SUPPLEMENTARY DATA

Supplementary Table S1. Eigenvalues and variance explained by the 15 extracted factors (PCA).

Factor	Eigenvalue	Variance explained (%)	Cumulative
Factor 1	53.35	25.77	25.77
Factor 2	31.76	15.35	41.12
Factor 3	23.83	11.51	52.63
Factor 4	14.25	6.88	59.51
Factor 5	9.94	4.8	64.32
Factor 6	8.33	4.03	68.34
Factor 7	6.38	3.08	71.42
Factor 8	5.88	2.84	74.26
Factor 9	4.70	2.27	76.54
Factor 10	3.77	1.82	78.36
Factor 11	2.91	1.41	79.76
Factor 12	2.53	1.22	80.99
Factor 13	2.43	1.17	82.16
Factor 14	2.19	1.06	83.22
Factor 15	2.00	0.97	84.19

SUPPLEMENTARY DATA

Supplementary Table S2. Association between baseline lipid factors (PCA extracted) and T2D risk (adjusted for age, sex and intervention group

	Factor	Description	Components
Inverse association with T2D	3	PC-plasmalogens Sphingomyelines (SM) Lysophosphatidylcholines (LPC) and Lysophosphatidylethanolamines (LPE) Cholesterol esters (CE)	364pca 182ce 386pcplasmalogen 160ce 407pcplasmalogen 241ceramided181 343pc 382pc 364pcplasmalogen 343pcplasmalogen 362pcplasmalogen 341pcplasmalogenb 363pc 361psplasmalogen 384pcplasmalogen 341pcplasmalogena 361pcplasmalogen 342pcplasmalogen 360pc 320pc 363pcplasmalogen 382pe 342pc 362pc 340pc 362psplasmalogen 220ceramided181 240ceramided181 5410tag 180ce 160ceramided181 182sm 140sm 241sm 181sm 240sm cholesterol 161sm 180sm 221sm 200sm 160sm 220sm
	7		c340pc 181lpe 140lpc 226lpe 204lpe 182lpc 205lpc 161lpc 204lpc c226lpc 160lpe 220lpe 200lpe 180lpe 181lpc 180lpc 203lpc 160lpc
	10		406ps 361peplasmalogen 200lpe 513tag 340pe 532tag 533tag 553tag 382pe
	13		361psplasmalogen 320pc 342pcplasmalogen 341pcplasmalogena 364pcplasmalogen
Direct association with T2D	1	Triacylglycerides (TAG) with≤56 C and ≤3 double bonds Diacylglycerides (DAG) Phosphatidylethanolamines (PE)	182ce* 224ce* 160ce* 226ce* 204ce* 181ce* 382pc 161lpc 361pc 320pc 384dag 406pe 362dag 385dag 161ce 341pc 140ce 527tag 542tag 526tag 364pe 383pc 532tag 513tag 562tag 343pc 362pe 406ps 361pe 342pe 343dag 344pc 340pe 522tag 552tag 322pc 504tag 342dag 505tag 140lpc 320pe 341dag 340dag 561tag 361dag 321pc 503tag 484tag 541tag 512tag 300pc 301pc 493tag 300dag 521tag 321dag 520tag 502tag 510tag 463tag 483tag 320dag 501tag 492tag 442tag 420tag 491tag 511tag 451tag 471tag 500tag 480tag 472tag 441tag 462tag 482tag 460tag 440tag 481tag 461tag
	5		160ce 533tag 341pc 341dag 541tag 361dag 544tag 523tag 361pc 241ceramided181 361pe 532tag 564tag 552tag 522tag 553tag 562tag 362dag 542tag 563tag 543tag
	11		406pe 362pe 384pe 385pe 363pe 386pe 342pe 364pe

*Negative loading factors

SUPPLEMENTARY DATA

Supplementary Table S3. Baseline lipid scores of the subcohort depending on intervention arm of the trial

	Control	**MedDiet+EVOO**	**MedDiet+Nuts**	**p value**
LP score	2.56 (12.75)	0.26 (12.19)	0.5 (13.28)	0.113
PC-PL score	0.12 (10.31)	1.37 (11.65)	0.82 (12.23)	0.523
SM score	0.94 (8.62)	0.91 (9.26)	0.69 (9.41)	0.950
CE score	-0.36 (8.46)	1.78 (7.5)	1.19 (8.92)	0.021
TAG score	0.81 (31.46)	-3.13 (29.73)	-5.86 (32.78)	0.068
DAG score	0.58 (10.50)	-1.77 (9.60)	-1.78 (10.39)	0.015
PE score	0.14 (8.97)	-0.44 (8.14)	-1.56 (8.95)	0.097

Supplementary Table S4. Association (hazard ratios, 95% confidence intervals) between 1-y changes lipid scores and T2D risk

	Quartiles of scores				Linear trend	Per SD
	Q1	Q2	Q3	Q4		
Lysophospholipids (LP) score of changes (lysophosphatidylcholines and lysophosphatidylethanolamines); n of molecules=18						
M1*	Ref.	0.90 (0.50-1.60)	0.79 (0.44-1.43)	0.77 (0.42-1.43)	0.354	0.88 (0.70-1.11)
M2*	Ref.	0.97 (0.53-1.77)	0.90 (0.49-1.66)	0.75 (0.38-1.47)	0.343	0.87 (0.68-1.11)
M3*	Ref.	1.61 (0.77-3.37)	1.05 (0.47-2.31)	0.97 (0.44-2.14)	0.685	0.94 (0.69-1.30)
Phosphatidylcholines plasmalogens (phosphatidylcholines-pl) score of changes; n of molecules=15						
M1*	Ref.	0.64 (0.37-1.11)	0.61 (0.34-1.07)	0.57 (0.32-1.03)	0.084	0.88 (0.72-1.07)
M2*	Ref.	0.62 (0.35-1.12)	0.63 (0.35-1.13)	0.57 (0.31-1.05)	0.106	0.91 (0.75-1.11)
M3*	Ref.	0.97 (0.46-2.07)	0.93 (0.45-1.90)	0.61 (0.28-1.35)	0.235	0.88 (0.64-1.22)
Sphingomielines (SM) score of changes; n of molecules=11						
M1*	Ref.	0.95 (0.54-1.70)	0.93 (0.52-1.64)	0.68 (0.36-1.27)	0.261	0.86 (0.70-1.06)
M2*	Ref.	1.09 (0.60-1.99)	0.98 (0.53-1.80)	0.74 (0.39-1.44)	0.348	0.89 (0.71-1.11)
M3*	Ref.	1.06 (0.49-2.26)	1.72 (0.81-3.64)	0.69 (0.32-1.45)	0.658	0.92 (0.69-1.23)
Cholesterol esters (CE) score of changes; n of molecules=13						
M1*	Ref.	0.81 (0.47-1.40)	0.73 (0.42-1.28)	0.84 (0.47-1.49)	0.539	0.82 (0.65-1.04)
M2*	Ref.	0.88 (0.50-1.56)	0.81 (0.45-1.45)	0.92 (0.51-1.68)	0.788	0.85 (0.67-1.08)
M3*	Ref.	0.89 (0.46-1.70)	0.70 (0.32-1.52)	0.96 (0.46-2.00)	0.846	0.88 (0.60-1.28)
Triacylglycerides (TAG) score of changes (≤56C and ≤3 double bonds); n of molecules=40						
M1*	Ref.	0.83 (0.47-1.47)	1.08 (0.60-1.97)	1.52 (0.86-2.68)	0.098	1.19 (0.96-1.46)
M2*	Ref.	0.83 (0.47-1.49)	1.10 (0.60-2.02)	1.40 (0.76-2.60)	0.196	1.19 (0.97-1.47)
M3*	Ref.	1.04 (0.51-2.14)	1.37 (0.66-2.86)	1.45 (0.65-3.23)	0.286	1.24 (0.92-1.68)
Diacylglycerides (DAG) score of changes; n of molecules=14						
M1*	Ref.	1.33 (0.76-2.32)	1.04 (0.60-1.82)	1.49 (0.85-2.64)	0.228	1.19 (0.98-1.45)
M2*	Ref.	1.27 (0.71-2.25)	1.10 (0.61-1.95)	1.39 (0.77-2.52)	0.304	1.15 (0.94-1.40)
M3*	Ref.	**2.09 (1.03-4.26)**	1.92 (0.93-3.99)	1.64 (0.78-3.46)	0.212	1.20 (0.91-1.57)
Phosphatidylethanolamines (PE) score of changes; n of molecules=12						
M1*	Ref.	1.21 (0.69-2.11)	1.23 (0.68-2.22)	**1.87 (1.06-3.30)**	**0.035**	**1.25 (1.02-1.54)**
M2*	Ref.	1.23 (0.70-2.18)	1.29 (0.71-2.36)	**1.85 (1.01-3.38)**	**0.044**	**1.25 (1.01-1.56)**
M3*	Ref.	1.64 (0.79-3.40)	1.86 (0.82-4.21)	1.74 (0.79-3.84)	0.154	1.27 (0.93-1.73)

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Supplementary Table S5. Association (hazard ratios, 95% confidence intervals) between interventions and T2D risk after 1 year of follow-up considering lipid change scores: mediation analysis

	Intervention groups				
	Control	**MedDiet+EVOO**		**MedDiet+Nuts**	
	HR (95% CI)	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Reference model* 1: w/ LP baseline score	Ref	0.39 (0.19-0.79)	0.009	0.48 (0.25-0.94)	0.032
Reference model 1+ LP change score	Ref	0.39 (0.20-0.79)	0.008	0.49 (0.25-0.96)	0.038
Reference model* 2: w/ PC-pl baseline score	Ref	0.48 (0.23-0.98)	0.044	0.49 (0.24-1.00)	0.049
Reference model 2+PC-pl change score	Ref	0.45 (0.22-0.93)	0.031	0.50 (0.24-1.03)	0.061
Reference model* 3: w/ SP baseline score	Ref	0.46 (0.22-0.92)	0.029	0.43 (0.21-0.85)	0.016
Reference model 3+SP change score	Ref	0.40 (0.19-0.83)	0.014	0.40 (0.20-0.81)	0.011
Reference model* 4: w/ CE baseline score	Ref	0.45 (0.22-0.91)	0.027	0.55 (0.28-1.07)	0.079
Reference model 4+CE change score	Ref	0.43 (0.21-0.89)	0.022	0.55 (0.28-1.09)	0.085
Reference model* 5: w/ TAG baseline score	Ref	0.39 (0.19-0.80)	0.010	0.49 (0.25-0.96)	0.039
Reference model* 5+TAG change score	Ref	0.45 (0.22-0.93)	0.032	0.53 (0.26-1.06)	0.071
Reference model* 6: w/ DAG baseline score	Ref	0.38 (0.19-0.80)	0.010	0.54 (0.28-1.05)	0.071
Reference model 6+DAG change score	Ref	0.43 (0.21-0.89)	0.024	0.53 (0.27-1.04)	0.064
Reference model* 7: w/ PE baseline score	Ref	0.36 (0.18-0.73)	0.005	0.51 (0.26-0.99)	0.048
Reference model 7+PE change score	Ref	0.40 (0.18-0.87)	0.021	0.51 (0.26-1.00)	0.048

*Cox models were adjusted for age, BMI, smoking, hypertension, dyslipidemia, baseline glucose (linear and quadratic term), propensity scores (to estimate the probability of assignment to each of the intervention groups) and sex center and educational level as strata.

SUPPLEMENTARY DATA

Supplementary Table S6. Description of the studies used to compared and discuss lipidome profiles associated with T2D

Authors	Country	Year	Design	N of subjects	Lipid class	Association with T2D
Barber MN, et al	Australia	2012	Cross-sectional*	30	LPC	Inversely associated with T2D and obesity
Zhao X, et al	Germany	2010	Cross-sectional	51	LPC	Inversely associated with prediabetic stage
Tonks TK, et al	Australia	2016	Cross-sectional	51	LPC	Inversely associated with insulin resistance
Lehman R, et al	Germany	2013	Intervention study (9 months): energy restricted, low fat and high fiber diet	40	LPC	Associated with better insulin sensitivity in NAFL subjects
Garcia-Fontana B et al	Spain	2016	Cross-sectional	30	LPC and LPE	Inversely associated with T2D and inversely associated with the risk of CVD in diabetic patients
Floegel A, et al	Germany	2013	Case-cohort (EPIC Potsdam)	800/2,282	LPC and SM	Inversely associated with T2D
			Cross-sectional (KORA study)	876		
			Cross-sectional (TüF study)	76		
Morris JK, et al	USA	2017	Cross-sectional	126	SM	Inversely associated with T2D in cognitively healthy subjects
Xu F, et al	China	2013	Cross-sectional	111	SM	Inversely associated with impaired fasting glucose and T2D metabolomics profiles
Meikle PJ, et al	Australia	2013	Case-control (nested in AusDiab cohort)	117/234	CE, DAG,TAG and PE	Directly associated with T2D
			Cross-sectional (SAFHS cohort)	1,076	PC-PL	Inversely associated with T2D
Kopprasch S, et al	Germany	2016	Cross-sectional	90	CE, TAG, SM	Directly associated with T2D
Rhee EP, et al	USA	2011	Nested case-control (FHS cohort)	189/189	Short TAG	Directly associated with T2D

*The results are confirmed in human studies and murine models fed with different diets

Supplementary Figure S1. Flow-chart of the case-cohort design

Original PREDIMED study:
Cohort: 3,541 participants without T2D at baseline
(273 incident cases)

Selected for nested study:
Total = 914
Random 20% subcohort = 694
(including 53 of the 273 incident cases)
Non-cases = 641
Plus all incident cases = 273

22 incident cases without available
plasma samples

2 non-cases and 1 incident case
without lipidomics data

Participants included with metabolites measured at
baseline:
Total = 889
Sub-cohort = 692
(including 53 of the 250 incident cases)
Non-cases=639
Cases=250

231 not included in the 1-year change analysis:
-136 non-cases without available plasma samples
and 2 non-cases without lipidomics data
- 70 cases without available plasma samples - 23
incident cases within the first year of follow-up

Participants included with metabolites measured
at one year:
Total = 658
Sub-cohort = 537
(including 36 of the 157 incident cases)
Non-cases=501
Cases=157