Supplemental data

Large-scale lipidomics identifies associations between plasma sphingolipids and T2DM incidence.

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Supplemental Table 1. Gender differences in individual lipid species

Sphingolipid	Male average lipid concentration (nM)	Male Standard deviation	Female average lipid concentration (nM)	Female Standard deviation	T-test between Male and Female	Percentage changed in Female compared to Male
Cer d16:1/16:0	3.14	1.02	3.21	1.04	1.11E-01	2.19
Cer d16:1/18:0	6.31	2.81	6.17	2.66	2.30E-01	-2.18
Cer d16:1/20:0	15.82	7.38	14.97	6.89	**4.30E-03**	-5.41
Cer d16:1/22:0	50.64	24.23	45.75	22.40	**6.54E-07**	-9.65
Cer d16:1/23:0	21.39	9.10	22.03	9.56	1.01E-01	2.99
Cer d16:1/24:0	94.58	38.93	86.11	36.58	**9.72E-08**	-8.96
Cer d16:1/24:1	28.37	12.95	26.39	11.48	**1.27E-04**	-6.96
Cer d18:1/16:0	103.59	23.90	97.44	21.61	**1.67E-10**	-5.93
Cer d18:1/18:0	61.29	27.36	57.11	25.41	**1.67E-04**	-6.82
Cer d18:1/20:0	74.74	30.73	65.07	26.08	**1.25E-15**	-12.94
Cer d18:1/22:0	487.58	167.13	442.95	151.91	**3.56E-11**	-9.15
Cer d18:1/23:0	344.51	107.03	344.39	108.99	9.78E-01	-0.04
Cer d18:1/24:0	1584.05	488.14	1402.60	439.47	**3.35E-20**	-11.45
Cer d18:1/24:1	454.63	145.85	413.20	128.28	**1.01E-12**	-9.11
Cer d18:1/25:0	57.95	17.42	59.27	18.55	7.80E-02	2.28
Cer d18:1/25:1	10.85	4.16	11.49	4.31	**2.89E-04**	5.91
Cer d18:1/26:0	13.02	3.80	12.93	3.77	5.67E-01	-0.70
Cer d18:1/26:1	5.86	2.33	5.56	2.17	**1.51E-03**	-5.13
Cer d18:2/16:0	10.69	2.60	11.67	2.82	**1.15E-17**	9.13
Cer d18:2/18:0	9.07	3.13	9.28	3.29	1.20E-01	2.29
Cer d18:2/22:0	82.02	31.65	79.27	31.24	**3.69E-02**	-3.35
Cer d18:2/23:0	56.34	20.37	59.78	22.98	**1.47E-04**	6.10
Cer d18:2/24:0	257.49	87.65	240.73	84.80	**3.69E-06**	-6.51
Cer d18:2/24:1	73.76	26.56	70.71	24.97	**4.88E-03**	-4.13
Cer d18:2/25:0	9.97	3.40	10.97	4.06	**1.46E-10**	10.03
Cer d18:2/26:0	2.96	0.94	3.15	1.07	**1.29E-05**	6.17
Hex2Cer d16:1/16:0	16.89	6.22	17.33	6.12	8.30E-02	2.65
Hex2Cer d18:1/14:0	9.19	3.28	10.40	3.77	**4.21E-16**	13.10
Hex2Cer d18:1/16:0	477.56	134.96	469.82	129.26	1.62E-01	-1.62
Hex2Cer d18:1/24:0	40.03	17.80	36.06	15.50	**1.76E-08**	-9.92
Hex2Cer d18:1/24:1	54.98	20.35	52.42	18.62	**1.79E-03**	-4.66
Hex2Cer d18:2/16:0	33.81	9.96	35.92	10.64	**9.30E-07**	6.26
GM3 d18:1/16:0	9.32	2.63	9.45	2.61	2.39E-01	1.39
HexCer d16:1/16:0	6.67	2.63	6.98	2.71	**4.68E-03**	4.73
HexCer d16:1/22:0	33.13	15.01	34.23	14.68	7.65E-02	3.32
HexCer d16:1/24:0	30.02	13.27	27.26	11.90	**2.05E-07**	-9.19
HexCer d18:1/16:0	243.15	83.70	225.32	67.71	**3.18E-08**	-7.33

HexCer d18:1/18:0	28.04	9.47	30.24	11.02	**2.77E-07**	7.85
HexCer d18:1/22:0	608.83	230.13	545.69	198.38	**3.83E-12**	-10.37
HexCer d18:1/23:0	217.09	79.44	207.39	76.58	**3.02E-03**	-4.47
HexCer d18:1/24:0	825.13	302.52	703.06	255.81	**1.68E-24**	-14.79
HexCer d18:1/24:1	544.13	229.78	509.10	196.64	**1.03E-04**	-6.44
HexCer d18:1/25:0	15.38	5.65	14.63	5.78	**1.74E-03**	-4.87
HexCer d18:1/26:0	4.12	1.57	3.77	1.41	**1.99E-08**	-8.59
HexCer d18:2/16:0	15.21	4.41	15.93	4.79	**1.73E-04**	4.74
HexCer d18:2/22:0	63.15	23.94	63.19	23.83	9.72E-01	0.06
HexCer d18:2/23:0	25.83	10.15	27.21	10.34	**1.29E-03**	5.34
HexCer d18:2/24:0	115.47	44.92	105.28	40.68	**1.70E-08**	-8.82
HexCer d18:2/24:1	48.56	18.30	49.67	18.54	1.52E-01	2.27
SM d16:1/16:0	3338.34	1077.30	3698.78	1176.53	**2.58E-14**	10.80
SM d16:1/18:0	2154.68	699.56	2320.83	752.57	**4.63E-08**	7.71
SM d16:1/20:0	1143.92	346.16	1247.48	366.04	**4.25E-12**	9.05
SM d16:1/22:0	3189.33	1018.31	3382.29	1057.55	**8.97E-06**	6.05
SM d16:1/24:0	1736.55	600.21	1772.84	643.39	1.62E-01	2.09
SM d16:1/24:1	2299.22	665.25	2547.25	745.33	**5.83E-17**	10.79
SM d18:1/14:0	1320.33	380.56	1626.51	477.50	**7.10E-62**	23.19
SM d18:1/16:0	62803.92	9160.69	64083.78	9242.54	**8.94E-04**	2.04
SM d18:1/18:0	6230.33	1535.44	6518.43	1584.84	**1.03E-05**	4.62
SM d18:1/20:0	4048.35	1058.17	4043.16	1013.10	9.05E-01	-0.13
SM d18:1/22:0	12467.60	2955.68	12320.27	2881.02	2.28E-01	-1.18
SM d18:1/23:0	5174.14	1525.08	5536.48	1689.68	**7.15E-08**	7.00
SM d18:1/24:0	10462.91	3031.40	9886.45	2939.79	**4.26E-06**	-5.51
SM d18:1/24:1	19785.35	4664.26	20210.87	4496.29	**2.67E-02**	2.15
SM d18:2/14:0	254.29	74.93	361.98	113.36	**7.47E-141**	42.35
SM d18:2/16:0	9821.44	2254.59	11540.44	2845.35	**9.91E-56**	17.50
SM d18:2/18:0	3368.46	884.15	3683.11	894.77	**4.69E-17**	9.34
SM d18:2/20:0	1051.28	260.17	1178.81	284.76	**1.76E-28**	12.13
SM d18:2/22:0	6066.35	1443.42	6737.34	1644.69	**6.89E-25**	11.06
SM d18:2/23:0	1791.52	529.39	2210.40	704.56	**2.63E-56**	23.38
SM d18:2/24:0	5868.67	1667.41	6273.62	1860.43	**4.10E-08**	6.90
SM d18:2/24:1	7652.13	1735.79	8689.73	1899.56	**4.96E-41**	13.56
SPH d16:1	4.02	2.82	3.56	2.27	**2.82E-05**	-11.28
SPH d18:0	19.20	20.71	17.57	19.09	5.07E-02	-8.51
SPH d18:1	71.72	80.17	61.59	69.69	**1.37E-03**	-14.12
SPH d18:2	19.11	16.49	16.58	14.50	**1.05E-04**	-13.27
S1P d16:1	91.15	25.56	92.65	25.85	1.61E-01	1.65
S1P d17:1	19.50	4.70	20.40	4.85	**5.65E-06**	4.66
S1P d18:0	160.91	48.03	160.28	45.41	7.51E-01	-0.39
S1P d18:1	1092.77	277.45	1035.30	250.66	**2.48E-07**	-5.26
S1P d18:2	300.26	64.47	302.12	67.68	5.01E-01	0.62

Supplemental Table 2. Table with heatmap analysis indicating percentage differences of the average lipid concentration of each age group compared to the average total lipid. Scale is from -25% (Blue) to 25% (Red) difference. Values in the table are the average lipid concentration for each age group.

Sphingolipid	Average total lipid concentration (nM)	Standard deviation	Age Group (Years)				
			25-34	35-44	45-54	55-64	65+
Cer d16:1/16:0	3.18	1.03	2.86	3.07	3.21	3.36	3.44
Cer d16:1/18:0	6.24	2.73	5.55	6.05	6.36	6.61	6.55
Cer d16:1/20:0	15.38	7.13	12.49	14.24	16.20	16.71	16.99
Cer d16:1/22:0	48.07	23.40	36.75	43.81	51.42	53.29	53.30
Cer d16:1/23:0	21.76	9.36	16.85	19.93	22.99	24.43	24.08
Cer d16:1/24:0	90.12	37.92	71.28	82.81	95.20	100.24	98.63
Cer d16:1/24:1	27.33	12.22	22.54	25.21	28.64	29.81	30.31
Cer d18:1/16:0	100.27	22.91	97.78	98.75	100.43	101.91	104.31
Cer d18:1/18:0	59.05	26.40	52.96	55.90	61.39	61.42	62.93
Cer d18:1/20:0	69.58	28.73	60.41	66.20	73.06	72.64	72.94
Cer d18:1/22:0	463.98	160.62	399.64	441.72	488.85	488.38	476.14
Cer d18:1/23:0	344.78	108.09	293.15	326.20	358.84	374.21	360.17
Cer d18:1/24:0	1487.39	471.18	1280.34	1410.38	1553.67	1585.69	1555.86
Cer d18:1/24:1	432.50	138.25	390.17	411.78	445.86	452.02	461.71
Cer d18:1/25:0	58.73	18.05	52.88	56.27	60.93	62.14	58.88
Cer d18:1/25:1	11.21	4.25	9.83	10.38	11.48	12.12	12.65
Cer d18:1/26:0	12.99	3.78	11.56	12.43	13.50	13.60	13.46
Cer d18:1/26:1	5.70	2.26	5.17	5.47	5.79	5.95	6.26
Cer d18:2/16:0	11.22	2.77	11.14	11.02	11.13	11.42	11.88
Cer d18:2/18:0	9.18	3.22	8.70	8.94	9.40	9.44	9.24
Cer d18:2/22:0	80.63	31.47	69.45	75.15	85.12	85.00	86.17
Cer d18:2/23:0	58.28	21.89	49.03	53.75	61.04	63.88	62.69
Cer d18:2/24:0	248.72	86.55	215.54	233.30	260.21	265.11	263.31
Cer d18:2/24:1	72.15	25.77	65.44	67.52	74.66	75.62	78.17
Cer d18:2/25:0	10.53	3.80	9.50	9.89	10.96	11.31	10.58
Cer d18:2/26:0	3.07	1.01	2.77	2.90	3.14	3.26	3.29
Hex2Cer d16:1/16:0	17.13	6.16	16.21	17.88	17.39	16.35	17.07
Hex2Cer d18:1/14:0	9.85	3.61	10.05	10.47	9.82	9.08	9.46
Hex2Cer d18:1/16:0	473.15	132.03	505.33	510.17	472.89	419.65	431.02
Hex2Cer d18:1/24:0	37.90	16.74	37.43	38.72	39.25	36.05	34.77
Hex2Cer d18:1/24:1	53.59	19.48	57.07	55.82	53.77	48.74	51.15
Hex2Cer d18:2/16:0	34.94	10.38	35.65	36.36	35.30	32.10	34.27
GM3 d18:1/16:0	9.39	2.62	9.54	9.50	9.41	8.94	9.67
HexCer d16:1/16:0	6.84	2.68	6.14	6.85	7.11	6.76	6.97

HexCer d16:1/22:0	33.75	14.85	28.99	33.48	35.13	33.68	36.36
HexCer d16:1/24:0	28.54	12.63	24.47	27.85	29.86	28.46	31.56
HexCer d18:1/16:0	233.50	76.04	244.65	240.70	232.10	218.22	232.74
HexCer d18:1/18:0	29.23	10.39	30.44	31.05	29.73	25.41	28.03
HexCer d18:1/22:0	574.89	216.00	546.36	590.94	591.84	537.09	582.76
HexCer d18:1/23:0	211.83	78.11	208.07	216.28	216.21	199.30	213.03
HexCer d18:1/24:0	759.14	285.02	745.33	776.05	773.99	715.38	762.36
HexCer d18:1/24:1	525.17	213.43	548.39	539.69	527.48	475.48	539.35
HexCer d18:1/25:0	14.97	5.74	14.91	15.03	15.17	14.35	15.38
HexCer d18:1/26:0	3.93	1.50	3.85	3.95	4.02	3.75	4.04
HexCer d18:2/16:0	15.60	4.63	15.18	15.60	15.97	15.05	15.93
HexCer d18:2/22:0	63.19	23.90	60.41	63.95	63.82	61.19	66.83
HexCer d18:2/23:0	26.58	10.27	26.22	26.66	26.87	25.45	27.96
HexCer d18:2/24:0	110.00	43.01	103.56	107.96	113.38	105.80	120.26
HexCer d18:2/24:1	49.14	18.44	51.30	48.25	49.70	46.12	51.97
SM d16:1/16:0	3535.81	1145.20	3133.29	3412.85	3638.00	3693.68	3765.71
SM d16:1/18:0	2244.68	732.49	2131.26	2223.27	2270.06	2313.46	2239.81
SM d16:1/20:0	1200.43	360.27	1117.24	1194.20	1220.56	1226.52	1213.20
SM d16:1/22:0	3296.42	1043.53	2939.44	3261.35	3377.80	3423.33	3363.68
SM d16:1/24:0	1757.66	624.49	1523.17	1679.99	1820.77	1875.07	1844.20
SM d16:1/24:1	2433.81	720.71	2323.35	2427.36	2459.40	2455.55	2475.40
SM d18:1/14:0	1486.87	462.18	1388.00	1448.58	1504.89	1521.02	1601.56
SM d18:1/16:0	63497.52	9228.89	64060.13	63454.03	63213.86	63038.49	64765.30
SM d18:1/18:0	6383.29	1565.02	6414.49	6441.41	6420.32	6256.43	6284.42
SM d18:1/20:0	4046.49	1034.92	3987.07	4083.17	4108.88	3981.47	3922.28
SM d18:1/22:0	12395.37	2917.70	11658.01	12313.17	12720.20	12610.57	12043.16
SM d18:1/23:0	5373.73	1625.80	4827.78	5285.47	5543.35	5543.76	5440.85
SM d18:1/24:0	10159.63	2995.73	9359.93	10038.52	10424.48	10350.70	10285.59
SM d18:1/24:1	20014.30	4581.01	19657.30	19998.90	19987.97	20008.70	20705.92
SM d18:2/14:0	312.72	111.43	284.81	298.53	321.39	326.64	331.88
SM d18:2/16:0	10758.54	2726.17	10010.25	10312.82	10976.40	11031.78	11698.50
SM d18:2/18:0	3538.52	902.42	3658.96	3534.37	3545.86	3485.17	3444.07
SM d18:2/20:0	1120.30	281.18	1148.46	1124.74	1118.03	1115.41	1084.34
SM d18:2/22:0	6434.48	1591.21	6287.45	6394.25	6545.73	6400.17	6398.27
SM d18:2/23:0	2018.82	664.10	1879.74	1972.06	2061.25	2066.55	2095.39
SM d18:2/24:0	6091.69	1787.35	5760.64	5934.60	6241.70	6144.06	6325.59
SM d18:2/24:1	8213.25	1898.78	8343.58	8203.20	8196.68	8042.77	8441.22
SPH d16:1	3.77	2.55	3.57	3.71	3.95	3.90	3.31
SPH d18:0	18.32	19.89	16.92	18.09	19.21	18.66	16.97
SPH d18:1	66.27	74.96	64.72	65.11	69.05	67.49	58.56
SPH d18:2	17.74	15.51	17.32	17.14	18.68	18.26	15.32
S1P d16:1	91.99	25.74	90.50	91.16	93.03	93.34	89.72
S1P d17:1	20.00	4.81	20.61	19.79	19.97	19.93	19.85
S1P d18:0	160.60	46.63	163.47	160.16	163.25	157.45	153.25

S1P d18:1	1061.61	265.02	1102.78	1062.89	1076.48	1033.75	992.89
S1P d18:2	301.28	66.32	308.83	301.65	305.26	293.95	287.78

Supplemental Table 3. Univariate correlations between SPs and BMI in the normal versus overweight/obese ranges.

Sphingolipid	All BMI samples		Normal BMI (18.5 - 25)		Overweight and Obese (>25)	
	Pearson	P-value	Pearson	P-value	Pearson	P-value
Cer d16:1/16:0	0.23	**0.00E+00**	0.17	**3.01E-11**	0.01	8.73E-01
Cer d16:1/18:0	0.33	**0.00E+00**	0.24	**0.00E+00**	0.03	4.82E-01
Cer d16:1/20:0	0.30	**0.00E+00**	0.24	**0.00E+00**	-0.02	6.41E-01
Cer d16:1/22:0	0.28	**0.00E+00**	0.23	**0.00E+00**	-0.04	3.70E-01
Cer d16:1/23:0	0.20	**0.00E+00**	0.18	**3.23E-12**	-0.06	1.72E-01
Cer d16:1/24:0	0.20	**0.00E+00**	0.19	**6.17E-14**	-0.08	5.99E-02
Cer d16:1/24:1	0.23	**0.00E+00**	0.20	**5.33E-15**	-0.02	7.20E-01
Cer d18:1/16:0	0.04	9.17E-02	0.04	8.56E-02	-0.05	3.03E-01
Cer d18:1/18:0	0.30	**0.00E+00**	0.21	**0.00E+00**	0.09	**4.88E-02**
Cer d18:1/20:0	0.26	**0.00E+00**	0.20	**0.00E+00**	0.05	2.51E-01
Cer d18:1/22:0	0.23	**0.00E+00**	0.19	**2.53E-14**	-0.04	3.23E-01
Cer d18:1/23:0	0.19	**0.00E+00**	0.17	**2.17E-11**	-0.07	1.23E-01
Cer d18:1/24:0	0.17	**0.00E+00**	0.17	**3.22E-11**	-0.10	**2.52E-02**
Cer d18:1/24:1	0.14	**1.19E-11**	0.13	**2.77E-07**	0.01	8.54E-01
Cer d18:1/25:0	0.02	3.90E-01	0.04	1.19E-01	-0.04	3.88E-01
Cer d18:1/25:1	0.07	**5.24E-04**	0.07	**7.73E-03**	-0.01	7.90E-01
Cer d18:1/26:0	0.05	**1.83E-02**	0.04	8.07E-02	-0.07	9.13E-02
Cer d18:1/26:1	0.04	5.96E-02	0.07	**6.97E-03**	-0.06	1.96E-01
Cer d18:2/16:0	-0.07	**1.63E-03**	-0.04	1.17E-01	-0.04	3.74E-01
Cer d18:2/18:0	0.17	**0.00E+00**	0.13	**6.46E-07**	0.03	5.59E-01
Cer d18:2/22:0	0.14	**9.53E-12**	0.15	**7.44E-09**	-0.06	1.50E-01
Cer d18:2/23:0	0.10	**3.91E-06**	0.10	**1.27E-04**	-0.09	**4.06E-02**
Cer d18:2/24:0	0.06	**2.31E-03**	0.10	**1.14E-04**	-0.14	**9.24E-04**
Cer d18:2/24:1	0.06	**3.76E-03**	0.09	**7.60E-04**	-0.04	3.32E-01
Cer d18:2/25:0	-0.08	**9.18E-05**	-0.03	2.70E-01	-0.10	**2.34E-02**
Cer d18:2/26:0	-0.05	**1.28E-02**	-0.01	6.10E-01	-0.10	**2.71E-02**
Hex2Cer d16:1/16:0	0.10	**7.60E-07**	0.04	8.48E-02	-0.06	1.94E-01
Hex2Cer d18:1/14:0	-0.20	**0.00E+00**	-0.17	**4.14E-12**	-0.11	**8.81E-03**
Hex2Cer d18:1/16:0	-0.12	**1.10E-08**	-0.13	**3.83E-07**	-0.07	1.31E-01
Hex2Cer d18:1/24:0	0.02	4.41E-01	-0.01	7.56E-01	-0.01	8.21E-01
Hex2Cer d18:1/24:1	-0.12	**1.67E-08**	-0.10	**3.53E-05**	-0.04	3.47E-01
Hex2Cer d18:2/16:0	-0.06	**5.43E-03**	-0.09	**5.58E-04**	-0.02	6.61E-01
GM3 d18:1/16:0	-0.16	**2.22E-15**	-0.13	**3.05E-07**	-0.08	5.71E-02
HexCer d16:1/16:0	0.14	**4.34E-11**	0.09	**2.55E-04**	-0.02	6.83E-01
HexCer d16:1/22:0	0.05	**3.02E-02**	0.05	**3.06E-02**	-0.07	8.95E-02
HexCer d16:1/24:0	0.08	**8.49E-05**	0.09	**7.40E-04**	-0.11	**1.53E-02**
HexCer d18:1/16:0	-0.04	7.17E-02	-0.03	2.07E-01	0.01	8.66E-01
HexCer d18:1/18:0	-0.18	**0.00E+00**	-0.16	**4.80E-10**	-0.05	2.66E-01
HexCer d18:1/22:0	-0.05	**2.27E-02**	-0.02	3.92E-01	-0.11	**1.26E-02**
HexCer d18:1/23:0	-0.11	**2.08E-07**	-0.07	**8.21E-03**	-0.13	**3.64E-03**
HexCer d18:1/24:0	-0.08	**6.68E-05**	-0.04	1.11E-01	-0.13	**2.41E-03**

HexCer d18:1/24:1	-0.14	**5.49E-11**	-0.08	**1.11E-03**	-0.02	6.96E-01
HexCer d18:1/25:0	-0.18	**0.00E+00**	-0.11	**1.48E-05**	-0.14	**1.05E-03**
HexCer d18:1/26:0	-0.14	**1.06E-11**	-0.08	**1.67E-03**	-0.15	**6.65E-04**
HexCer d18:2/16:0	-0.01	5.71E-01	0.00	8.66E-01	-0.04	3.22E-01
HexCer d18:2/22:0	-0.12	**9.49E-09**	-0.06	**2.44E-02**	-0.13	**3.06E-03**
HexCer d18:2/23:0	-0.19	**0.00E+00**	-0.12	**2.30E-06**	-0.13	**4.09E-03**
HexCer d18:2/24:0	-0.08	**1.48E-04**	-0.04	1.59E-01	-0.14	**1.30E-03**
HexCer d18:2/24:1	-0.21	**0.00E+00**	-0.13	**2.37E-07**	-0.06	1.77E-01
SM d16:1/16:0	0.19	**0.00E+00**	0.11	**6.58E-06**	0.02	6.05E-01
SM d16:1/18:0	0.34	**0.00E+00**	0.24	**0.00E+00**	0.07	1.21E-01
SM d16:1/20:0	0.17	**0.00E+00**	0.14	**9.26E-09**	-0.04	3.67E-01
SM d16:1/22:0	0.16	**2.66E-14**	0.15	**7.09E-09**	-0.09	**4.03E-02**
SM d16:1/24:0	0.13	**9.19E-11**	0.12	**1.88E-06**	-0.09	**3.98E-02**
SM d16:1/24:1	0.09	**1.37E-05**	0.05	5.42E-02	0.00	9.49E-01
SM d18:1/14:0	-0.11	**1.11E-07**	-0.08	**2.02E-03**	-0.04	3.18E-01
SM d18:1/16:0	-0.12	**4.10E-09**	-0.12	**2.12E-06**	-0.06	1.58E-01
SM d18:1/18:0	0.10	**4.40E-06**	0.06	**1.87E-02**	0.07	1.27E-01
SM d18:1/20:0	0.05	**1.84E-02**	0.04	1.11E-01	-0.04	3.86E-01
SM d18:1/22:0	0.16	**1.89E-15**	0.12	**1.18E-06**	-0.04	3.78E-01
SM d18:1/23:0	0.17	**0.00E+00**	0.12	**4.47E-06**	-0.03	5.49E-01
SM d18:1/24:0	0.11	**7.16E-08**	0.10	**1.09E-04**	-0.06	1.79E-01
SM d18:1/24:1	-0.02	2.78E-01	-0.02	3.72E-01	0.02	6.18E-01
SM d18:2/14:0	0.08	**4.90E-05**	0.02	4.03E-01	0.05	2.28E-01
SM d18:2/16:0	0.08	**1.96E-04**	0.02	4.91E-01	0.08	7.57E-02
SM d18:2/18:0	0.13	**1.08E-09**	0.05	**4.55E-02**	0.14	**1.63E-03**
SM d18:2/20:0	-0.05	**1.60E-02**	-0.05	6.86E-02	-0.03	5.31E-01
SM d18:2/22:0	-0.03	1.02E-01	-0.02	4.26E-01	-0.09	**3.69E-02**
SM d18:2/23:0	-0.03	1.72E-01	-0.02	3.53E-01	-0.06	1.86E-01
SM d18:2/24:0	-0.05	**1.09E-02**	-0.03	2.86E-01	-0.11	**1.51E-02**
SM d18:2/24:1	-0.15	**8.95E-13**	-0.11	**9.82E-06**	0.01	8.63E-01
SPH d16:1	0.21	**0.00E+00**	0.12	**1.51E-06**	0.08	6.26E-02
SPH d18:0	0.10	**7.46E-07**	0.05	**3.11E-02**	0.09	**4.97E-02**
SPH d18:1	0.13	**1.43E-09**	0.06	**1.45E-02**	0.09	**3.38E-02**
SPH d18:2	0.15	**2.14E-13**	0.08	**7.88E-04**	0.09	5.08E-02
S1P d16:1	0.28	**0.00E+00**	0.19	**9.77E-15**	0.08	6.14E-02
S1P d17:1	0.03	1.96E-01	0.03	1.98E-01	0.00	9.95E-01
S1P d18:0	0.04	5.34E-02	0.05	**3.50E-02**	0.03	4.48E-01
S1P d18:1	0.04	5.30E-02	0.05	5.19E-02	0.05	2.79E-01
S1P d18:2	0.15	**1.25E-12**	0.07	**5.44E-03**	0.12	**4.38E-03**

Supplemental Table 4. Multivariate correlations between SPs and BMI, and SPs and HOMA-IR. Statistically significant P-values (P < 0.05) are indicated in bold. Red shading indicates positive slope. Blue shading indicates negative slope.

Sphingolipid	BMI ~ SP + Age + Gender + LDL + HDL+ Triglyceride		HOMA-IR ~ SP + Age + Gender + LDL + HDL+ Triglyceride + BMI	
	Adjusted P-value	Slope	Adjusted P-value	Slope
Cer d16:1/16:0	**2.10E-15**	1.64E-01	**1.15E-02**	5.43E-02
Cer d16:1/18:0	**1.28E-32**	2.46E-01	**3.34E-04**	7.98E-02
Cer d16:1/20:0	**1.82E-16**	1.93E-01	**2.58E-03**	7.47E-02
Cer d16:1/22:0	**1.71E-11**	1.65E-01	6.29E-01	1.24E-02
Cer d16:1/23:0	**3.86E-07**	1.16E-01	2.79E-01	-2.71E-02
Cer d16:1/24:0	**4.81E-05**	9.32E-02	2.81E-01	-2.61E-02
Cer d16:1/24:1	**3.65E-04**	8.71E-02	6.22E-01	1.26E-02
Cer d18:1/16:0	**6.07E-04**	-7.09E-02	6.71E-01	8.54E-03
Cer d18:1/18:0	**1.42E-11**	1.57E-01	**2.77E-05**	1.02E-01
Cer d18:1/20:0	**1.18E-04**	9.55E-02	**1.53E-03**	8.05E-02
Cer d18:1/22:0	**1.25E-02**	6.25E-02	2.62E-01	3.00E-02
Cer d18:1/23:0	**1.09E-02**	6.43E-02	1.74E-01	-3.68E-02
Cer d18:1/24:0	5.90E-01	1.36E-02	4.90E-01	-1.77E-02
Cer d18:1/24:1	**2.54E-02**	-5.32E-02	**4.12E-02**	4.93E-02
Cer d18:1/25:0	**5.12E-03**	-6.36E-02	6.95E-02	-4.28E-02
Cer d18:1/25:1	6.24E-01	-1.05E-02	7.31E-01	7.05E-03
Cer d18:1/26:0	5.42E-02	-4.52E-02	8.05E-02	-4.21E-02
Cer d18:1/26:1	**2.23E-02**	-5.01E-02	3.44E-01	2.14E-02
Cer d18:2/16:0	**3.18E-02**	-4.46E-02	4.01E-01	-1.84E-02
Cer d18:2/18:0	**2.19E-04**	7.73E-02	2.69E-01	2.49E-02
Cer d18:2/22:0	4.35E-01	-1.89E-02	5.95E-02	-4.53E-02
Cer d18:2/23:0	1.82E-01	-3.21E-02	**4.26E-05**	-9.74E-02
Cer d18:2/24:0	**2.25E-03**	-7.00E-02	**1.80E-04**	-8.74E-02
Cer d18:2/24:1	**2.78E-06**	-1.05E-01	**4.55E-03**	-6.49E-02
Cer d18:2/25:0	**1.86E-09**	-1.27E-01	**2.18E-08**	-1.22E-01
Cer d18:2/26:0	**5.23E-07**	-1.06E-01	**2.47E-05**	-9.40E-02
Hex2Cer d16:1/16:0	**4.96E-09**	1.19E-01	2.12E-01	-2.83E-02
Hex2Cer d18:1/14:0	**6.30E-07**	-1.04E-01	**8.31E-03**	-5.65E-02
Hex2Cer d18:1/16:0	**4.07E-03**	-6.19E-02	**3.11E-03**	-6.40E-02
Hex2Cer d18:1/24:0	7.82E-02	-3.77E-02	4.57E-01	1.67E-02
Hex2Cer d18:1/24:1	**3.80E-06**	-9.65E-02	2.93E-01	-2.33E-02
Hex2Cer d18:2/16:0	8.04E-01	-5.06E-03	**1.20E-03**	-6.99E-02
GM3 d18:1/16:0	**1.86E-09**	-1.30E-01	**3.11E-03**	-6.69E-02
HexCer d16:1/16:0	**1.21E-09**	1.27E-01	6.43E-01	-9.96E-03
HexCer d16:1/22:0	1.92E-01	2.80E-02	6.71E-01	-8.81E-03
HexCer d16:1/24:0	2.70E-01	2.43E-02	2.62E-01	-2.61E-02
HexCer d18:1/16:0	**2.46E-02**	-4.80E-02	3.44E-01	-2.11E-02

HexCer d18:1/18:0	**1.14E-09**	-1.23E-01	4.56E-01	-1.68E-02
HexCer d18:1/22:0	**2.21E-07**	-1.09E-01	2.62E-01	-2.62E-02
HexCer d18:1/23:0	**8.36E-10**	-1.28E-01	2.81E-01	-2.41E-02
HexCer d18:1/24:0	**1.22E-11**	-1.44E-01	2.62E-01	-2.70E-02
HexCer d18:1/24:1	**8.80E-14**	-1.52E-01	9.08E-01	2.17E-03
HexCer d18:1/25:0	**1.64E-21**	-1.96E-01	**3.73E-02**	-4.58E-02
HexCer d18:1/26:0	**2.37E-18**	-1.83E-01	1.53E-01	-3.35E-02
HexCer d18:2/16:0	5.47E-01	-1.33E-02	**2.86E-02**	-4.73E-02
HexCer d18:2/22:0	**8.39E-08**	-1.11E-01	**1.18E-02**	-5.33E-02
HexCer d18:2/23:0	**1.01E-11**	-1.41E-01	**3.72E-03**	-6.20E-02
HexCer d18:2/24:0	**4.67E-10**	-1.33E-01	**6.55E-03**	-5.95E-02
HexCer d18:2/24:1	**7.23E-16**	-1.66E-01	**5.48E-03**	-5.93E-02
SM d16:1/16:0	**1.85E-26**	2.38E-01	1.81E-01	3.40E-02
SM d16:1/18:0	**2.11E-51**	3.02E-01	**3.98E-04**	7.88E-02
SM d16:1/20:0	**4.97E-18**	1.76E-01	**2.65E-02**	4.78E-02
SM d16:1/22:0	**3.74E-16**	1.67E-01	4.68E-01	1.62E-02
SM d16:1/24:0	**9.42E-12**	1.47E-01	5.24E-01	-1.46E-02
SM d16:1/24:1	**6.48E-12**	1.41E-01	1.17E-01	3.51E-02
SM d18:1/14:0	8.46E-02	-4.37E-02	2.79E-01	-2.85E-02
SM d18:1/16:0	**2.98E-04**	-8.06E-02	2.12E-01	-3.02E-02
SM d18:1/18:0	**2.59E-03**	6.44E-02	**4.55E-03**	6.09E-02
SM d18:1/20:0	4.50E-01	1.70E-02	**3.11E-03**	6.53E-02
SM d18:1/22:0	**1.02E-06**	1.11E-01	1.45E-01	3.65E-02
SM d18:1/23:0	**3.09E-10**	1.57E-01	8.37E-01	5.02E-03
SM d18:1/24:0	**4.49E-03**	7.08E-02	4.57E-01	1.96E-02
SM d18:1/24:1	2.67E-01	-2.50E-02	**4.12E-02**	4.58E-02
SM d18:2/14:0	**1.69E-20**	2.30E-01	5.32E-01	1.66E-02
SM d18:2/16:0	**6.92E-13**	1.85E-01	2.12E-01	-3.57E-02
SM d18:2/18:0	**1.59E-14**	1.55E-01	**1.35E-02**	5.16E-02
SM d18:2/20:0	2.03E-01	2.74E-02	5.07E-01	1.47E-02
SM d18:2/22:0	8.80E-02	3.83E-02	6.03E-01	-1.20E-02
SM d18:2/23:0	1.08E-01	3.90E-02	**3.11E-03**	-7.12E-02
SM d18:2/24:0	6.24E-01	-1.20E-02	**1.18E-02**	-6.09E-02
SM d18:2/24:1	1.03E-01	-3.71E-02	1.55E-01	-3.41E-02
SPH d16:1	**1.03E-14**	1.52E-01	**2.47E-05**	8.91E-02
SPH d18:0	**3.37E-04**	7.07E-02	**3.06E-04**	7.25E-02
SPH d18:1	**1.80E-06**	9.34E-02	**2.77E-05**	8.53E-02
SPH d18:2	**9.00E-09**	1.12E-01	**3.11E-03**	5.95E-02
S1P d16:1	**5.49E-37**	2.43E-01	**8.29E-05**	8.24E-02
S1P d17:1	**2.46E-02**	4.51E-02	**2.78E-04**	7.35E-02
S1P d18:0	1.13E-01	3.18E-02	**4.94E-03**	5.58E-02
S1P d18:1	7.05E-01	7.51E-03	**3.06E-04**	7.33E-02
S1P d18:2	**6.81E-11**	1.27E-01	**4.12E-04**	7.08E-02

Supplemental Table 5. Multivariate correlations between SPs and HOMA-IR before and after elastic net regularization. Lipids that remained significant after correction for age, gender, LDL, HDL, triglycerides, and BMI were evaluated for interactions among all SPs.

Sphingolipid	HOMA-IR ~ SP + Age + Gender + LDL + HDL+ Triglyceride + BMI		HOMA-IR ~ SP + Age + Gender + LDL + HDL+ Triglyceride + BMI With elastic net regularization
	Adjusted P-value	Slope	
Cer d16:1/16:0	1.15E-02	5.43E-02	0.247
Cer d16:1/18:0	3.34E-04	7.98E-02	0
Cer d16:1/20:0	2.58E-03	7.47E-02	0.0394
Cer d18:1/18:0	2.77E-05	1.02E-01	0.307
Cer d18:1/20:0	1.53E-03	8.05E-02	0
Cer d18:1/24:1	4.12E-02	4.93E-02	0.873
Cer d18:2/23:0	4.26E-05	-9.74E-02	-0.297
Cer d18:2/24:0	1.80E-04	-8.74E-02	-0.000361
Cer d18:2/24:1	4.55E-03	-6.49E-02	-0.593
Cer d18:2/25:0	2.18E-08	-1.22E-01	-0.685
Cer d18:2/26:0	2.47E-05	-9.40E-02	-0.129
Hex2Cer d18:1/14:0	8.31E-03	-5.65E-02	-0.0494
Hex2Cer d18:1/16:0	3.11E-03	-6.40E-02	-0.419
Hex2Cer d18:2/16:0	1.20E-03	-6.99E-02	-0.141
GM3 d18:1/16:0	3.11E-03	-6.69E-02	-0.228
HexCer d18:1/25:0	3.73E-02	-4.58E-02	0.0904
HexCer d18:2/16:0	2.86E-02	-4.73E-02	0
HexCer d18:2/22:0	1.18E-02	-5.33E-02	0
HexCer d18:2/23:0	3.72E-03	-6.20E-02	0
HexCer d18:2/24:0	6.55E-03	-5.95E-02	0
HexCer d18:2/24:1	5.48E-03	-5.93E-02	-0.248
SM d16:1/18:0	3.98E-04	7.88E-02	0
SM d16:1/20:0	2.65E-02	4.78E-02	0
SM d18:1/18:0	4.55E-03	6.09E-02	0
SM d18:1/20:0	3.11E-03	6.53E-02	0
SM d18:1/24:1	4.12E-02	4.58E-02	0
SM d18:2/18:0	1.35E-02	5.16E-02	0.592
SM d18:2/23:0	3.11E-03	-7.12E-02	-0.0521
SM d18:2/24:0	1.18E-02	-6.09E-02	0
SPH d16:1	2.47E-05	8.91E-02	0.205
SPH d18:0	3.06E-04	7.25E-02	0
SPH d18:1	2.77E-05	8.53E-02	0
SPH d18:2	3.11E-03	5.95E-02	0
S1P d16:1	8.29E-05	8.24E-02	0.177
S1P d17:1	2.78E-04	7.35E-02	0.198

S1P d18:0	4.94E-03	5.58E-02	-0.0873
S1P d18:1	3.06E-04	7.33E-02	0
S1P d18:2	4.12E-04	7.08E-02	1.03
BMI			0.0998
Age			0.00231
Gender			0.196
LDL			0
HDL			-0.0977
Triglyceride			0.281

Supplemental Table 6. Baseline plasma SP content of normal versus individuals subsequently diagnosed with T2DM, showing mean values and standard deviations. P-values were determined by two-tailed Student's T-test with unequal variance. Significant differences ($P < 0.05$) are indicated in bold. Values in red depict significant increases. Values in blue depict significant decreases.

Sphingolipid	Normal average concentration (nM)	Standard deviation of Normal	Diabetes average concentration (nM)	Standard deviation of Diabetes	T-test between Normal and Diabetes
Cer d16:1/16:0	3.14	1.03	3.54	0.99	**1.43E-06**
Cer d16:1/18:0	6.12	2.68	7.66	2.94	**3.85E-10**
Cer d16:1/20:0	15.07	7.08	18.97	6.73	**1.00E-11**
Cer d16:1/22:0	47.15	23.08	58.54	24.56	**2.14E-08**
Cer d16:1/23:0	21.46	9.30	25.23	9.35	**9.37E-07**
Cer d16:1/24:0	89.02	37.69	102.27	38.60	**2.54E-05**
Cer d16:1/24:1	26.81	12.00	33.43	13.23	**1.80E-09**
Cer d18:1/16:0	100.17	22.95	101.47	22.18	4.64E-01
Cer d18:1/18:0	57.81	25.68	74.37	30.30	**6.44E-11**
Cer d18:1/20:0	68.44	28.34	82.87	29.98	**6.84E-09**
Cer d18:1/22:0	458.74	159.58	522.19	162.12	**1.86E-06**
Cer d18:1/23:0	341.32	107.84	383.68	103.43	**7.07E-07**
Cer d18:1/24:0	1474.89	465.37	1623.15	519.87	**3.98E-04**
Cer d18:1/24:1	427.58	134.70	490.23	165.49	**3.09E-06**
Cer d18:1/25:0	58.64	18.09	59.05	17.47	7.69E-01
Cer d18:1/25:1	11.11	4.16	12.29	5.12	**3.86E-03**
Cer d18:1/26:0	12.95	3.77	13.26	3.92	3.22E-01
Cer d18:1/26:1	5.67	2.23	6.01	2.52	9.04E-02
Cer d18:2/16:0	11.24	2.76	10.91	2.82	1.37E-01
Cer d18:2/18:0	9.12	3.20	10.02	3.28	**6.34E-04**
Cer d18:2/22:0	79.93	31.44	88.02	30.81	**1.18E-03**
Cer d18:2/23:0	57.95	22.04	61.39	19.61	**3.06E-02**
Cer d18:2/24:0	247.81	87.18	256.06	77.39	1.87E-01
Cer d18:2/24:1	71.75	25.66	76.55	26.55	**2.42E-02**
Cer d18:2/25:0	10.57	3.84	9.74	3.10	**1.10E-03**
Cer d18:2/26:0	3.07	1.02	2.97	0.95	1.74E-01
Hex2Cer d16:1/16:0	17.13	6.22	17.11	5.47	9.64E-01
Hex2Cer d18:1/14:0	9.94	3.63	8.70	3.11	**1.55E-06**
Hex2Cer d18:1/16:0	477.12	132.28	426.40	118.03	**2.45E-07**
Hex2Cer d18:1/24:0	38.01	16.91	36.17	13.92	1.03E-01
Hex2Cer d18:1/24:1	54.04	19.55	47.93	17.48	**2.20E-05**
Hex2Cer d18:2/16:0	35.23	10.44	31.49	8.93	**5.30E-07**
GM3 d18:1/16:0	9.45	2.63	8.59	2.42	**1.40E-05**
HexCer d16:1/16:0	6.82	2.70	7.02	2.38	3.18E-01
HexCer d16:1/22:0	33.67	14.93	34.37	13.55	5.19E-01
HexCer d16:1/24:0	28.55	12.77	28.23	10.55	7.07E-01

HexCer d18:1/16:0	234.56	76.45	220.28	68.56	**1.03E-02**
HexCer d18:1/18:0	29.45	10.46	26.39	9.03	**3.88E-05**
HexCer d18:1/22:0	577.37	217.05	540.62	196.77	**2.11E-02**
HexCer d18:1/23:0	213.37	79.13	192.59	59.73	**3.18E-05**
HexCer d18:1/24:0	764.09	286.86	695.84	248.62	**7.99E-04**
HexCer d18:1/24:1	529.27	213.57	473.74	201.47	**7.00E-04**
HexCer d18:1/25:0	15.14	5.80	12.84	4.31	**4.73E-10**
HexCer d18:1/26:0	3.97	1.51	3.50	1.24	**7.08E-06**
HexCer d18:2/16:0	15.66	4.66	14.87	4.20	**1.98E-02**
HexCer d18:2/22:0	63.68	24.02	56.86	21.03	**8.21E-05**
HexCer d18:2/23:0	26.86	10.32	23.03	9.00	**3.26E-07**
HexCer d18:2/24:0	110.67	43.14	100.93	39.81	**2.59E-03**
HexCer d18:2/24:1	49.69	18.50	42.55	16.26	**1.45E-07**
SM d16:1/16:0	3509.87	1145.99	3828.92	1107.68	**3.95E-04**
SM d16:1/18:0	2214.61	721.79	2620.82	773.09	**3.38E-10**
SM d16:1/20:0	1194.56	358.64	1267.91	380.05	**1.59E-02**
SM d16:1/22:0	3280.31	1040.89	3462.59	1070.39	**3.35E-02**
SM d16:1/24:0	1750.30	622.52	1830.15	640.63	1.19E-01
SM d16:1/24:1	2426.82	724.56	2516.91	660.18	9.08E-02
SM d18:1/14:0	1489.97	467.23	1436.90	381.50	8.80E-02
SM d18:1/16:0	63604.06	9165.19	62149.74	9876.38	6.48E-02
SM d18:1/18:0	6360.40	1533.69	6710.71	1930.63	**2.21E-02**
SM d18:1/20:0	4039.21	1031.51	4124.96	1062.00	3.11E-01
SM d18:1/22:0	12360.27	2908.56	12733.80	2992.22	1.18E-01
SM d18:1/23:0	5338.86	1617.98	5764.12	1678.65	**1.67E-03**
SM d18:1/24:0	10115.48	2972.11	10595.05	3249.20	6.39E-02
SM d18:1/24:1	20008.78	4560.82	20102.11	4801.76	8.07E-01
SM d18:2/14:0	312.21	112.73	317.18	93.07	5.11E-01
SM d18:2/16:0	10742.84	2734.15	10865.28	2662.89	5.65E-01
SM d18:2/18:0	3535.25	896.94	3582.91	983.08	5.41E-01
SM d18:2/20:0	1123.28	279.64	1083.06	295.55	8.81E-02
SM d18:2/22:0	6442.04	1572.82	6272.72	1799.16	2.35E-01
SM d18:2/23:0	2024.98	664.82	1933.77	647.23	7.91E-02
SM d18:2/24:0	6107.27	1769.78	5844.40	1962.09	9.21E-02
SM d18:2/24:1	8257.03	1901.92	7671.01	1760.63	**4.88E-05**
SPH d16:1	3.74	2.58	4.13	2.07	**2.07E-02**
SPH d18:0	18.18	20.04	20.09	17.39	1.75E-01
SPH d18:1	65.61	75.73	74.12	62.25	9.33E-02
SPH d18:2	17.68	15.72	18.51	12.28	4.10E-01
S1P d16:1	91.40	25.72	99.04	24.64	**1.44E-04**
S1P d17:1	19.97	4.80	20.19	4.89	5.78E-01
S1P d18:0	160.28	46.64	164.15	46.33	2.96E-01
S1P d18:1	1060.70	266.41	1073.73	243.93	5.07E-01
S1P d18:2	300.49	66.37	310.98	63.67	**4.07E-02**

Supplemental Table 7. Cox regression analysis between SP concentrations at baseline and subsequent diagnosis of T2DM. Models with increasing covariates are depicted from left to right (increasing stringency). Significant associations ($P < 0.05$) are indicated in bold. BMI = body mass index, HDL = high density lipoprotein, HR = hazard ratio, LDL = low density lipoprotein, SP = sphingolipid.

Lipid	Diabetes (Incidence, Time) ~ SP		Diabetes (Incidence, Time) ~ SP + Age + Gender		Diabetes (Incidence, Time) ~ SP + Age + Gender + LDL + HDL+ Triglyceride		Diabetes (Incidence, Time) ~ SP + Age + Gender + LDL + HDL+ Triglyceride + BMI		Diabetes (Incidence, Time) ~ SP + Age + Gender + LDL + HDL+ Triglyceride + BMI + HbA1c	
	Adjusted P-value	HR	Adjusted P-value	HR	Adjusted P-value	HR	Adjusted P-value	HR	Adjusted P-value	HR
Cer d16:1/16:0	**1.33E-06**	1.50	**4.57E-04**	1.36	**4.59E-03**	1.33	1.14E-01	1.22	7.78E-01	1.09
Cer d16:1/18:0	**2.90E-11**	1.78	**7.88E-09**	1.67	**5.92E-05**	1.52	**3.37E-02**	1.35	4.05E-01	1.24
Cer d16:1/20:0	**1.97E-12**	1.79	**1.54E-08**	1.63	**1.15E-03**	1.42	5.81E-02	1.31	4.69E-01	1.21
Cer d16:1/22:0	**6.13E-10**	1.67	**5.45E-06**	1.48	1.23E-01	1.20	5.09E-01	1.10	8.53E-01	0.95
Cer d16:1/23:0	**2.46E-07**	1.56	**5.80E-04**	1.36	1.54E-01	1.18	3.62E-01	1.15	9.93E-01	1.00
Cer d16:1/24:0	**9.97E-06**	1.45	**4.91E-03**	1.28	2.44E-01	1.13	6.17E-01	1.06	8.42E-01	0.96
Cer d16:1/24:1	**2.90E-11**	1.74	**2.14E-07**	1.57	**2.94E-02**	1.28	1.65E-01	1.23	5.62E-01	1.16
Cer d18:1/16:0	4.62E-01	1.06	9.55E-01	1.00	3.35E-01	0.91	8.81E-01	0.98	8.26E-01	0.95
Cer d18:1/18:0	**1.28E-12**	1.79	**9.98E-10**	1.69	**3.71E-04**	1.50	**4.14E-02**	1.36	1.16E-01	1.35
Cer d18:1/20:0	**5.11E-10**	1.64	**1.89E-07**	1.56	**2.67E-02**	1.31	1.96E-01	1.23	4.75E-01	1.19
Cer d18:1/22:0	**6.06E-07**	1.48	**1.10E-04**	1.39	2.07E-01	1.15	4.17E-01	1.14	7.82E-01	1.10
Cer d18:1/23:0	**6.06E-07**	1.50	**5.80E-04**	1.35	1.81E-01	1.17	3.05E-01	1.17	7.85E-01	1.08
Cer d18:1/24:0	**2.36E-04**	1.36	**1.64E-02**	1.23	3.66E-01	1.10	6.14E-01	1.07	9.93E-01	1.01
Cer d18:1/24:1	**2.68E-07**	1.51	**1.39E-04**	1.39	2.18E-01	1.15	2.67E-01	1.17	4.69E-01	1.19
Cer d18:1/25:0	6.80E-01	1.04	7.12E-01	0.97	2.93E-01	0.90	6.45E-01	0.95	7.85E-01	0.93
Cer d18:1/25:1	**1.06E-02**	1.29	3.73E-01	1.09	3.66E-01	0.92	5.09E-01	0.92	9.93E-01	1.00
Cer d18:1/26:0	3.46E-01	1.08	8.57E-01	0.98	1.81E-01	0.87	4.82E-01	0.91	7.85E-01	0.93
Cer d18:1/26:1	9.41E-02	1.15	7.72E-01	1.03	4.19E-01	0.92	6.14E-01	0.94	8.53E-01	0.96
Cer d18:2/16:0	1.08E-01	0.88	**1.61E-02**	0.82	1.81E-01	0.88	4.26E-01	0.90	5.85E-01	0.89
Cer d18:2/18:0	**9.69E-04**	1.32	**4.91E-03**	1.27	1.63E-01	1.16	4.82E-01	1.10	7.12E-01	1.10
Cer d18:2/22:0	**6.83E-04**	1.32	**3.11E-02**	1.20	9.37E-01	0.99	9.70E-01	1.01	9.27E-01	0.98
Cer d18:2/23:0	**2.09E-02**	1.22	4.77E-01	1.07	2.58E-01	0.89	5.18E-01	0.92	4.75E-01	0.84
Cer d18:2/24:0	1.38E-01	1.13	8.45E-01	1.02	2.66E-01	0.89	5.47E-01	0.93	6.97E-01	0.90
Cer d18:2/24:1	**1.98E-02**	1.22	3.20E-01	1.09	1.70E-01	0.86	5.09E-01	0.92	7.78E-01	0.92
Cer d18:2/25:0	**1.98E-02**	0.83	**8.65E-04**	0.76	**5.62E-04**	0.72	5.57E-02	0.79	1.16E-01	0.78
Cer d18:2/26:0	2.46E-01	0.91	**1.08E-02**	0.81	**2.21E-03**	0.76	8.72E-02	0.83	3.86E-01	0.83
Hex2Cer d16:1/16:0	6.80E-01	1.03	5.17E-01	1.06	3.46E-01	1.09	9.15E-01	1.01	8.26E-01	1.05
Hex2Cer d18:1/14:0	**1.45E-05**	0.71	**5.80E-04**	0.75	2.07E-01	0.88	6.14E-01	0.94	8.53E-01	0.96
Hex2Cer d18:1/16:0	**1.12E-06**	0.68	**8.29E-03**	0.80	1.81E-01	0.87	5.09E-01	0.92	9.39E-01	0.98
Hex2Cer d18:1/24:0	2.82E-01	0.91	6.95E-01	0.96	3.63E-01	0.92	6.59E-01	0.95	8.36E-01	0.96
Hex2Cer d18:1/24:1	**3.65E-05**	0.71	**2.79E-03**	0.78	**3.90E-02**	0.82	2.67E-01	0.87	6.25E-01	0.89
Hex2Cer d18:2/16:0	**1.48E-05**	0.71	**1.03E-03**	0.77	**1.95E-02**	0.80	8.66E-02	0.82	4.69E-01	0.84
GM3 d18:1/16:0	**1.43E-05**	0.71	**6.26E-05**	0.72	**1.17E-02**	0.79	3.42E-01	0.88	7.85E-01	0.93
HexCer d16:1/16:0	2.24E-01	1.11	4.05E-01	1.08	7.71E-01	1.03	8.36E-01	0.98	9.22E-01	0.97

HexCer d16:1/22:0	4.19E-01	1.07	9.55E-01	1.00	9.58E-01	1.00	9.70E-01	1.00	9.93E-01	1.00
HexCer d16:1/24:0	8.26E-01	1.02	5.18E-01	0.94	3.35E-01	0.91	4.95E-01	0.91	7.78E-01	0.92
HexCer d18:1/16:0	**1.29E-02**	0.81	8.44E-02	0.86	2.90E-01	0.91	6.91E-01	0.96	9.93E-01	1.00
HexCer d18:1/18:0	**2.51E-04**	0.74	**1.64E-02**	0.82	2.93E-01	0.91	9.70E-01	1.00	9.22E-01	1.02
HexCer d18:1/22:0	**2.15E-02**	0.83	**3.92E-02**	0.84	1.35E-01	0.85	5.39E-01	0.93	8.26E-01	0.95
HexCer d18:1/23:0	**1.63E-03**	0.78	**5.27E-03**	0.80	6.10E-02	0.83	6.14E-01	0.94	9.93E-01	1.00
HexCer d18:1/24:0	**1.65E-03**	0.78	**3.99E-03**	0.78	**2.94E-02**	0.81	4.46E-01	0.90	8.36E-01	0.96
HexCer d18:1/24:1	**5.40E-04**	0.76	**4.91E-03**	0.79	**3.42E-02**	0.82	4.64E-01	0.91	7.85E-01	0.94
HexCer d18:1/25:0	**1.72E-07**	0.66	**1.89E-07**	0.66	**1.38E-04**	0.69	5.81E-02	0.79	4.69E-01	0.86
HexCer d18:1/26:0	**6.86E-05**	0.72	**1.32E-04**	0.73	**8.45E-04**	0.73	1.65E-01	0.84	6.92E-01	0.90
HexCer d18:2/16:0	5.11E-02	0.85	5.32E-02	0.85	6.34E-02	0.84	2.67E-01	0.87	7.85E-01	0.93
HexCer d18:2/22:0	**1.91E-04**	0.75	**1.23E-04**	0.74	**8.69E-03**	0.79	2.33E-01	0.86	8.26E-01	0.95
HexCer d18:2/23:0	**2.46E-07**	0.68	**1.72E-07**	0.66	**5.62E-04**	0.73	8.66E-02	0.81	6.04E-01	0.89
HexCer d18:2/24:0	**1.40E-03**	0.77	**1.45E-04**	0.74	**5.77E-04**	0.73	5.81E-02	0.80	4.69E-01	0.84
HexCer d18:2/24:1	**8.58E-08**	0.69	**1.89E-07**	0.69	**3.71E-04**	0.73	5.81E-02	0.80	6.41E-01	0.90
SM d16:1/16:0	**3.29E-04**	1.35	**1.37E-02**	1.24	**4.59E-03**	1.36	2.12E-01	1.20	6.92E-01	1.12
SM d16:1/18:0	**1.60E-10**	1.74	**9.98E-10**	1.74	**7.92E-08**	1.73	**1.27E-03**	1.50	**1.47E-02**	1.45
SM d16:1/20:0	**1.98E-02**	1.22	**3.53E-02**	1.20	**4.59E-03**	1.33	1.16E-01	1.22	4.69E-01	1.20
SM d16:1/22:0	**4.76E-02**	1.19	1.65E-01	1.13	**1.98E-02**	1.26	2.67E-01	1.16	7.85E-01	1.07
SM d16:1/24:0	1.38E-01	1.13	6.21E-01	1.05	1.42E-01	1.16	5.09E-01	1.08	9.50E-01	1.02
SM d16:1/24:1	9.39E-02	1.16	1.65E-01	1.13	**1.51E-02**	1.28	1.65E-01	1.19	4.75E-01	1.16
SM d18:1/14:0	3.51E-01	0.92	**3.08E-02**	0.82	3.39E-01	0.90	6.45E-01	0.94	7.85E-01	0.93
SM d18:1/16:0	**4.56E-02**	0.85	**3.11E-02**	0.84	5.76E-01	0.95	8.00E-01	1.03	8.26E-01	1.05
SM d18:1/18:0	5.40E-02	1.18	**1.61E-02**	1.23	**1.34E-03**	1.38	**2.61E-02**	1.34	**1.47E-02**	1.40
SM d18:1/20:0	3.68E-01	1.08	1.65E-01	1.12	**3.01E-02**	1.25	6.86E-02	1.26	6.25E-02	1.34
SM d18:1/22:0	1.53E-01	1.13	1.65E-01	1.12	1.81E-01	1.16	4.64E-01	1.11	7.29E-01	1.11
SM d18:1/23:0	**1.56E-03**	1.30	**1.07E-02**	1.25	**1.02E-02**	1.39	5.81E-02	1.35	4.69E-01	1.24
SM d18:1/24:0	1.07E-01	1.14	2.47E-01	1.11	1.23E-01	1.21	2.15E-01	1.20	7.85E-01	1.08
SM d18:1/24:1	8.71E-01	1.01	7.85E-01	0.97	7.02E-01	1.04	6.63E-01	1.05	8.21E-01	1.06
SM d18:2/14:0	2.55E-01	1.10	9.55E-01	1.01	5.61E-01	1.07	6.45E-01	0.94	7.85E-01	0.92
SM d18:2/16:0	5.60E-01	1.05	4.05E-01	0.93	7.60E-01	0.97	5.04E-01	0.90	8.26E-01	0.94
SM d18:2/18:0	8.26E-01	1.02	4.49E-01	1.07	5.87E-02	1.21	4.53E-01	1.11	5.38E-01	1.15
SM d18:2/20:0	**4.56E-02**	0.85	1.34E-01	0.88	3.82E-01	1.09	4.64E-01	1.11	5.51E-01	1.15
SM d18:2/22:0	6.59E-02	0.86	8.44E-02	0.86	6.20E-01	1.05	6.32E-01	1.06	9.72E-01	1.01
SM d18:2/23:0	1.04E-01	0.88	**2.13E-02**	0.83	3.70E-01	0.91	6.14E-01	0.94	7.85E-01	0.93
SM d18:2/24:0	**1.98E-02**	0.83	**3.38E-03**	0.79	2.58E-01	0.88	5.09E-01	0.92	6.92E-01	0.89
SM d18:2/24:1	**2.22E-04**	0.76	**1.38E-04**	0.74	1.70E-01	0.87	5.09E-01	0.92	7.85E-01	0.93
SPH d16:1	**2.21E-03**	1.28	**1.34E-03**	1.31	**3.42E-02**	1.22	4.64E-01	1.10	6.96E-01	1.10
SPH d18:0	**1.68E-02**	1.21	**3.42E-02**	1.19	2.58E-01	1.11	6.45E-01	1.05	8.20E-01	1.05
SPH d18:1	**2.93E-03**	1.26	**4.91E-03**	1.26	8.37E-02	1.18	5.09E-01	1.08	7.78E-01	1.08
SPH d18:2	8.46E-02	1.15	8.24E-02	1.16	1.81E-01	1.13	7.89E-01	1.03	9.18E-01	1.02
S1P d16:1	**2.59E-04**	1.37	**2.19E-04**	1.38	**8.45E-04**	1.37	1.65E-01	1.19	4.75E-01	1.16
S1P d17:1	5.97E-01	1.05	5.29E-01	1.06	1.81E-01	1.14	4.17E-01	1.11	4.69E-01	1.18
S1P d18:0	2.77E-01	1.10	9.44E-02	1.15	2.07E-01	1.13	2.67E-01	1.14	4.69E-01	1.15

S1P d18:1	4.15E-01	1.07	7.76E-02	1.17	1.70E-01	1.15	2.67E-01	1.15	4.75E-01	1.15
S1P d18:2	5.40E-02	1.19	**9.24E-03**	1.27	**1.82E-02**	1.27	2.12E-01	1.17	3.86E-01	1.22

Supplemental Table 8. Multivariate Cox regression analysis between SP concentrations at baseline and subsequent diagnosis of T2DM before and after elastic net regularization. BMI = body mass index, HDL = high density lipoprotein, HR = hazard ratio, LDL = low density lipoprotein, SP = sphingolipid.

Sphingolipid	Diabetes (Incidence, Time) ~ SP + Age + Gender + LDL + HDL+ Triglyceride + BMI + HbA1c		Diabetes (Incidence, Time) ~ SP + Age + Gender + LDL + HDL+ Triglyceride + BMI + HbA1c With elastic net regularization
	Adjusted P-value	HR	
SM d16:1/18:0	1.47E-02	1.45	1.77
SM d18:1/18:0	1.47E-02	1.40	2.08
Age			0.0516
Gender			0.344
LDL			-0.338
HDL			-0.722
Triglyceride			0.309
BMI			0.127
HbA1c			1.91

Supplemental Table 9. The net reclassification index (NRI) across different models. NRI+ indicates 'event NRI' where the event is the subsequent diagnosis of incident diabetes while NRI- indicates 'nonevent NRI' where there is an absence of diabetes incidence. Values indicate the difference between the proportion of individuals whose probability improved with the new model and the proportion of individuals whose probability became less accurate with the new model. A positive number indicates that the new model improved the accuracy of the probability more frequently than it worsened the accuracy. NRI is the sum of NRI+ and NRI-. Cumulative distribution reclassification (survIDINRI) represents the probability difference in discrimination slopes between the two indicated models. Values represent the proportion increase in improved probabilities. The 95% confidence interval for the values are indicated in brackets. Values with a 95% confidence interval that does not include zero are regarded as "significant" and highlighted in bold. "ARIC" indicates the use of the following covariates: Age + HDL + Systolic BP + Glucose + Triglyceride + Waist + Height.

Model	NRI+	NRI-	NRI	survIDINRI
Diabetes (Incidence, Time) ~ HbA1c vs Diabetes (Incidence, Time) ~ HbA1c + SM d16:1/18:0	**0.239 (0.115 – 0.379)**	**0.197 (0.101 – 0.291)**	**0.436 (0.243 – 0.652)**	**0.223 (0.122 – 0.335) P<0.001**
Diabetes (Incidence, Time) ~ HbA1c vs Diabetes (Incidence, Time) ~ HbA1c + SM d18:1/18:0	0.0986 (-0.0390 – 0.212)	0.113 (-0.0117 – 0.208)	0.211 (-0.0225 – 0.390)	0.102 (-0.0980 – 0.188) P=0.159
Diabetes (Incidence, Time) ~ HbA1c vs Diabetes (Incidence, Time) ~ HbA1c + SM d16:1/18:0 + SM d18:1/18:0	**0.211 (0.133 – 0.392)**	**0.184 (0.114 – 0.289)**	**0.396 (0.281 – 0.650)**	**0.202 (0.138 – 0.321) P<0.001**
Diabetes (Incidence, Time) ~ HbA1c vs Diabetes (Incidence, Time) ~ HbA1c + BMI	0.127 (-0.0133 – 0.254)	**0.327 (0.234 – 0.423)**	**0.453 (0.258 – 0.637)**	**0.231 (0.125 – 0.309) P<0.001**
Diabetes (Incidence, Time) ~ HbA1c + BMI vs Diabetes (Incidence, Time) ~ HbA1c + BMI + SM d16:1/18:0	**0.183 (0.049 – 0.338)**	**0.199 (0.112 – 0.313)**	**0.382 (0.189 – 0.624)**	**0.188 (0.0670 – 0.289) P<0.001**
Diabetes (Incidence, Time) ~ HbA1c + BMI vs Diabetes (Incidence, Time) ~ HbA1c + BMI + SM d18:1/18:0	0.0986 (-0.0813 – 0.207)	0.104 (-0.0355 – 0.207)	0.202 (-0.102 – 0.372)	0.0980 (-0.145 – 0.179) P=0.286
Diabetes (Incidence, Time) ~ HbA1c + BMI vs Diabetes (Incidence, Time) ~ HbA1c + BMI + SM d16:1/18:0 + SM d18:1/18:0	**0.183 (0.034 – 0.321)**	**0.199 (0.125 – 0.321)**	**0.382 (0.204 – 0.607)**	**0.188 (0.0820 – 0.296) P=0.0130**
Diabetes (Incidence, Time) ~ ARIC vs Diabetes (Incidence, Time) ~ ARIC + SM d16:1/18:0	**0.247 (0.0968 – 0.343)**	**0.217 (0.0945 – 0.313)**	**0.464 (0.224 – 0.619)**	**0.236 (0.0950 – 0.324) P=0.00700**
Diabetes (Incidence, Time) ~ ARIC vs Diabetes (Incidence, Time) ~ ARIC + SM d18:1/18:0	0.106 (-0.0389 – 0.220)	0.101 (-0.0129 – 0.220)	0.207 (-0.00558 – 0.385)	0.100 (-0.0550 – 0.183) P=0.100
Diabetes (Incidence, Time) ~ ARIC vs Diabetes (Incidence, Time) ~ ARIC + SM d16:1/18:0 + SM d18:1/18:0	**0.247 (0.0886 – 0.338)**	**0.215 (0.114 – 0.325)**	**0.462 (0.247 – 0.627)**	**0.235 (0.0950 – 0.322) P<0.001**

Supplemental Table 10. Linear regression analysis of the relationship between adiponectin HMW and individual SPs with and without the use of BMI as a covariate.

	Adiponectin HMW ~ SP (P-value)	Adiponectin HMW ~ SP + BMI (P-value)	Adiponectin HMW ~ SP + BMI (slope)	Adiponectin HMW ~ SP + BMI with elastic net regularization
Cer d16:1/16:0	2.20E-08	7.38E-02	-4.03E-02	
Cer d16:1/18:0	4.53E-43	1.14E-14	-1.72E-01	-6.13E-01
Cer d16:1/20:0	2.90E-25	1.15E-07	-1.17E-01	0
Cer d16:1/22:0	2.05E-25	1.06E-08	-1.26E-01	0
Cer d16:1/23:0	1.20E-08	1.79E-02	-5.27E-02	0
Cer d16:1/24:0	3.47E-11	2.66E-04	-7.90E-02	-6.39E-02
Cer d16:1/24:1	7.21E-20	2.18E-07	-1.11E-01	-3.88E-01
Cer d18:1/16:0	8.96E-04	7.11E-03	-5.79E-02	-4.29E-01
Cer d18:1/18:0	9.20E-38	2.17E-13	-1.60E-01	-4.98E-01
Cer d18:1/20:0	1.56E-29	5.31E-11	-1.43E-01	0
Cer d18:1/22:0	3.06E-24	1.63E-09	-1.29E-01	-3.34E-01
Cer d18:1/23:0	1.54E-09	1.83E-02	-5.22E-02	0
Cer d18:1/24:0	4.93E-12	4.19E-05	-8.80E-02	-2.96E-05
Cer d18:1/24:1	1.27E-13	2.27E-06	-1.00E-01	0
Cer d18:1/25:0	2.27E-01	1.38E-01	3.27E-02	
Cer d18:1/25:1	1.75E-01	9.32E-01	1.69E-03	
Cer d18:1/26:0	3.67E-01	1.47E-01	3.20E-02	
Cer d18:1/26:1	8.93E-02	5.55E-01	-1.37E-02	
Cer d18:2/16:0	4.18E-16	2.21E-10	1.33E-01	1.89E+00
Cer d18:2/18:0	2.41E-16	5.83E-06	-9.68E-02	0
Cer d18:2/22:0	1.30E-08	4.26E-04	-7.54E-02	-2.47E-01
Cer d18:2/23:0	3.84E-02	5.14E-01	-1.53E-02	
Cer d18:2/24:0	3.67E-02	1.04E-01	-3.60E-02	
Cer d18:2/24:1	1.83E-04	4.94E-03	-6.06E-02	-5.27E-02
Cer d18:2/25:0	1.85E-07	8.06E-04	7.13E-02	0
Cer d18:2/26:0	3.18E-08	5.24E-05	8.54E-02	1.19E-01
Hex2Cer d16:1/16:0	1.23E-01	5.26E-01	1.48E-02	
Hex2Cer d18:1/14:0	3.19E-16	1.20E-07	1.12E-01	0
Hex2Cer d18:1/16:0	7.31E-02	4.73E-01	1.68E-02	
Hex2Cer d18:1/24:0	5.28E-01	6.20E-01	-1.12E-02	
Hex2Cer d18:1/24:1	3.05E-06	1.76E-03	6.72E-02	2.65E-01
Hex2Cer d18:2/16:0	1.73E-06	1.56E-05	9.11E-02	-4.62E-01
GM3 d18:1/16:0	5.69E-16	2.46E-08	1.18E-01	9.52E-02
HexCer d16:1/16:0	1.86E-01	1.12E-01	3.53E-02	
HexCer d16:1/22:0	7.12E-01	2.46E-01	2.63E-02	
HexCer d16:1/24:0	6.92E-02	6.39E-01	-1.05E-02	
HexCer d18:1/16:0	4.80E-01	4.72E-01	-1.69E-02	
HexCer d18:1/18:0	9.45E-04	3.53E-01	2.18E-02	

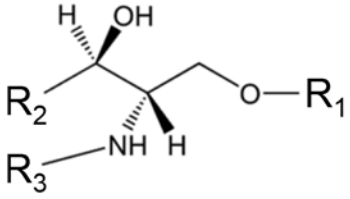
HexCer d18:1/22:0	7.12E-01	8.06E-01	-5.14E-03	
HexCer d18:1/23:0	1.08E-02	3.43E-01	2.23E-02	
HexCer d18:1/24:0	2.41E-01	7.36E-01	-7.22E-03	
HexCer d18:1/24:1	3.45E-03	3.53E-01	2.16E-02	
HexCer d18:1/25:0	5.50E-12	2.35E-04	7.96E-02	1.74E-01
HexCer d18:1/26:0	3.63E-06	3.74E-02	4.62E-02	0
HexCer d18:2/16:0	2.98E-05	5.06E-05	8.56E-02	0
HexCer d18:2/22:0	4.03E-09	4.26E-04	7.52E-02	0
HexCer d18:2/23:0	9.79E-19	8.55E-08	1.14E-01	0
HexCer d18:2/24:0	2.82E-04	6.05E-02	4.13E-02	
HexCer d18:2/24:1	5.58E-19	4.80E-08	1.17E-01	0
SM d16:1/16:0	1.80E-01	3.32E-06	9.96E-02	4.49E-01
SM d16:1/18:0	1.92E-22	8.52E-05	-8.88E-02	-5.17E-01
SM d16:1/20:0	9.95E-04	7.24E-01	-7.89E-03	
SM d16:1/22:0	2.52E-03	7.01E-01	-8.73E-03	
SM d16:1/24:0	8.35E-01	6.28E-02	4.09E-02	
SM d16:1/24:1	6.97E-01	4.89E-02	4.34E-02	0
SM d18:1/14:0	2.07E-33	1.93E-23	2.04E-01	8.69E-01
SM d18:1/16:0	1.82E-18	5.41E-10	1.30E-01	4.79E-01
SM d18:1/18:0	4.13E-04	1.80E-01	-2.99E-02	
SM d18:1/20:0	5.57E-03	5.19E-02	-4.26E-02	
SM d18:1/22:0	2.44E-08	9.32E-03	-5.66E-02	-1.17E+00
SM d18:1/23:0	1.45E-02	4.29E-01	1.87E-02	
SM d18:1/24:0	1.09E-02	5.67E-01	-1.32E-02	
SM d18:1/24:1	2.31E-02	6.28E-02	4.06E-02	
SM d18:2/14:0	1.24E-22	9.67E-29	2.26E-01	9.86E-01
SM d18:2/16:0	1.31E-22	3.55E-27	2.19E-01	1.66E+00
SM d18:2/18:0	9.63E-01	3.00E-02	4.78E-02	0
SM d18:2/20:0	6.34E-06	4.77E-04	7.40E-02	0
SM d18:2/22:0	1.33E-06	1.51E-04	8.02E-02	-5.13E-04
SM d18:2/23:0	2.02E-12	8.77E-11	1.35E-01	0
SM d18:2/24:0	1.18E-14	1.55E-09	1.26E-01	0
SM d18:2/24:1	4.85E-25	4.68E-14	1.58E-01	0
SPH d16:1	5.91E-08	5.43E-03	-6.13E-02	0
SPH d18:0	8.97E-02	5.86E-01	-1.25E-02	
SPH d18:1	1.08E-03	1.10E-01	-3.57E-02	
SPH d18:2	2.84E-03	3.57E-01	-2.14E-02	
S1P d16:1	3.26E-12	6.54E-03	-6.09E-02	0
S1P d17:1	3.01E-02	4.38E-02	-4.42E-02	1.55E-03
S1P d18:0	9.55E-03	8.28E-03	-5.68E-02	0
S1P d18:1	1.10E-07	6.87E-08	-1.13E-01	-8.67E-02
S1P d18:2	1.28E-05	2.24E-03	-6.58E-02	-1.17E+00

Supplemental Figure 1. Structure and nomenclature for human plasma SPs quantified in this study. (A) Generic SP structure demonstrating the core components and the variants described in this study. (B) An example of a specific SP with individual structural components indicated.

A

R_2: Sphingoid backbone
- 16-18 carbons
- 0-3 hydroxy groups
- 0-2 double bonds

R_2: N-linked fatty acid
- 18-26 carbons
- 0-1 double bonds



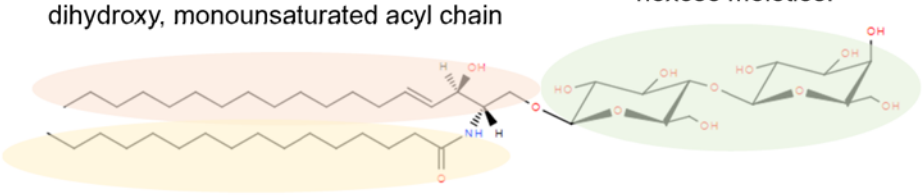
R_1: Head group
- Hydrogen = SPH or Cer
- Phosphocholine = SM
- Hexose(s) = HexCer or Hex2Cer
- Phosphate = S1P

Generic SP structure

B

Sphingoid Base
"d18:1" indicates an 18-carbon, dihydroxy, monounsaturated acyl chain

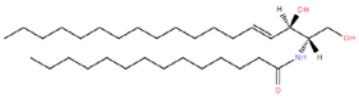
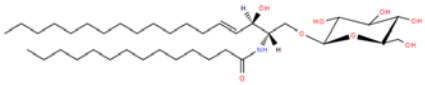
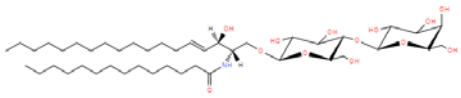
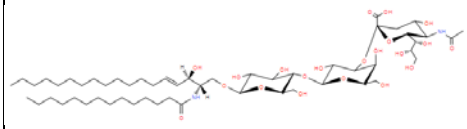
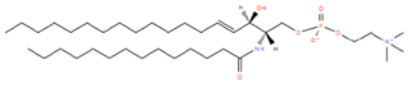
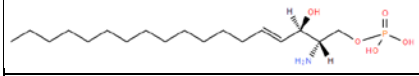
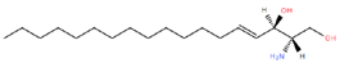
Head group
"Hex2Cer" indicates two hexose moieties.



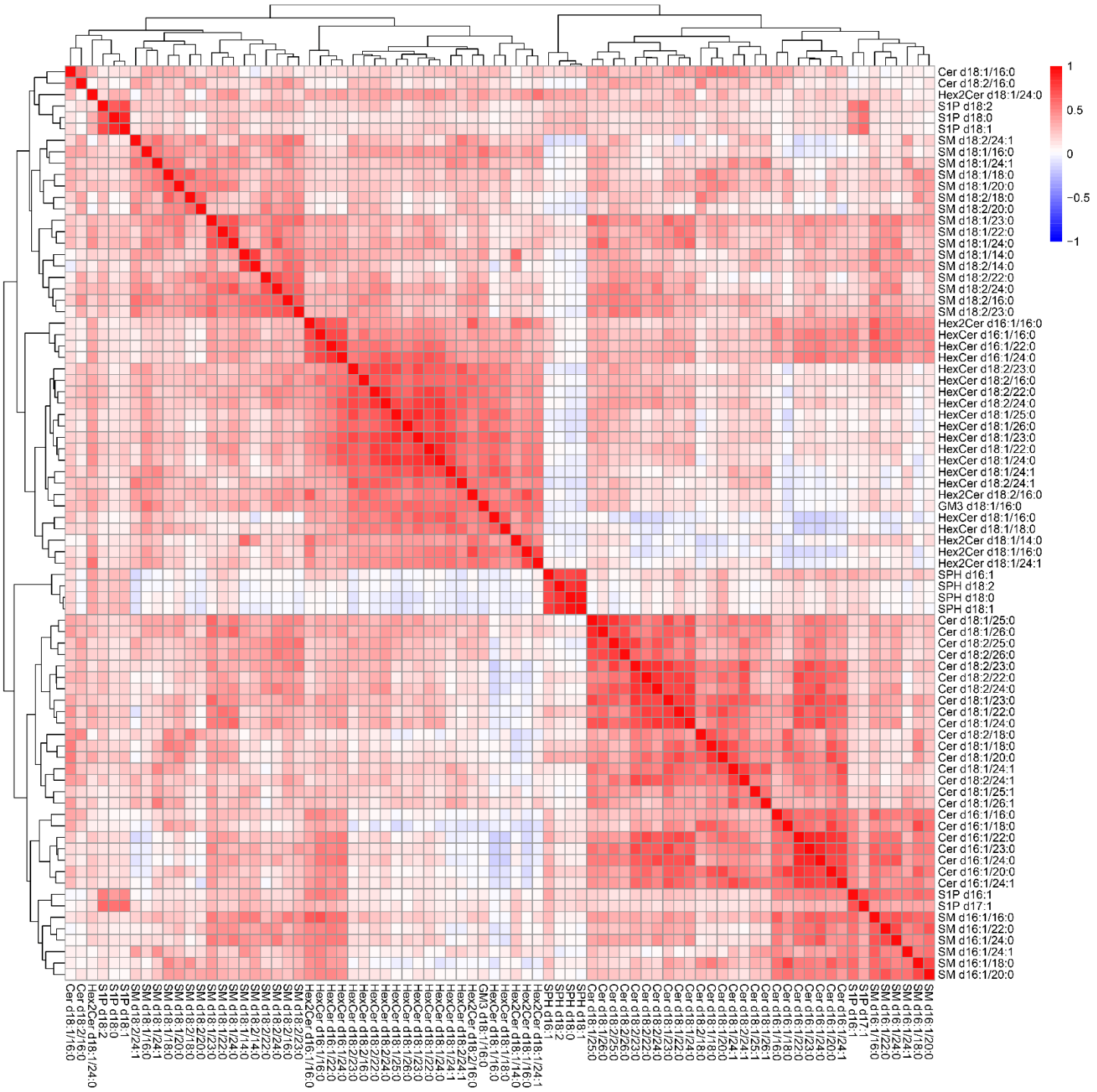
N-linked fatty acid
"16:0" indicates a 16-carbon saturated acyl chain

Lipid example: Hex2Cer d18:1/16:0

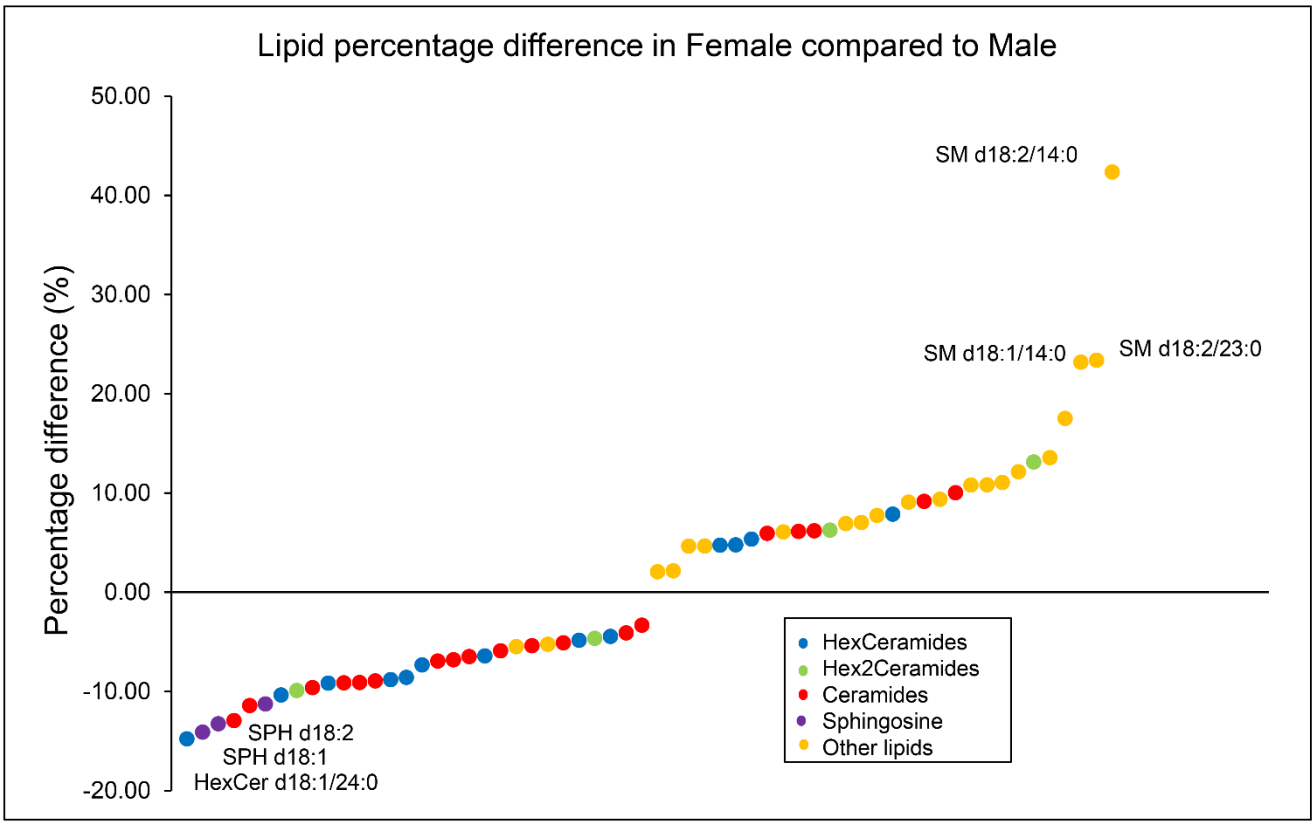
Supplemental Figure 2. List of lipids quantified in this study

Sphingolipid class	Lipid list			
Ceramides (26 peaks quantified) 	Cer d16:1/16:0 Cer d16:1/18:0 Cer d16:1/20:0 Cer d16:1/22:0 Cer d16:1/23:0 Cer d16:1/24:0 Cer d16:1/24:1	Cer d18:1/16:0 Cer d18:1/18:0 Cer d18:1/20:0 Cer d18:1/22:0 Cer d18:1/23:0 Cer d18:1/24:0 Cer d18:1/24:1	Cer d18:1/25:0 Cer d18:1/25:1 Cer d18:1/26:0 Cer d18:1/26:1 Cer d18:2/16:0 Cer d18:2/18:0 Cer d18:2/22:0	Cer d18:2/23:0 Cer d18:2/24:0 Cer d18:2/24:1 Cer d18:2/25:0 Cer d18:2/26:0
Cerebrosides (16 peaks quantified) "monohexosylceramides" 	HexCer d16:1/16:0 HexCer d16:1/22:0 HexCer d16:1/24:0 HexCer d18:1/16:0	HexCer d18:1/18:0 HexCer d18:1/22:0 HexCer d18:1/23:0 HexCer d18:1/24:0	HexCer d18:1/24:1 HexCer d18:1/25:0 HexCer d18:1/26:0 HexCer d18:2/16:0	HexCer d18:2/22:0 HexCer d18:2/23:0 HexCer d18:2/24:0 HexCer d18:2/24:1
Globosides (6 peaks quantified) "dihexosylceramides" 	Hex2Cer d16:1/16:0 Hex2Cer d18:1/14:0	Hex2Cer d18:1/16:0 Hex2Cer d18:1/24:0	Hex2Cer d18:1/24:1	Hex2Cer d18:2/16:0
Gangliosides (1 peaks quantified) 	GM3 d18:1/16:0			
Sphingomyelins (22 peaks quantified) 	SM d16:1/16:0 SM d16:1/18:0 SM d16:1/20:0 SM d16:1/22:0 SM d16:1/24:0 SM d16:1/24:1	SM d18:1/14:0 SM d18:1/16:0 SM d18:1/18:0 SM d18:1/20:0 SM d18:1/22:0 SM d18:1/23:0	SM d18:1/24:0 SM d18:1/24:1 SM d18:2/14:0 SM d18:2/16:0 SM d18:2/18:0 SM d18:2/20:0	SM d18:2/22:0 SM d18:2/23:0 SM d18:2/24:0 SM d18:2/24:1
Sphingosine 1-phosphates (5 peaks quantified) 	S1P d16:1 S1P d17:1	S1P d18:0	S1P d18:1	S1P d18:2
Sphingosines (4 peaks quantified) 	SPH d16:1	SPH d18:1	SPH d18:2	SPH d18:0

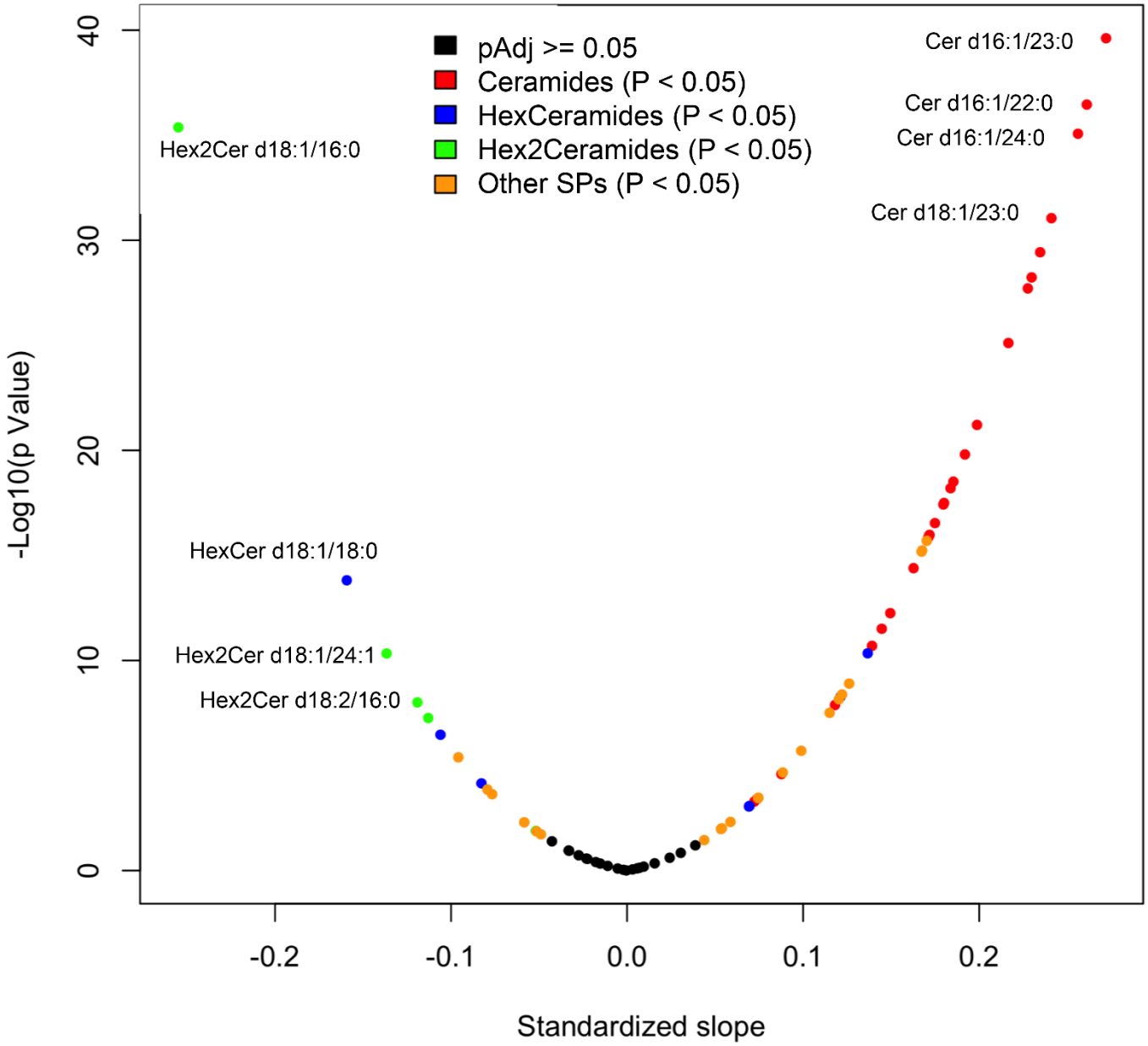
Supplemental Figure 3. Pearson correlation coefficients among plasma SP concentrations for all study subjects



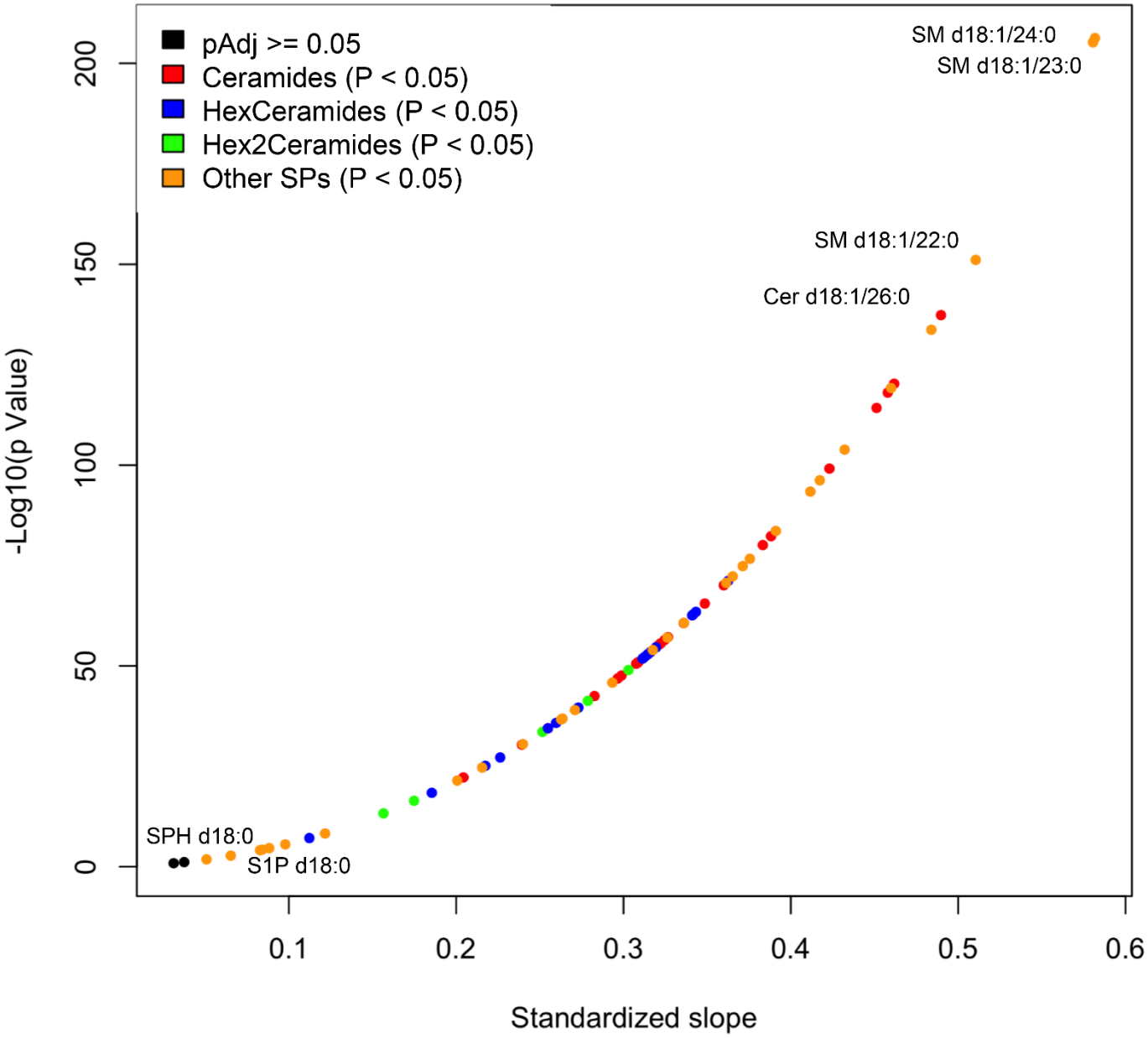
Supplemental Figure 4. Significant differences in lipid composition between genders. Positive values indicate SPs that are more abundant in female subjects.



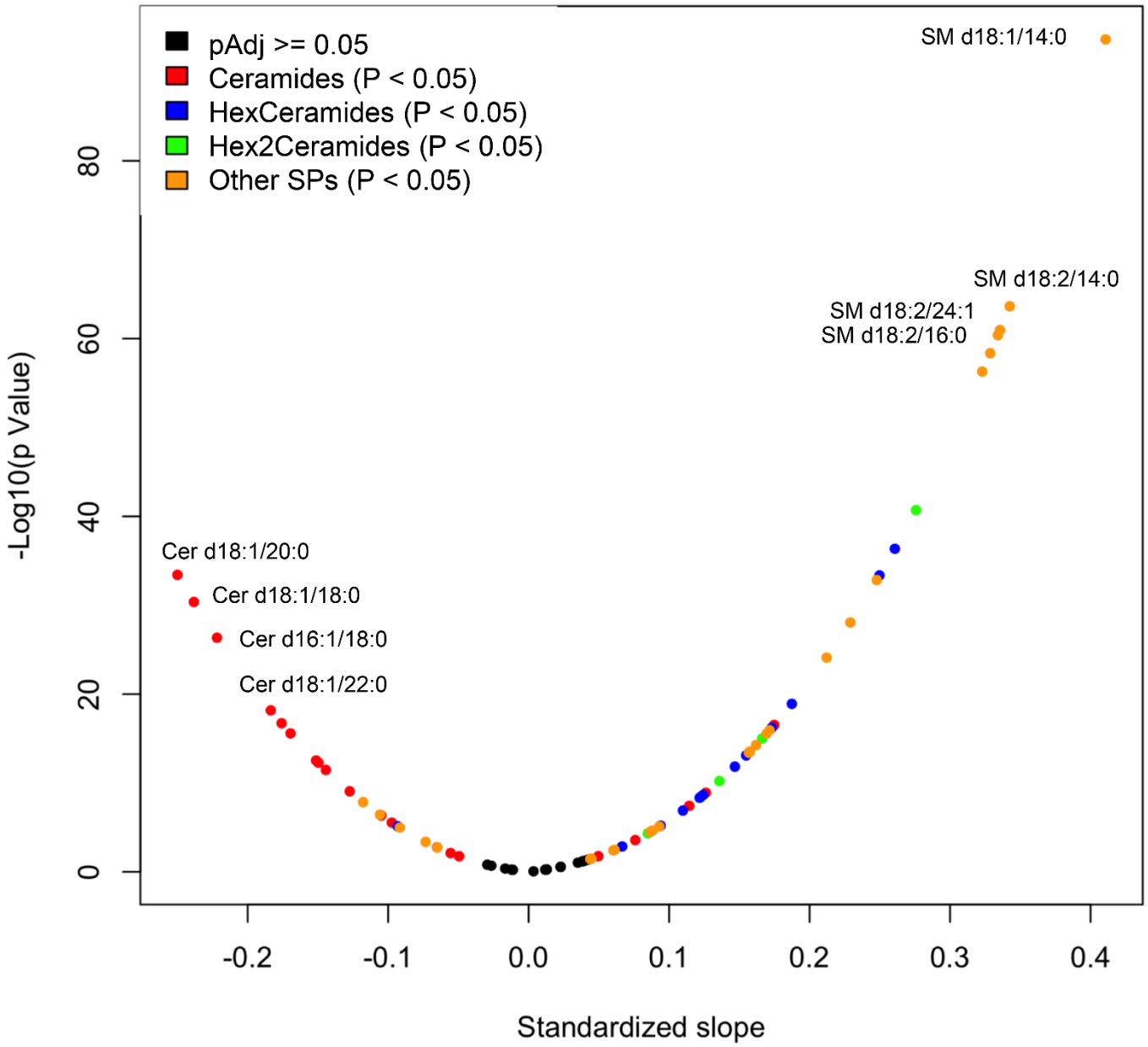
Supplemental Figure 5. Volcano plot of the effects of age on lipid concentration representing the normalized slope of the lipid:age relationship versus the significance of this relationship. Points to the right represent positive correlations between age and the indicated lipid. Points are color-coded by lipid class, except that those without a significant relationship (P > 0.05) are indicated in black.



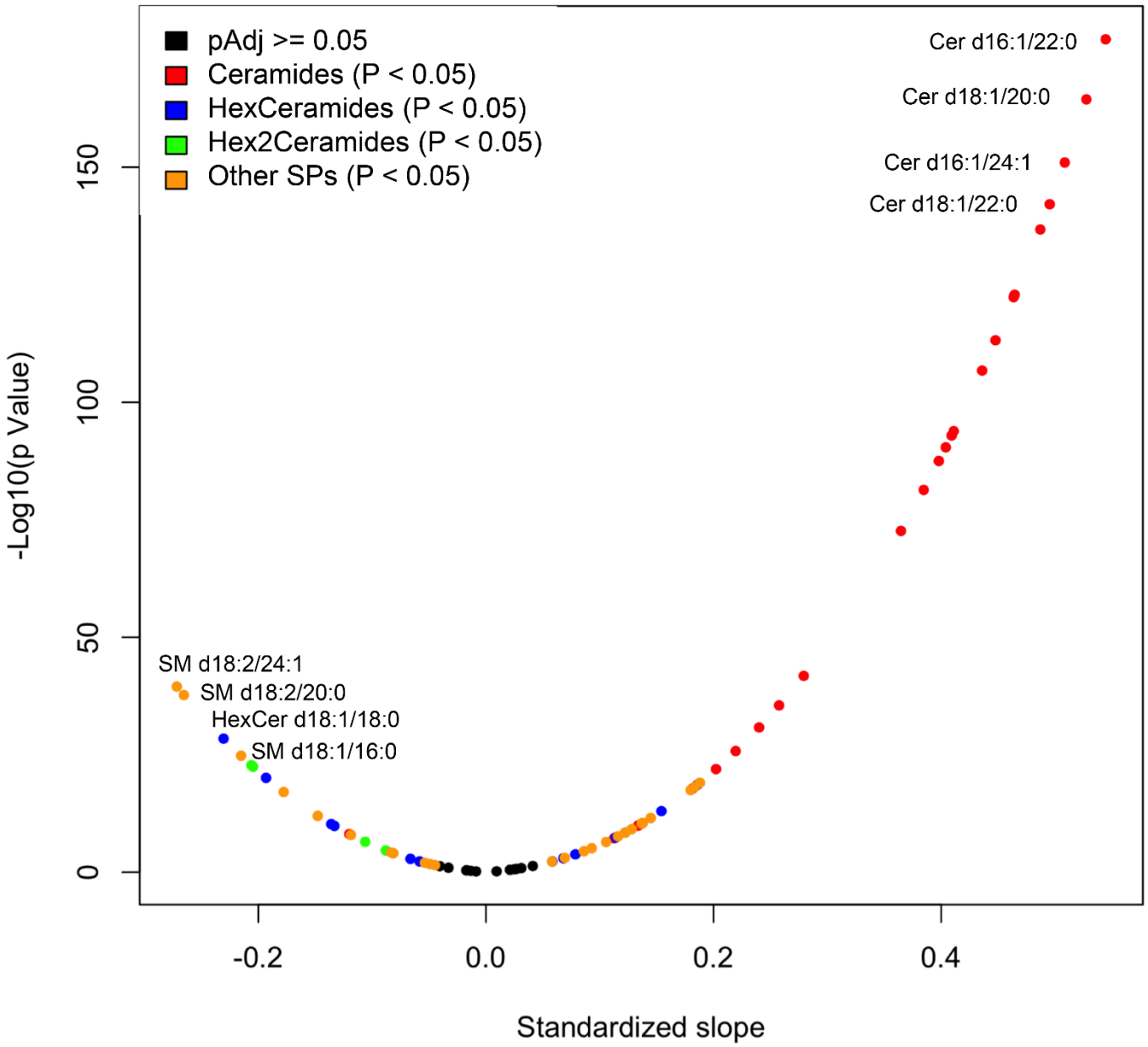
Supplemental Figure 6. Volcano plot of the effects of LDL on lipid concentration representing the normalized slope of the lipid:LDL relationship versus the significance of this relationship. Points to the right represent positive correlations between LDL and the indicated lipid. Points are color-coded by lipid class, except that those without a significant relationship (P > 0.05) are indicated in black.



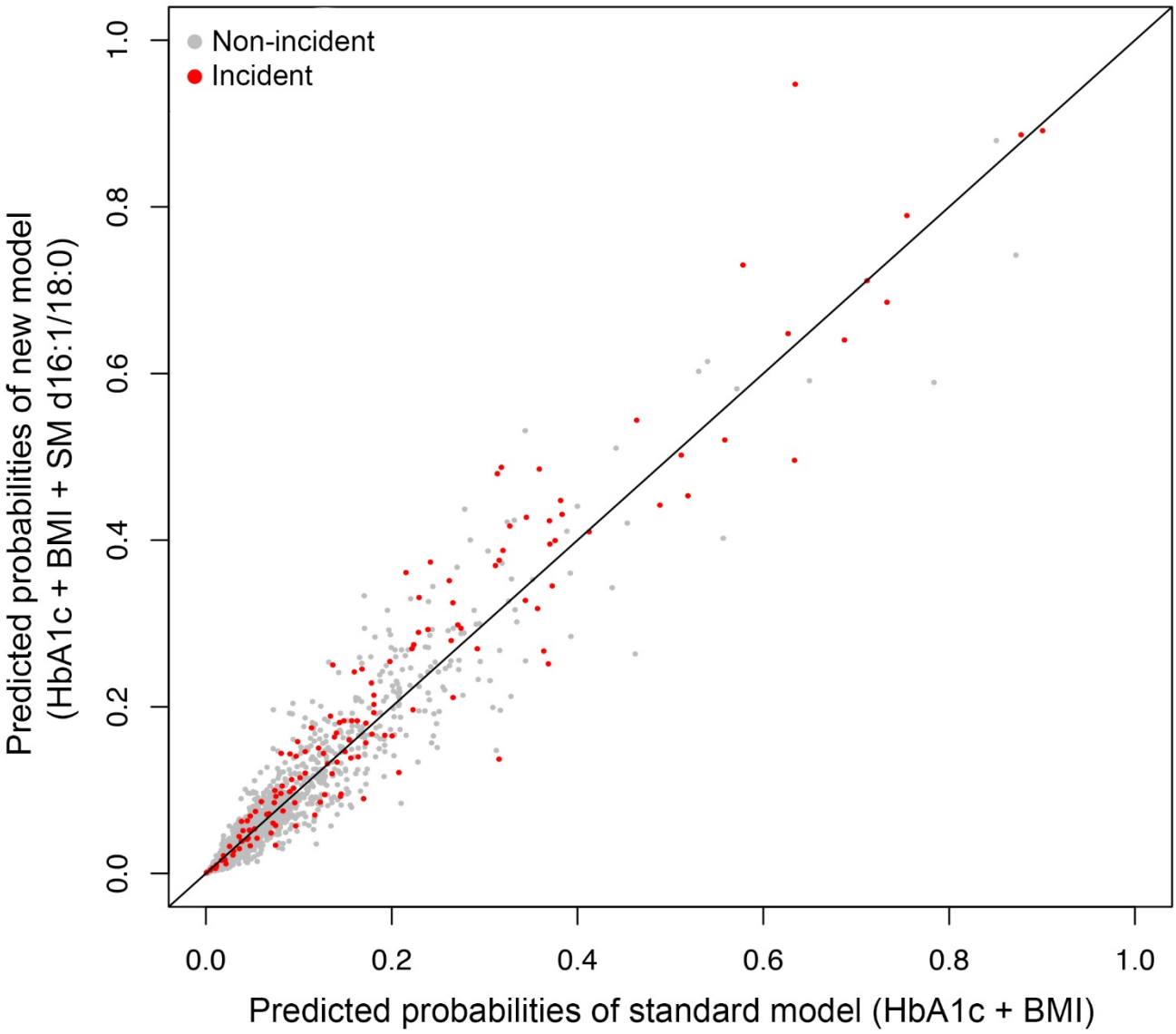
Supplemental Figure 7. Volcano plot of the effects of HDL on lipid concentration representing the normalized slope of the lipid:HDL relationship versus the significance of this relationship. Points to the right represent positive correlations between HDL and the indicated lipid. Points are color-coded by lipid class, except that those without a significant relationship (P > 0.05) are indicated in black.



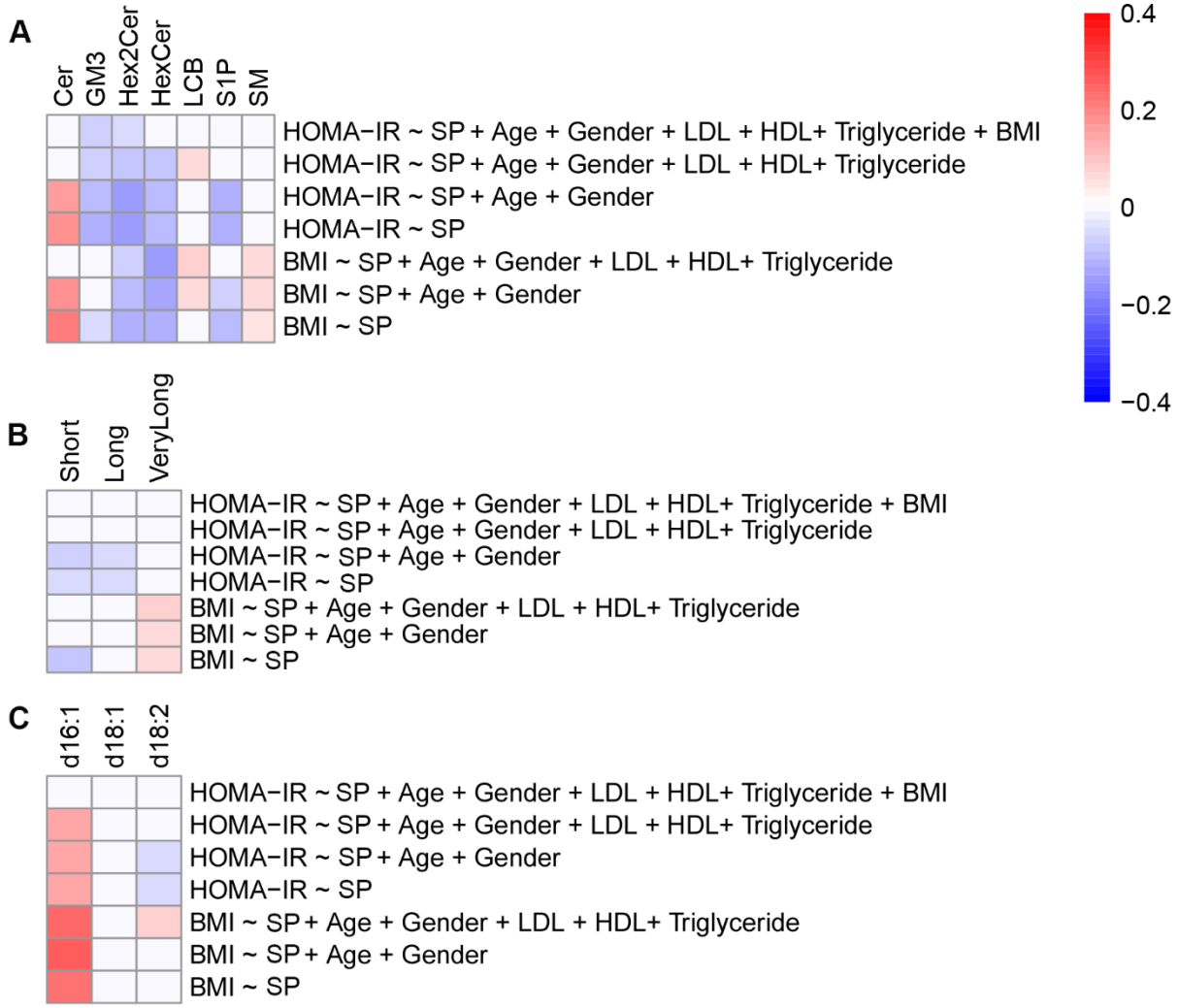
Supplemental Figure 8. Volcano plot of the effects of triglyceride on lipid concentration representing the normalized slope of the lipid:triglyceride relationship versus the significance of this relationship. Points to the right represent positive correlations between trigyceride and the indicated lipid. Points are color-coded by lipid class, except that those without a significant relationship (P > 0.05) are indicated in black.



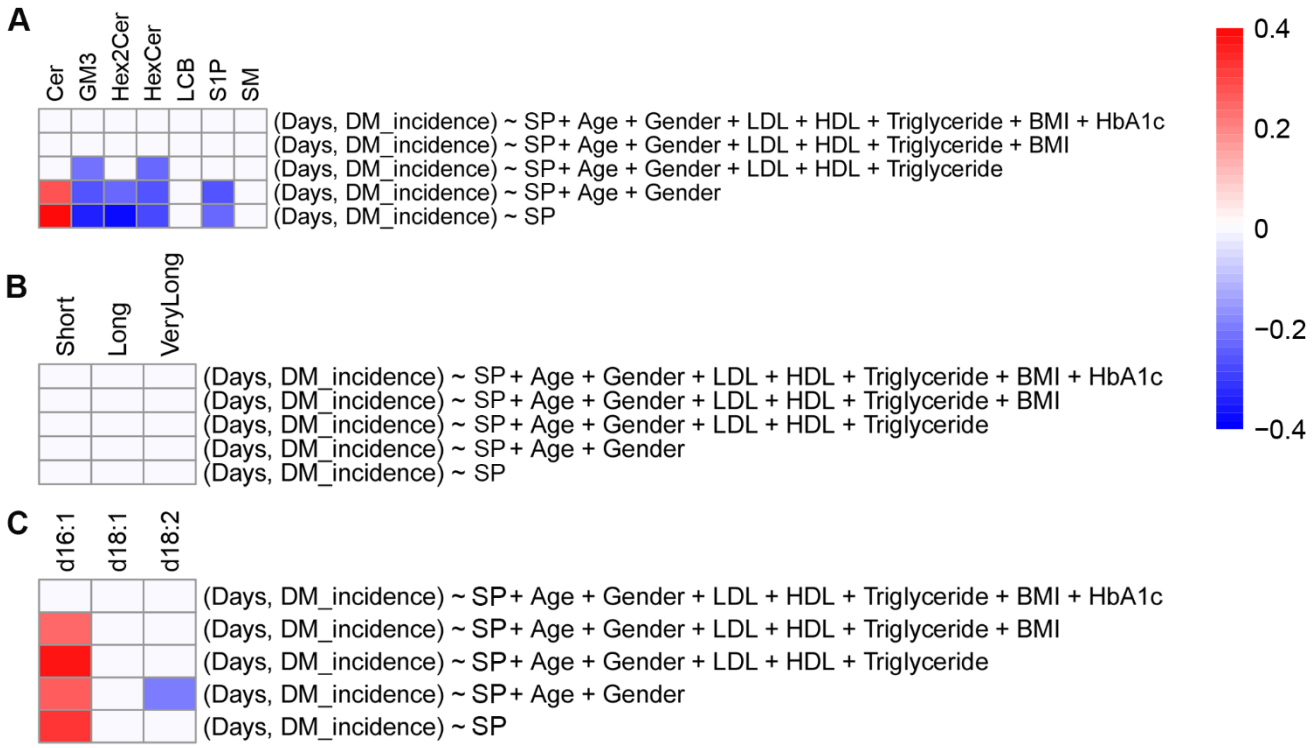
Supplemental Figure 9. Comparison of event probabilities predicted by two models in NRI analysis. Datapoints in gray represent individuals that did not develop diabetes. Datapoints in red represent individuals that developed diabetes. When the new model improves upon the old model, a greater number of red points appear above the diagonal while a greater number of gray points appear below the diagonal.



Supplemental Figure 10. Multivariate linear regression analysis between aggregated classes of SPs and BMI & HOMA-IR. Each indicated class of SPs represents an aggregation of the concentrations of all individual species within that class. (A) SPs aggregated into broad classes per Supplemental Figure 1. (B) SPs aggregated into subclasses based on N-acyl chain length: Short = C14, Long = C16-C18, Very long = C20-C26. (C) SPs aggregated into sphingoid backbone subtype. Models with increasing covariates are depicted from bottom to top (increasing stringency). The shading intensity is proportional to the slope of the regression line. Relationships that are not significant (P > 0.05) are indicated with a white box.



Supplemental Figure 11. Cox regression analysis between aggregated classes of SPs and subsequent diagnosis of T2DM. Each indicated class of SPs represents an aggregation of the concentrations of all individual species within that class. (A) SPs aggregated into broad classes per Supplemental Figure 1. (B) SPs aggregated into subclasses based on N-acyl chain length: Short = C14, Long = C16-C18, Very long = C20-C26. (C) SPs aggregated into sphingoid backbone subtype. Models with increasing covariates are depicted from bottom to top (increasing stringency). The shading intensity is proportional to the slope of the regression line. Relationships that are not significant (P > 0.05) are indicated with a white box.



Supplemental Figure 12. Comparison of the absolute concentrations of plasma sphingolipids between the current study (Chew, et al) and a recent comparable study (Huynh, et al, 2019). Each datapoint represents the mean plasma concentration of a particular SP (or pooled SP peaks) reported by Huynh, et al, versus the mean concentration of the same SPs as determined in the current study.