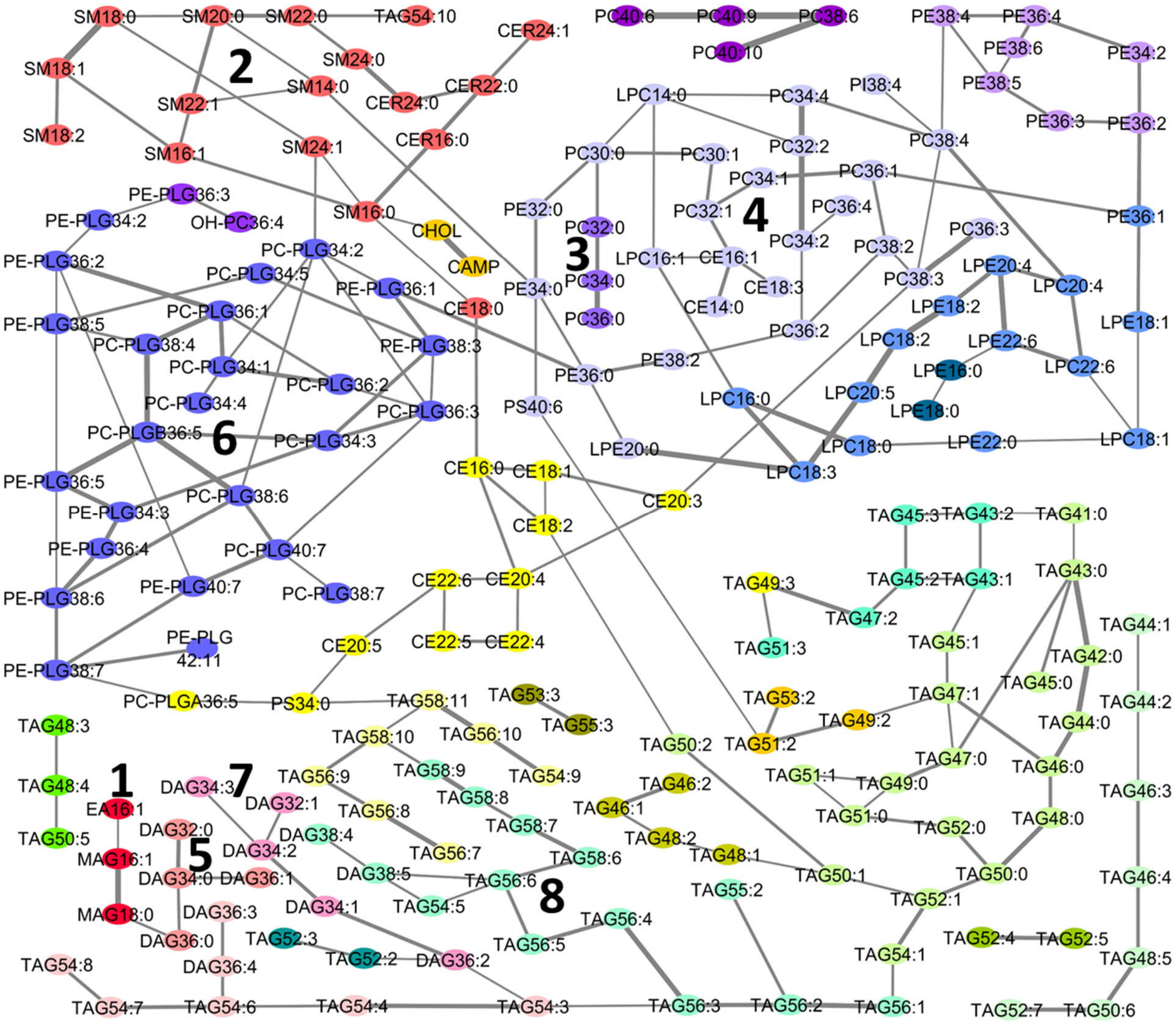
M2 is adjusted for other HF-risk factors as in the main analyses.

P(IA) is the p-value for the multiplicative interaction term from separate models that contained each lipid as continuous exposure and the MedDiet-groups as dummy-variables, plus interaction terms of the MEdDiet-groups with the lipids.

Online Figures



Online Figure I: Case-control design for HF in PREDIMED



Online Figure II: The robust lipidomics network. Based on the conditional independence structure among the 216 targeted lipids, we constructed a robust data-driven lipid network. Fourteen lipids were not robustly linked to other measured lipid metabolites. The 241 edges connecting the remaining 202 lipids largely reflected plausible biological links. The walktrap-algorithm identified 26 densely connected network-clusters. Colors indicate the network-clusters, identified with the walktrap-algorithm. Numbers correspond to variable importance ranks. They mark the clusters that were selected as containing important lipids for heart failure prediction, based on joint variable importance of the cluster variables in a random forest model.