Supplemental Material

Shared and distinct lipid-lipid interactions in plasma and affected tissues in a diabetic mouse model

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Supplemental Table S1: Significantly different lipid features in between control and diabetic mouse plasma

Lipid Name	P value	Mean Change (*db/db*)
PC 42:6	3.94E-13	-1.92464
lysoPC 20:0	1.17E-11	-1.91035
SM 36:1	2.02E-08	1.85480
SM 42:1	4.36E-08	-1.84277
PC 42:7	5.66E-08	-1.83674
PC 38:1	1.19E-07	-1.82290
PC 44:7	1.19E-07	-1.82201
PC 38:2	1.78E-07	-1.81394
PC 40:3	2.15E-07	-1.80737
PC 42:5	2.15E-07	-1.80755
PC 40:2	8.19E-07	-1.78063
PC 44:9	8.19E-07	-1.78033
lysoPC 20:1	8.25E-07	-1.77860
PC 38:3	8.64E-07	1.77623
lysoPC 22:1	9.32E-07	-1.77331
PC 44:6	1.00E-06	-1.77047
SM 36:2	1.71E-06	1.75780
SM 40:2	2.41E-06	-1.74861
SM 36:0	2.65E-06	1.74517
Plasmenyl-PC 20:0	3.27E-06	-1.73790
Plasmenyl-PE 38:6	3.27E-06	-1.73760
PC 30:0	5.67E-06	-1.72235
PC 46:7	5.72E-06	-1.71997
Plasmenyl-PE 40:3	5.72E-06	1.71981
PC 42:3	7.56E-06	-1.71108
lysoPC 24:1	8.07E-06	-1.70812
SM 38:5	8.08E-06	1.70701
PC 40:6	1.01E-05	1.69850
SM 40:1	1.01E-05	-1.69938
Plasmenyl-PE 34:2	2.18E-05	-1.67356
lysoPC 22:5	2.66E-05	-1.66490
PC 32:3	2.66E-05	-1.66545
CL 80:11	2.70E-05	-1.66333
Plasmenyl-PE 42:0	2.92E-05	1.65958
lysoPE 20:4	3.11E-05	1.65645
PE 38:4	3.26E-05	1.65378
Plasmenyl-PC 24:0	4.70E-05	-1.63961
Plasmenyl-PE 34:1	4.99E-05	-1.63642
SM 40:5	5.26E-05	1.63346
lysoPC 24:0	5.54E-05	-1.63054
TAG 64:13	5.80E-05	-1.62787
lysoPC 22:4	7.34E-05	-1.61685
PE 38:3	7.34E-05	1.61621
Plasmenyl-PE 38:5	7.34E-05	-1.61587
lysoPC 18:0	8.82E-05	1.60749

Lipid Name	P value	Mean Change (*db/db*)
lysoPE 20:2	0.00010165	-1.60068
PC 32:0	0.00010214	-1.59957
MAG 18:3	0.00010844	1.59615
PC 22:2	0.00011018	-1.59442
PC 36:4	0.00011018	1.59372
PC 42:1	0.0001496	-1.57945
Plasmenyl-PC 38:5	0.00015274	-1.57764
PC 36:2	0.00019936	-1.56454
Plasmenyl-PE 36:5	0.00022859	-1.55719
lysoPC 20:2	0.00023031	-1.55595
PI 34:2	0.00025426	-1.55030
Plasmenyl-PE 36:3	0.00029594	-1.54195
lysoPC 26:1	0.00030663	-1.53931
PC 44:3	0.00034626	-1.53229
CL 82:7	0.00034881	1.53091
PE 40:3	0.00034881	1.53020
lysoPC 22:6	0.00042454	-1.51910
Plasmenyl-PC 38:0	0.00042725	1.51767
SM 34:1	0.00042725	1.51708
lysoPC 14:0	0.00051163	-1.50651
CL 78:5	0.00062182	1.49484
PC 42:2	0.00062601	-1.49362
PI 40:4	0.00093155	-1.46964
PE 40:4	0.00098133	1.46517
Plasmenyl-PE 38:3	0.00098133	1.46432
SM 38:2	0.00098133	1.46390
lysoPC 22:0	0.00101204	-1.46117
Plasmenyl-PC 40:5	0.00104655	-1.45828
CL 82:3	0.0010903	-1.45491
PC 46:6	0.00113471	-1.45159
PI 38:6	0.00163812	-1.42631
TAG 62:8	0.00163812	-1.42692
lysoPE 18:0	0.00163912	1.42542
PI 38:4	0.00171403	1.42160
TAG 64:12	0.00218313	-1.40428
PC 42:8	0.00250443	-1.39292
SM 38:4	0.00250443	1.39296
lysoPE 20:1	0.00304066	-1.37805
CE 16:1	0.00308553	-1.37610
PC 32:1	0.00308913	-1.37514
TAG 54:4	0.00340292	1.36709
CL 82:15	0.00356956	1.36262
PE 36:4	0.00357241	1.36169
SM 38:1	0.00359285	1.36041
TAG 58:9	0.00371073	1.35710
TAG 64:14	0.00396967	-1.35106
Plasmenyl-PC 44:4	0.00399287	-1.34976
DAG 36:3	0.00430236	1.34309

Lipid Name	P value	Mean Change (*db/db*)
lysoPC 20:3	0.00459934	-1.33697
DAG 40:6	0.00462446	1.33403
PE 40:2	0.00462446	-1.33555
PE 42:7	0.00462446	-1.33443
PC 40:8	0.00483639	1.32961
PC 44:5	0.00493647	-1.32713
PE 36:2	0.0053378	1.31994
PE 38:5	0.00536936	1.31863
PE 40:1	0.00538177	-1.31763
CL 76:5	0.00561198	1.31335
PC 32:2	0.00576788	-1.31007
Plasmenyl-PE 40:4	0.00576788	1.30946
PC 38:5	0.0059273	1.30637
CL 76:7	0.00617162	1.30204
CL 82:11	0.00617162	1.30058
MAG 18:2	0.00617162	1.30100
DAG 38:6	0.00622492	1.29907
TAG 54:3	0.00657623	1.29357
TAG 58:8	0.00686564	1.28906
PA 36:2	0.0072227	-1.28385
DAG 36:4	0.00758699	1.27868
PC 42:4	0.00758699	-1.27795
PC 40:0	0.00759795	-1.27651
Plasmenyl-PE 42:5	0.00759795	1.27553
TAG 62:7	0.00759795	-1.27596
CL 78:8	0.00769641	1.27362
Plasmenyl-PE 38:2	0.00793454	1.27013
CE 18:0	0.00802506	1.26836
Plasmenyl-PC 22:0	0.008128	-1.26646
PC 34:5	0.00833598	-1.26342
DAG 34:2	0.00835529	1.26247
CerP 42:2	0.00872469	-1.25703
TAG 60:7	0.00872469	-1.25744
DAG 38:5	0.00892688	1.25400
Plasmenyl-PC 40:3	0.00892688	1.25345
DAG 40:8	0.00896304	1.25235
lysoPC 18:1	0.00920821	-1.24840
TAG 58:10	0.00920821	1.24860
TAG 54:5	0.00989517	1.24090
Plasmenyl-PE 38:4	0.00996146	1.23954

Value given as mean difference in 24-week-old *db/db* versus *db/+*. CE = cholesterol ester, CerP = ceramide-1-phosphate, CL = cardiolipin, DAG = diacylglycerol, MAG = monoacylglycerol, PA = phosphatidic acid, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PI = phosphatidylinositol, SM = sphingomyelin, TAG = triacylglycerol. $P < 0.01$ based on a two-sample t-test with FDR correction, n = 10/group. Related to Figure 1.

Supplemental Table S2: Significantly different lipid features in between control and diabetic mouse kidney

Lipid Name	P value	Mean Change (*db/db*)
Plasmenyl-PE 36:4	6.92E-08	1.85568
PE 38:5	7.13E-08	1.84768
PC 40:6	5.37E-07	-1.81532
PC 22:3	1.77E-06	-1.78638
Plasmenyl-PE 34:1	1.77E-06	1.7904
lysoPC 20:0	2.22E-06	-1.77547
PC 22:1	2.22E-06	-1.77815
PC 22:0	2.72E-06	-1.76857
CL 84:13	2.99E-06	-1.76185
PG 32:0	2.99E-06	-1.76195
PC 30:4	3.46E-06	-1.75648
PC 20:0	3.50E-06	-1.75431
PG 38:6	3.70E-06	-1.75121
lysoPE 22:6	4.17E-06	-1.7467
SM 40:5	5.32E-06	-1.73916
PC 24:0	5.91E-06	-1.73308
PG 40:5	5.91E-06	-1.73203
Plasmenyl-PE 38:4	5.91E-06	1.73328
PC 28:1	6.03E-06	-1.72795
PC 28:3	6.03E-06	-1.72859
PC 32:5	6.03E-06	-1.72757
PC 24:2	6.12E-06	-1.72597
PE 40:8	6.59E-06	1.72285
CL 84:14	9.01E-06	-1.71296
SM 36:2	9.01E-06	1.71211
MAG 18:3	9.58E-06	1.70932
CL 70:4	1.09E-05	1.70352
Plasmenyl-PE 38:5	1.09E-05	1.70359
PE 30:0	1.10E-05	-1.70228
DAG 30:6	1.12E-05	1.69989
lysoPC 18:1	1.12E-05	1.69973
PG 30:0	1.19E-05	-1.6971
SM 40:2	1.24E-05	1.69489
PS 36:4	1.75E-05	1.68342
PE 30:1	1.91E-05	-1.67979
PC 30:6	2.00E-05	-1.67739
PC 26:0	2.07E-05	-1.67546
Plasmenyl-PC 18:0	2.07E-05	1.67447
PC 36:8	2.11E-05	-1.67308
CL 72:5	2.17E-05	1.67127
PC 26:3	3.12E-05	-1.65576
PG 34:1	3.12E-05	1.65605
PI 38:0	3.12E-05	-1.65742
SM 36:1	3.12E-05	1.6558
Plasmenyl-PE 38:3	3.32E-05	1.65278

Lipid Name	P value	Mean Change (*db/db*)
lysoPC 18:2	3.79E-05	1.64733
PC 34:1	4.34E-05	1.64164
CL 80:9	4.38E-05	-1.63978
PC 28:2	4.38E-05	-1.63981
CL 76:9	5.71E-05	1.62903
Plasmenyl-PE 32:0	6.46E-05	-1.62348
PE 40:9	9.36E-05	1.60786
CL 72:6	9.37E-05	1.60707
PC 18:0	0.000128061	-1.59312
PE 22:1	0.000143305	-1.58745
PS 34:2	0.00019132	1.57375
PC 20:1	0.000258821	-1.55803
PC 42:10	0.000258821	1.55856
PA 36:2	0.00028417	1.55273
SM 36:0	0.000286523	1.55151
DAG 38:5	0.000290384	1.55006
Plasmenyl-PE 42:6	0.00031589	-1.54513
lysoPE 18:1	0.000334495	1.54141
Plasmenyl-PE 36:2	0.000334495	1.54071
CL 78:8	0.000385124	1.5328
CL 78:4	0.000431274	1.5254
SM 38:2	0.000431274	1.52589
DAG 42:8	0.000437997	1.52382
PC 38:0	0.000455938	1.52095
PA 38:5	0.00051163	-1.51406
CL 80:7	0.000670036	-1.49852
CL 74:5	0.000725876	1.49324
CL 70:6	0.000792391	1.48673
PE 20:1	0.000792391	-1.48668
PA 38:3	0.00080971	1.48466
PC 36:4	0.000914604	-1.47679
CL 84:11	0.000985927	-1.47157
PG 42:7	0.001057635	-1.46659
PE 46:6	0.001155486	-1.46044
PE 20:0	0.001171605	-1.45806
SM 42:4	0.001171605	1.45863
lysoPC 18:0	0.001293516	1.45116
PE 24:6	0.001363825	-1.44708
PA 38:2	0.001473412	1.44141
PE 40:6	0.001557109	-1.4371
DAG 26:1	0.001607046	-1.4343
CE 18:1	0.001712551	1.42858
PC 34:5	0.001712551	-1.4279
PS 36:2	0.001712551	1.42866
CL 74:4	0.001894674	1.41971
CL 76:3	0.001894674	-1.42017
CL 80:11	0.002013761	-1.41413
DAG 40:7	0.002013761	1.41473

Lipid Name	P value	Mean Change (*db/db*)
PI 34:2	0.002075818	1.41134
DAG 36:1	0.002181429	1.40651
Plasmenyl-PE 34:2	0.002181429	1.40648
lysoPC 26:0	0.002249844	-1.40363
CL 74:7	0.002371661	1.39843
DAG 40:8	0.002371661	1.39782
PA 28:4	0.002371661	1.39783
CL 72:2	0.002603337	1.39051
PC 38:5	0.002763535	-1.38552
DAG 40:5	0.002904574	1.38121
TAG 56:7	0.002942141	1.37957
SM 42:5	0.003057463	1.37605
CL 80:13	0.003136642	-1.37347
PG 36:1	0.003158504	-1.37226
PC 28:0	0.003226254	-1.36999
PE 34:2	0.003281669	1.36803
DAG 44:12	0.003384505	1.36503
PE 36:4	0.003411991	1.36374
Plasmenyl-PC 20:0	0.003544161	1.36019
PE 22:2	0.003568379	-1.35899
lysoPC 22:0	0.003744823	-1.35463
PA 40:2	0.003846549	-1.35141
PE 42:6	0.003846549	-1.35123
PC 30:0	0.00389019	1.34848
PC 32:4	0.00389019	-1.34936
PC 48:6	0.00389019	-1.34837
PS 38:5	0.003894242	1.34764
PI 40:6	0.004152704	-1.34196
CL 68:2	0.004278136	1.33896
lysoPE 20:5	0.004478752	-1.33466
TAG 60:8	0.004860414	1.32743
SM 38:1	0.004943341	1.32541
DAG 42:6	0.005057641	1.3229
PS 40:7	0.005571147	1.31428
PA 36:1	0.005820718	1.30997
MAG 18:4	0.006326456	1.30229
CL 72:8	0.006450182	1.29961
DAG 42:10	0.006450182	1.29868
TAG 58:9	0.006450182	1.29918
CL 76:6	0.006670464	1.29515
DAG 38:4	0.006670481	1.2945
Plasmenyl-PE 36:0	0.006670481	-1.29345
TAG 58:10	0.006670481	1.29323
PE 38:4	0.006747928	1.29159
DAG 36:4	0.006831171	1.2899
CL 80:16	0.006926106	-1.28807
DAG 34:2	0.006959525	1.28702
PC 40:8	0.006977652	1.28617

Lipid Name	P value	Mean Change (*db/db*)
PG 42:11	0.007485171	-1.27937
CL 78:5	0.007763837	1.27549
PE 42:4	0.008092702	1.27115
PC 40:9	0.008126464	1.27015
SM 40:1	0.008363943	1.26693
DAG 42:7	0.008445594	1.26543
CL 82:13	0.009355705	-1.2548
TAG 62:13	0.009355705	1.25506
TAG 62:14	0.009439657	1.25335
TAG 64:9	0.009722039	1.24998
PE 36:3	0.009917738	1.2466
PG 42:8	0.009917738	-1.24668
PI 38:3	0.009917738	-1.24627
PC 44:12	0.009940639	1.24545

Value given as mean difference in 24-week-old *db/db* versus *db/+*. CE = cholesterol ester, CL = cardiolipin, DAG = diacylglycerol, MAG = monoacylglycerol, PA = phosphatidic acid, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, PI = phosphatidylinositol, PS = phosphatidylserine, SM = sphingomyelin, TAG = triacylglycerol. $P < 0.01$ based on a two-sample t-test with FDR correction, n = 10/group. Related to Figure 1.

Supplemental Table S3: Significantly different lipid features in between control and diabetic mouse nerve

Lipid Name	P value	Mean Change (*db/db*)
DAG 36:2	4.39E-17	1.93969
DAG 36:3	4.39E-17	1.93972
DAG 34:2	9.49E-16	1.93512
DAG 34:1	3.90E-15	1.93214
TAG 54:2	8.29E-14	1.92454
TAG 54:1	1.01E-13	1.92346
PC 34:0	1.15E-13	1.92262
TAG 54:7	1.37E-13	1.92168
DAG 34:0	5.28E-13	1.91676
TAG 52:1	1.42E-12	1.91250
Plasmenyl-PE 36:3	2.24E-12	1.91017
TAG 54:8	3.64E-12	1.90757
Plasmenyl-PE 36:4	4.03E-12	1.90670
TAG 58:10	1.06E-11	1.90140
TAG 52:6	1.47E-11	1.89923
DAG 32:0	6.12E-11	1.89010
Plasmenyl-PE 40:5	6.43E-11	1.88936
TAG 54:6	9.35E-11	1.88637
TAG 56:6	9.94E-11	1.88555
TAG 52:2	1.94E-10	1.88015
Plasmenyl-PE 38:5	2.36E-10	1.87822
PC 40:7	3.53E-10	1.87452
TAG 58:2	3.77E-10	1.87358
TAG 56:2	6.95E-10	1.86740
TAG 52:0	6.95E-10	1.86758
PC 46:6	8.17E-10	1.86551
Plasmenyl-PE 38:6	1.73E-09	1.85769
PC 38:6	1.82E-09	1.85675
TAG 54:5	2.43E-09	1.85330
PS 36:3	3.25E-09	1.84971
TAG 56:7	4.05E-09	1.84682
PS 40:7	4.05E-09	1.84644
PE 40:5	4.24E-09	1.84555
DAG 32:1	4.82E-09	1.84331
TAG 58:9	4.82E-09	1.84359
SM 42:2	4.85E-09	1.84289
DAG 34:3	7.30E-09	1.83749
PE 42:10	8.52E-09	1.83514
Plasmenyl-PE 34:2	8.88E-09	1.83427
PC 40:1	9.81E-09	1.83229
TAG 56:1	9.81E-09	1.83247
DAG 36:1	1.04E-08	1.83055
DAG 40:6	1.04E-08	1.83070
TAG 52:7	1.04E-08	1.83091
DAG 36:4	1.07E-08	1.82958

Lipid Name	P value	Mean Change (*db/db*)
PC 36:1	1.07E-08	1.82958
PC 42:1	1.12E-08	1.82862
PS 40:5	1.39E-08	1.82536
PC 44:6	1.57E-08	1.82327
TAG 56:9	1.65E-08	1.82232
TAG 58:3	1.86E-08	1.82026
TAG 54:3	1.97E-08	1.81913
PC 36:4	2.25E-08	1.81681
Plasmenyl-PE 34:3	2.41E-08	1.81553
TAG 58:4	2.96E-08	1.81117
PE 38:1	2.96E-08	1.81132
TAG 58:12	2.96E-08	1.81133
TAG 56:8	2.96E-08	1.81164
PE 36:1	3.04E-08	1.81050
TAG 56:5	3.13E-08	1.80979
PE 36:3	3.31E-08	1.80859
PE 40:6	3.32E-08	1.80829
TAG 60:11	3.81E-08	1.80580
TAG 52:3	4.04E-08	1.80455
SM 34:1	5.63E-08	1.79867
PE 44:12	5.68E-08	1.79825
PC 42:3	5.73E-08	1.79732
PS 40:6	5.73E-08	1.79742
PE 38:6	5.73E-08	1.79752
DAG 38:6	5.83E-08	1.79678
TAG 52:5	6.45E-08	1.79473
SM 36:1	6.58E-08	1.79415
DAG 36:5	7.84E-08	1.79074
TAG 58:8	8.58E-08	1.78883
lysoPE 18:1	8.78E-08	-1.78815
PE 36:2	1.13E-07	1.78316
lysoPE 22:4	1.20E-07	-1.78177
TAG 58:11	1.36E-07	1.77912
PE 40:7	1.39E-07	1.77833
PC 40:2	1.41E-07	1.77764
TAG 56:10	1.41E-07	1.77765
PE 34:2	1.60E-07	1.77486
PE 38:4	2.07E-07	1.76933
PC 40:10	2.09E-07	1.76882
PS 34:2	2.22E-07	1.76733
TAG 50:5	3.11E-07	1.75985
TAG 60:5	3.21E-07	1.75889
SM 42:4	3.24E-07	1.75846
TAG 58:0	4.00E-07	1.75344
TAG 54:4	4.44E-07	1.75083
PC 34:4	4.47E-07	1.75041
DAG 44:12	5.58E-07	1.74496
TAG 60:13	6.16E-07	1.74233

Lipid Name	P value	Mean Change (*db/db*)
PS 40:8	6.51E-07	1.74073
DAG 36:0	6.64E-07	1.74000
Plasmenyl-PE 40:6	8.21E-07	1.73452
PE 44:3	8.34E-07	1.73359
PC 38:4	8.34E-07	1.73377
TAG 52:4	9.42E-07	1.73024
PE 32:1	9.57E-07	1.72959
FFA 16:0	9.64E-07	1.72915
TAG 48:0	1.07E-06	-1.72591
DAG 38:4	1.07E-06	1.72602
Plasmenyl-PE 40:1	1.30E-06	-1.72048
lysoPC 16:1	1.30E-06	-1.72038
Plasmenyl-PE 36:2	1.36E-06	1.71884
DAG 40:7	1.39E-06	1.71804
lysoPE 22:1	1.39E-06	-1.71769
DAG 32:2	1.43E-06	1.71671
FFA 18:0	1.48E-06	1.71522
PG 34:0	1.48E-06	1.71533
TAG 58:5	1.65E-06	1.71209
TAG 56:3	1.84E-06	1.70843
PC 38:7	1.84E-06	1.70852
lysoPE 20:1	2.01E-06	-1.70575
PC 38:1	2.23E-06	1.70245
PE 42:9	2.68E-06	1.69686
TAG 58:1	2.70E-06	1.69638
TAG 60:6	2.81E-06	1.69493
PE 34:1	2.83E-06	1.69443
PE 38:3	3.33E-06	1.68927
PE 38:7	3.39E-06	1.68844
TAG 46:0	3.43E-06	-1.68789
lysoPE 16:1	3.45E-06	-1.68745
TAG 58:6	3.96E-06	1.68285
PC 42:10	4.50E-06	1.67860
PC 40:3	5.37E-06	1.67263
DAG 30:0	6.13E-06	1.66799
lysoPC 20:1	6.88E-06	-1.66386
lysoPC 26:0	7.38E-06	1.66118
PI 36:1	8.17E-06	1.65742
TAG 56:0	8.28E-06	1.65672
PC 46:5	9.00E-06	1.65353
TAG 60:12	9.27E-06	1.65223
lysoPC 18:1	9.38E-06	-1.65101
PC 30:0	9.38E-06	1.65121
PC 38:3	9.38E-06	1.65131
DAG 42:10	9.55E-06	1.65011
PE 34:3	9.80E-06	1.64892
SM 36:2	1.16E-05	1.64265
TAG 54:0	1.16E-05	1.64227

Lipid Name	P value	Mean Change (*db/db*)
Plasmenyl-PE 36:5	1.37E-05	1.63548
DAG 32:3	1.37E-05	1.63560
DAG 38:5	1.37E-05	1.63582
DAG 34:4	1.39E-05	1.63452
PE 42:1	1.53E-05	1.63072
PC 40:8	1.56E-05	1.62971
TAG 58:7	1.95E-05	1.62079
DAG 40:8	2.54E-05	1.60984
FFA 18:1	2.55E-05	1.60953
PE 42:8	2.89E-05	1.60404
FFA 18:2	2.89E-05	1.60376
PS 38:6	2.98E-05	1.60229
SM 40:2	2.99E-05	1.60185
PE 36:5	3.08E-05	1.60031
PE 40:9	3.46E-05	1.59505
FFA 20:2	3.52E-05	1.59403
PS 36:4	3.84E-05	1.59010
PE 42:5	4.51E-05	1.58274
lysoPC 18:0	6.17E-05	1.56826
PC 36:5	6.54E-05	1.56523
PE 40:4	7.75E-05	1.55691
PI 34:2	9.47E-05	1.54694
lysoPC 24:0	0.00010099	1.54344
PE 40:8	0.00010794	1.53982
PC 40:9	0.00011742	1.53527
PE 40:1	0.00013333	1.52846
PC 42:2	0.0001382	1.52629
PG 40:8	0.00015168	1.52111
PC 32:4	0.00015581	1.51907
CL 74:5	0.00015581	1.51911
DAG 40:2	0.00015904	1.51767
PC 32:0	0.00017874	1.51110
DAG 40:3	0.00019841	1.50510
FFA 20:0	0.00021649	1.49997
DAG 40:5	0.00023452	1.49518
lysoPC 18:2	0.00026216	1.48853
CL 82:1	0.00026341	1.48794
TAG 46:3	0.00026715	1.48681
PE 42:2	0.00029498	1.48075
lysoPC 22:0	0.00034246	1.47163
PG 44:12	0.00035542	1.46908
TAG 62:14	0.00042657	1.45767
PC 34:1	0.00046904	1.45144
PS 36:1	0.00047871	1.44983
lysoPC 22:6	0.00064407	1.43047
lysoPC 22:5	0.00067489	1.42704
SM 40:1	0.00067742	1.42644
TAG 60:8	0.00069164	1.42472

Lipid Name	P value	Mean Change (*db/db*)
PE 44:2	0.0007028	1.42330
Arachidonic acid (FFA 20:4)	0.00073726	1.41976
PI 34:1	0.00086724	1.40802
PS 42:7	0.00086724	1.40828
PE 44:11	0.0008873	1.40609
lysoPE 24:4	0.00090071	-1.40434
TAG 50:1	0.00090071	1.40455
TAG 44:2	0.00094681	1.40052
TAG 40:0	0.00094699	1.40015
PS 44:11	0.00095909	1.39891
TAG 62:13	0.00105867	1.39157
SM 34:2	0.0010796	1.38982
TAG 62:6	0.00110436	1.38784
DAG 38:2	0.00118878	1.38217
SM 40:0	0.00132057	1.37411
TAG 56:4	0.0014089	1.36894
Plasmenyl-PE 38:3	0.00150967	1.36339
Plasmenyl-PE 38:1	0.00185708	-1.34714
PS 34:0	0.0019724	1.34204
CL 70:5	0.0020662	1.33799
PS 40:1	0.00213267	1.33509
PC 44:5	0.00222744	1.33084
PC 38:8	0.00222744	1.33104
FFA 24:3	0.00227288	1.32884
TAG 62:7	0.00237835	1.32478
DAG 28:2	0.00252013	1.31966
PA 34:0	0.00276955	1.31146
PE 40:10	0.00284602	1.30841
PS 40:2	0.00284602	1.30875
PS 38:3	0.00301273	1.30283
TAG 62:12	0.00301273	1.30284
PS 38:1	0.0030726	1.30077
PG 38:7	0.00324449	1.29572
FFA 20:1	0.003483	1.28920
Plasmenyl-PE 40:3	0.00358244	1.28635
PA 40:6	0.00373124	1.28239
lysoPC 26:1	0.00379083	1.28021
PG 40:6	0.00379083	1.28047
PE 42:3	0.00383139	1.27887
TAG 50:4	0.00387915	1.27739
PC 44:3	0.00388192	1.27693
PG 36:3	0.00391695	-1.27575
FFA 24:1	0.00412609	-1.27070
PG 38:4	0.00437931	1.26492
PG 40:7	0.00439375	1.26423
Plasmenyl-PE 42:6	0.00439754	1.26376
PC 18:0	0.00452707	1.26033
PE 38:5	0.00452707	1.26045

Lipid Name	P value	Mean Change (*db/db*)
SM 42:5	0.0052948	1.24538
PC 44:10	0.00539616	1.24320
PS 42:2	0.00552378	1.24059
DAG 38:1	0.0056464	1.23810
DAG 38:7	0.0057642	1.23573
PG 42:10	0.00586016	1.23375
lysoPC 14:0	0.00652943	-1.22286
PC 32:1	0.00659485	1.22069
DAG 38:0	0.00659485	1.22086
PS 46:6	0.00659485	1.22120
TAG 60:9	0.00696456	1.21490
PA 34:1	0.00701159	1.21383
lysoPC 22:1	0.00701237	-1.21342
PS 38:2	0.00754344	1.20571
PC 46:2	0.0075621	-1.20506
PA 38:4	0.00844056	1.19345
SM 30:1	0.0085969	1.19115
PI 38:3	0.00893498	-1.18633
PC 36:6	0.00893498	1.18663
PC 38:5	0.0089512	1.18533
PE 36:6	0.0089512	1.18544

Value given as mean difference in 24-week-old *db/db* versus *db/+*. CL = cardiolipin, DAG = diacylglycerol, FFA = free fatty acid, PA = phosphatidic acid, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, PI = phosphatidylinositol, PS = phosphatidylserine, SM = sphingomyelin, TAG = triacylglycerol. $P < 0.01$ based on a two-sample t-test with FDR correction, n = 10/group. Related to Figure 1.

Supplemental Table S4: Significantly different lipid features in between control and diabetic mouse retina

Lipid Name	P value	Mean Change (*db/db*)
lysoPC 22:6	2.22E-07	-1.84000
PS 34:0	2.60E-07	-1.82885
lysoPC 20:1	8.18E-07	-1.80549
FFA 18:2	3.45E-06	-1.77388
PE 40:9	7.33E-06	1.75289
FFA 20:2	1.57E-05	-1.73011
lysoPC 16:0	2.02E-05	-1.71942
lysoPC 22:5	5.96E-05	-1.68416
lysoPC 18:1	6.61E-05	-1.67714
SM 36:2	9.90E-05	1.66023
lysoPC 20:4	0.0001004	-1.65343
lysoPE 22:6	0.0001004	-1.65582
DAG 40:6	0.00010722	-1.64771
FFA 20:1	0.00010722	-1.64559
Plasmenyl-PE 34:1	0.00012311	-1.63799
DAG 38:6	0.00015057	-1.62795
DAG 36:1	0.00016034	-1.62316
CL 72:1	0.00016217	-1.61911
Plasmenyl-PE 36:4	0.00016217	1.61834
PG 32:0	0.00016241	-1.61624
PS 36:1	0.00017431	-1.61143
PE 42:9	0.00018058	1.60809
PC 36:4	0.00035495	1.57710
PE 30:0	0.0004722	-1.56198
DAG 36:2	0.00053181	-1.54308
DAG 38:5	0.00053181	-1.54754
DAG 44:12	0.00053181	-1.54297
PC 18:0	0.00053181	-1.54229
PE 34:2	0.00053181	-1.54510
PG 36:2	0.00053181	-1.54390
PG 38:4	0.00053181	-1.55085
Plasmenyl-PE 36:1	0.00053181	-1.54359
PC 36:6	0.0008485	-1.51664
Plasmenyl-PE 34:0	0.00085062	-1.51491
Arachidonic acid (FFA 20:4)	0.00093821	-1.50805
PS 36:2	0.00098676	-1.50374
Plasmenyl-PE 32:0	0.00136863	-1.48373
SM 38:1	0.00168063	-1.47008
MAG 18:1	0.00173429	1.46663
CL 74:3	0.00199804	-1.45492
DAG 36:5	0.00199804	-1.45552
DAG 40:7	0.00220425	-1.44728
FFA 18:1	0.00220504	-1.44577
PS 36:4	0.00242422	1.43826
Plasmenyl-PE 36:5	0.00243739	-1.43646

Lipid Name	P value	Mean Change (*db/db*)
FFA 22:3	0.00252388	-1.43277
PE 38:1	0.00255964	-1.43044
PE 42:10	0.00265253	1.42672
DAG 34:1	0.00294049	-1.41848
DAG 40:5	0.00313145	-1.41285
Plasmenyl-PE 40:5	0.0039436	-1.39549
lysoPC 16:1	0.00502859	-1.37659
SM 34:2	0.00545568	1.36914
DAG 34:0	0.00654437	-1.35125
DAG 34:2	0.00654437	-1.35389
lysoPC 18:2	0.00654437	-1.35114
PC 40:6	0.00708678	1.34356
PE 32:1	0.00728405	-1.34003
DAG 32:0	0.00940724	-1.31675
lysoPC 20:2	0.00940724	-1.31661
DAG 38:3	0.00967331	-1.31292

Value given as mean difference in 24-week-old *db/db* versus *db/+*. CL = cardiolipin, DAG = diacylglycerol, FFA = free fatty acid, MAG = monoacylglycerol, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, PS = phosphatidylserine, SM = sphingomyelin. $P < 0.01$ based on a two-sample t-test with FDR correction, n = 10/group. Related to Figure 1.

Supplemental Table S5: Summary of significant class-level lipid changes in diabetic tissues

Lipid Class	Kidney	Nerve	Retina
CE	Increased	NS	NS
CerP	NS	NS	NS
CL	Increased short- and medium-chain, decreased long-chain	Increased	Decreased
DAG	Mostly increased	Increased	Decreased
FFA	ND	Mostly increased	Decreased
lysoPC	Increased short-chain, decreased long-chain	Mostly decreased short-chain, increased long-chain	Decreased
lysoPE	Increased short-chain, decreased long-chain	Decreased	Decreased
MAG	Increased	NS	Increased
PA	Increased short-chain, decreased long-chain	Increased	NS
PC	Decreased short- and medium-chain, mostly increased long-chain	Mostly increased	Mix
PE	Decreased short-chain, mostly increased medium- and long-chain	Increased	Decreased short-chain, increased long-chain
PG	Mostly decreased	Mostly increased	NS
PI	Mostly decreased	Mostly increased	NS
Plasmenyl-PC	Increased	NS	NS
Plasmenyl-PE	Mostly increased, saturated decreased	Mostly increased, monounsaturated decreased	Mostly decreased
PS	Increased	Increased	Mostly decreased
SM	Mostly increased	Increased	Mix
TAG	Increased	Mostly increased	NS

Trends in significantly different lipid features per class in 24-week-old *db/db* versus *db/+* mice. ND = not determined, NS = no significant lipids, CE = cholesterol ester, CerP = ceramide-1-phosphate, CL = cardiolipin, DAG = diacylglycerol, FFA = free fatty acid, MAG = monoacylglycerol, PA = phosphatidic acid, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, PI = phosphatidylinositol, PS = phosphatidylserine, SM = sphingomyelin, TAG = triacylglycerol. $P < 0.01$ based on a two-sample t-test with FDR correction, n = 10/group. Related to Table 2.

Supplemental Table S6: Acyl chain length sub-groups of shared lipid features

Lipid Class	Acyl-chain lengths detected	Bottom (number of carbons)	Middle (number of carbons)	Top (number of carbons)
CE	16-22	16	18, 20	22
CerP	34	Not split		
CL	68-80	68, 70	72, 74, 76	78, 80
DAG	30-42	30, 32	34, 36, 38	40, 42
lysoPC	14-26	14, 16	18, 20, 22	24, 26
lysoPE	16-24	16, 18	20	22, 24
MAG	16-18	Not split		
PA	34-38	34	36	38
PC	18-46	18, 20, 22, 24*, 26*	28, 30, 32, 34, 36	38, 40, 42, 44, 46
PE	30-42	30, 32	34, 36, 38	40, 42
PG	32-44	32, 34	36, 38, 40	42*, 44
PI	34-40	34	36, 38	40
PlasmenylPC	18, 24, 44	Not split		
PlasmenylPE	32-42	32, 34	36, 38	40, 42
PS	38-42	Not split		
SM	30-44	30, 32, 34	36, 38	40, 42, 44
TAG	40-66	40, 42, 44, 46, 48	50, 52, 54, 56	58, 60, 62, 64, 66

CE = cholesterol ester, CerP = ceramide-1-phosphate, CL = cardiolipin, DAG = diacylglycerol, MAG = monoacylglycerol, PA = phosphatidic acid, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, PI = phosphatidylinositol, PS = phosphatidylserine, SM = sphingomyelin, TAG = triacylglycerol. Lipid classes were not split into sub-groups if there were less 2 lipid features in 2 or more sub-groups (bottom, middle, and top). *Not included in analysis as not present in all tissues. Related to Methods, Table 3, and Tables S7-S8.

Supplemental Table S7: Commonly co-regulated lipid sub-classes between plasma and each tissue by saturation

Lipid Sub-Class	Kidney		Nerve		Retina		Liver	
	Control	Diabetic	Control	Diabetic	Control	Diabetic	Control	Diabetic
CE low		X		X		X	X	X
CE high					X		X	
CerP low								
CL high			X					
DAG low	X		X				X	
DAG high								
LPC low				X			X	
LPC high								
LPE low	X	X	X	X			X	X
LPE high			X			X	X	
PA low	X	X		X				X
PA high	X		X	X	X	X		X
PC low	X							
PC high								
PE low								
PE high								
PG low		X		X	X	X	X	X
PG high					X		X	
PI high								
PI low								
PlPC low								
PlPE low					X		X	
PlPE high				X				
PS high								
SM low							X	
SM high		X						
TAG low								
TAG high								
Total:	5	5	5	7	5	4	10	5

Commonly co-regulated ("X") lipid sub-classes between plasma and each tissue in 24-week-old *db/db* (diabetic) and *db/+* (control) mice. CE = cholesterol ester, CerP = ceramide-1-phosphate, CL = cardiolipin, DAG = diacylglycerol, PA = phosphatidic acid, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, PI = phosphatidylinositol, PlPC = plasmenyl-PC, PlPE = plasmenyl-PE, PS = phosphatidylserine, SM = sphingomyelin, TAG = triacylglycerol. $P < 0.1$ using correlation analysis at the set level, n = 10/group. Related to Table 3 and S8.

Supplemental Table S8: Commonly co-regulated lipid sub-classes between plasma and each tissue by acyl-chain length

Lipid Sub-Class	Kidney		Nerve		Retina		Liver	
	Control	Diabetic	Control	Diabetic	Control	Diabetic	Control	Diabetic
CE bottom								
CE mid					X		X	
CE top								
CerP								
CL bottom								
CL mid			X					
CL high								
DAG bottom							X	
DAG mid								
DAG top							X	
LPC bottom	X		X	X		X	X	X
LPC mid			X					
LPC top								
LPE bottom			X	X		X	X	
LPE mid	X		X	X		X	X	
LPE top		X	X	X	X	X	X	
PA bottom		X		X	X			
PA mid	X		X	X	X	X	X	
PA top	X		X	X	X	X	X	X
PC mid								
PC top								
PE bottom			X					
PE mid								
PE top								
PG bottom					X		X	
PG mid			X		X		X	
PG top								
PI bottom								
PI mid								
PI top	X	X		X			X	X
PlPC								
PlPE bottom		X					X	
PlPE mid								
PlPE top								
PS								
SM bottom		X	X		X			

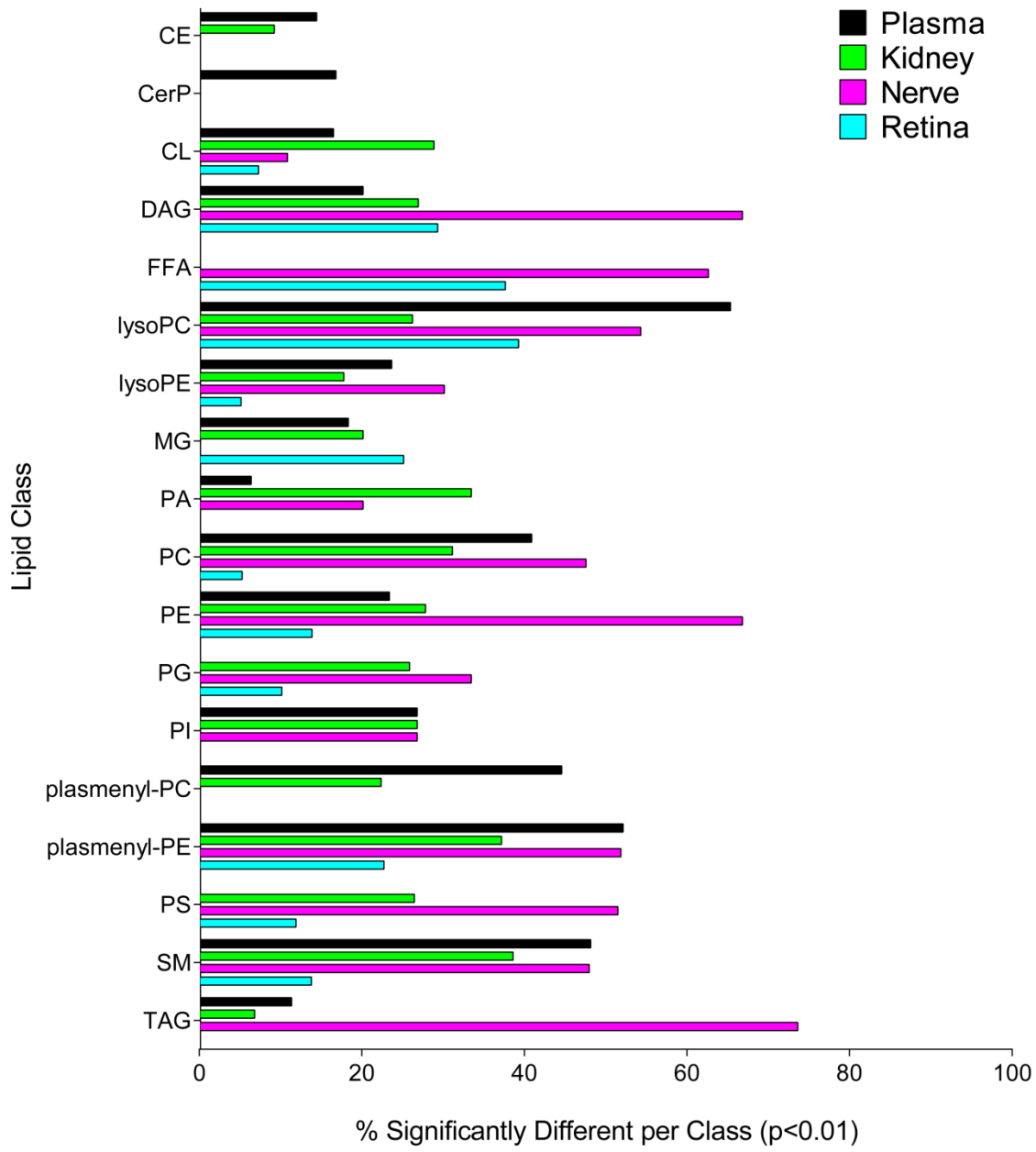
Lipid Sub-Class	Kidney		Nerve		Retina		Liver	
	Control	**Diabetic**	**Control**	**Diabetic**	**Control**	**Diabetic**	**Control**	**Diabetic**
SM mid		X			X			
SM top								
TAG bottom								
TAG mid								
TAG top								
Total:	5	6	11	8	9	6	13	3

Commonly co-regulated ("X") lipid sub-classes between plasma and each tissue in 24-week-old *db/db* (diabetic) and *db/+* (control) mice. CE = cholesterol ester, CerP = ceramide-1-phosphate, CL = cardiolipin, DAG = diacylglycerol, PA = phosphatidic acid, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, PI = phosphatidylinositol, PlPC = plasmenyl-PC, PlPE = plasmenyl-PE, PS = phosphatidylserine, SM = sphingomyelin, TAG = triacylglycerol. $P < 0.1$ using correlation analysis at the set level, n = 10/group. Related to Table 3 and S7.

Supplemental Table S9: Significantly different lipid correlations in diabetic kidney, nerve and retina

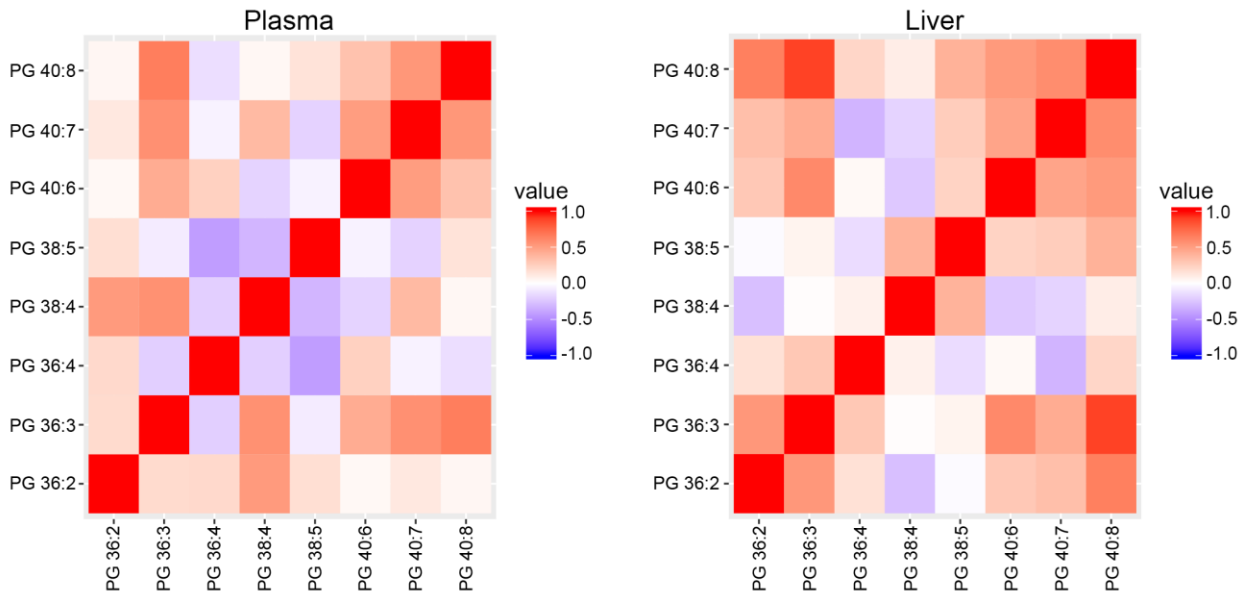
Lipids	Kidney		Nerve		Retina	
	P value	Pearson's r	P value	Pearson's r	P value	Pearson's r
PE 36:5 – PE 40:6	0.0317	0.7851	0.0879	0.8699	0.0973	0.8422
TAG 48:2 – TAG 50:3	<0.0001	0.9665	0.0139	0.9285	0.0851	0.8493

Significantly correlated lipid features present in diabetic kidney, nerve and retina that were not significantly different in control kidney, nerve and retina from 24-week-old *db/+* and *db/db* mice. PE = phosphatidylethanolamine, TAG = triacylglycerol. $P < 0.1$ in each tissue using Pearson's correlation with Fisher's transformation and Benjamini-Hochberg FDR correction, n = 10/group. Related to Figure S3.



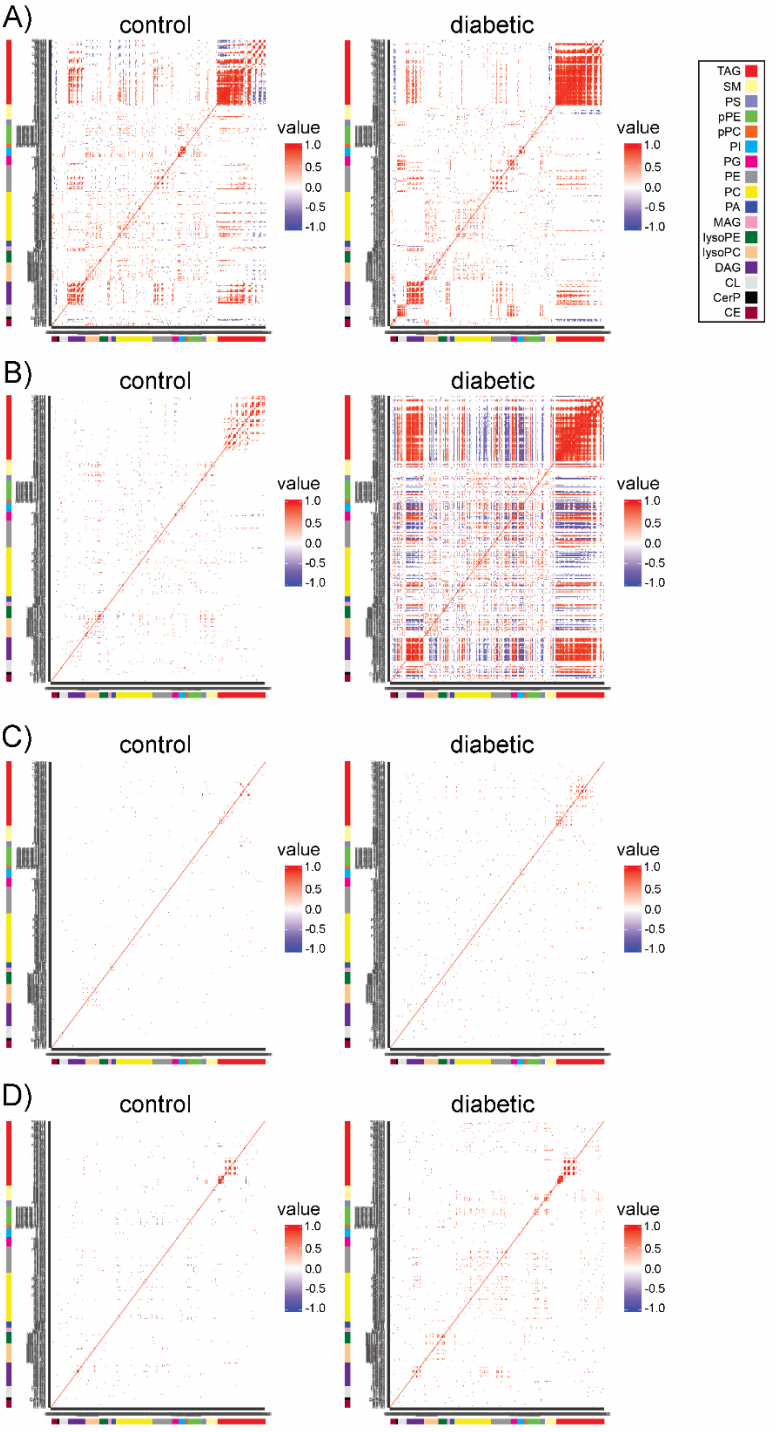
Supplemental Figure S1: Differential lipid expression by class in diabetic plasma, kidney, nerve and retina.

Percent of significantly different lipids per class in plasma (black), kidney (green), nerve (magenta) and retina (blue) from 24-week-old db/+ and db/db mice. CE = cholesterol ester, CerP = ceramide-1-phosphate, CL = cardiolipin, DAG = diacylglycerol, FFA = free fatty acid, MAG = monoacylglycerol, PA = phosphatidic acid, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, PI = phosphatidylinositol, PS = phosphatidylserine, SM = sphingomyelin, TAG = triacylglycerol. $P < 0.01$ based on a two-sample t-test with FDR correction, n = 10/group. Related to Table 2.



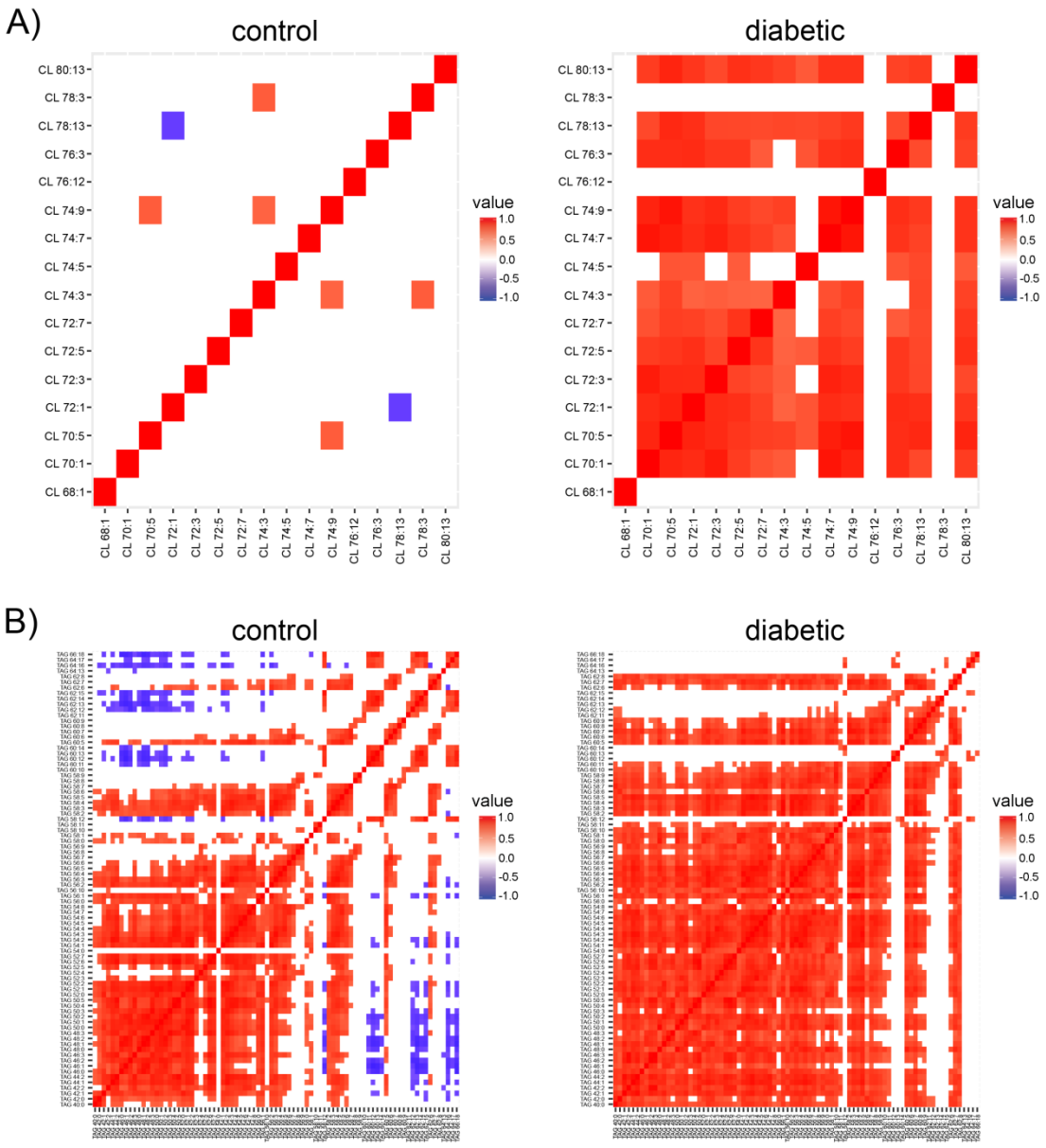
Supplemental Figure S2: Commonly co-regulated medium acyl-chain phosphatidylglycerols between control plasma and liver.

Lipid correlation data was analyzed at the set level to determine commonly co-expressed sub-classes of lipids. Mid acyl-chain phosphatidylglycerols (PGs) in 24-week-old control mouse plasma and liver were commonly co-expressed. $P < 0.1$ using correlation analysis at the set level, n = 10/group. Related to Tables 3, S7-S8.



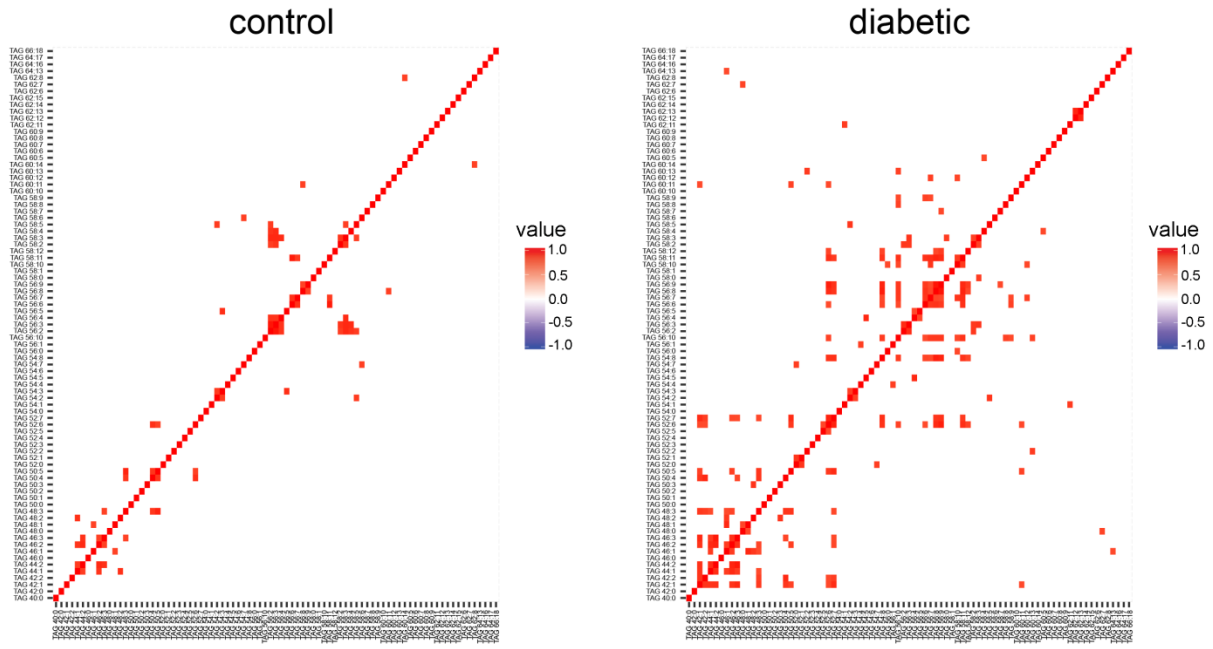
Supplemental Figure S3: Correlation analysis of lipid features from control and diabetic mice.

Correlation analysis of 364 shared lipid features detected in 24-week-old control and diabetic mouse (A) plasma, (B) kidney cortex, (C) sciatic nerve and (D) retina. Significant correlations are shown as positive (red) or negative (blue). The x-axis and the y-axis are identical and alphabetized by class, beginning at the origin. The color bar along each axis identifies lipids by class. $P < 0.1$ using Pearson's correlation with Fisher's transformation and FDR correction, n = 10/group.



Supplemental Figure S4: Cardiolipin and triacylglycerol correlation analyses in control and diabetic plasma.

Zoom-in views of intra-class correlations between (A) cardiolipin (CL) and (B) triacylglycerol (TAG) lipid classes in plasma from 24-week-old control and diabetic mice. Significant correlations are shown as positive (red) or negative (blue). $P < 0.1$ using Pearson's correlation with Fisher's transformation and FDR correction, n = 10/group. Related to Figure S3.



Supplemental Figure S5: Correlation analysis of triacylglycerols in control and diabetic nerve.

Zoom-in view of triacylglycerols (TAGs) from correlation analysis of sciatic nerve from 24-week-old control and diabetic mice. Significant correlations are shown as positive (red) or negative (blue). $P < 0.1$ using Pearson's correlation with Fisher's transformation and FDR correction, n = 10/group. Related to Figure S3.