

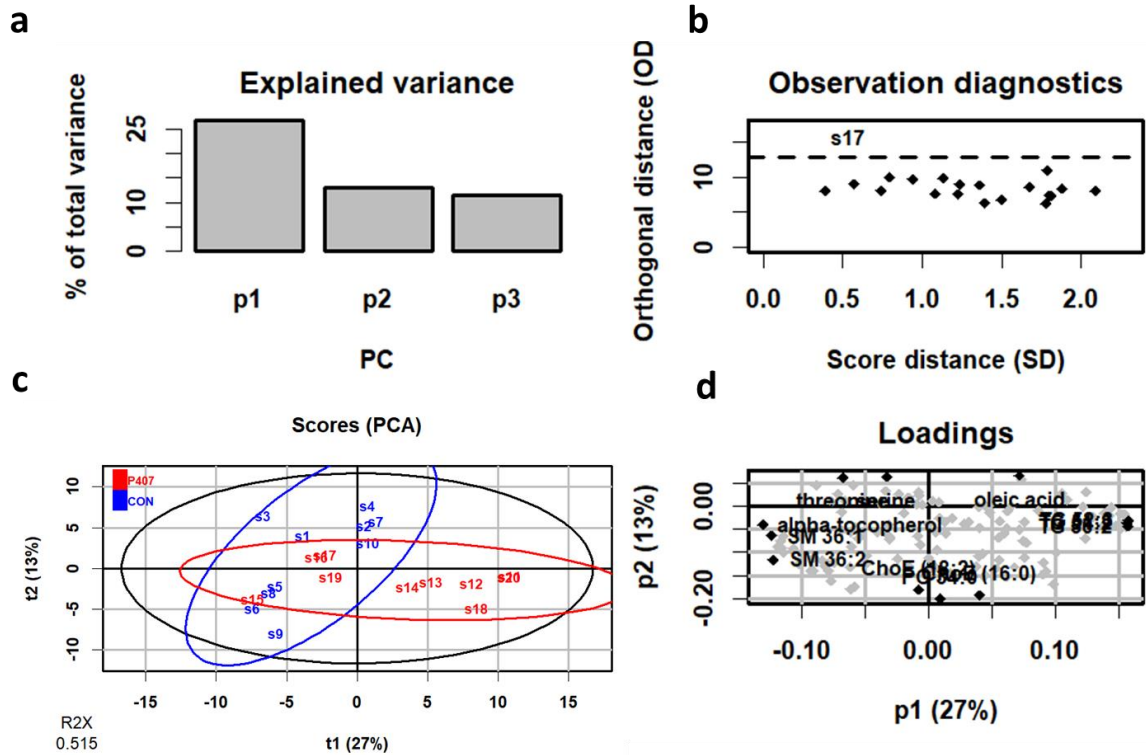
Supplementary Table 1. Summary of univariate/multivariate plasma analysis of the preclinical model in Wistar male rats. The 126 metabolites are represented by the mean \pm SEM ($n = 10$, group). Summary of univariate analysis includes p -value, q -value (pFDR) and FC (P407/CON). Summary of multivariate analysis is presented by VIP values of OPLS-DA. Metabolites are listed according to VIP values. * Denotes $p < 0.1$ (trend), ** $p < 0.05$ (significantly different) and *** $p < 0.01$ (highly significantly different). Groups: CON, control HTG; P407, Poloxamer 407 induced HTG. Groups: CON, control HTG; P407, Poloxamer 407 induced HTG. Abbreviations: DG, diacylglycerol; PC, phosphatidylcholine; ChoE, cholesteryl ester; LPC, lysophospholipid; TG, triglyceride; SM, sphingomyelin.

Metabolite	CON	P407	p -value	q -value	FC	VIP
PC 38:4	14.02 \pm 0.61	20.4 \pm 0.88	<0.01***	<0.01***	1.46	2.21
DG 36:4	1.53 \pm 0.05	2.02 \pm 0.03	<0.01***	<0.01***	1.33	2.03
DG 34:3	0.2 \pm 0.01	0.31 \pm 0.02	<0.01***	<0.01***	1.50	1.86
LPC 18:0	50.4 \pm 1.83	58.86 \pm 1.39	<0.01***	0.03**	1.17	1.85
PC 36:4	13.76 \pm 0.61	17.73 \pm 0.7	<0.01***	0.01**	1.29	1.83
ChoE (17:0)	0.13 \pm 0	0.16 \pm 0.01	<0.01***	0.01**	1.28	1.75
ChoE (18:0)	0.12 \pm 0.01	0.18 \pm 0.01	<0.01***	0.03**	1.51	1.72
DG 34:2	0.85 \pm 0.04	1.05 \pm 0.05	<0.01***	0.04**	1.24	1.70
PC 36:2	11.88 \pm 0.63	14.81 \pm 0.67	<0.01***	0.05*	1.25	1.70
TG 54:6	15.66 \pm 1.84	32.62 \pm 4.94	<0.01***	0.07*	2.08	1.65
ChoE (16:0)	2.02 \pm 0.09	2.39 \pm 0.07	<0.01***	0.04**	1.18	1.61
ChoE (18:1)	2.52 \pm 0.11	3.54 \pm 0.25	<0.01***	0.04**	1.41	1.59
ChoE (20:4)	65.98 \pm 1.98	74.78 \pm 2.06	<0.01***	0.06*	1.13	1.55
PC 34:0	0.29 \pm 0.01	0.32 \pm 0.01	0.03**	0.13	1.13	1.55
TG 54:4	10.76 \pm 1.6	25.48 \pm 5.24	0.02**	0.13	2.37	1.43
TG 48:0	1.26 \pm 0.11	2.19 \pm 0.31	0.02**	0.13	1.73	1.43
PC 40:4	0.14 \pm 0.01	0.18 \pm 0.01	0.04**	0.14	1.26	1.40
TG 54:2	0.69 \pm 0.07	1.36 \pm 0.24	0.02**	0.13	1.97	1.39
TG 52:1	0.65 \pm 0.06	1.22 \pm 0.21	0.02**	0.13	1.88	1.38
TG 54:7	6.06 \pm 0.92	12.67 \pm 2.51	0.03**	0.13	2.09	1.37
TG 52:3	40.05 \pm 6.14	81.4 \pm 15.33	0.03**	0.13	2.03	1.36
TG 50:2	10.73 \pm 1.62	22 \pm 4.08	0.03**	0.13	2.05	1.36
TG 54:3	3.84 \pm 0.45	7.75 \pm 1.47	0.03**	0.13	2.02	1.35
TG 50:1	3.12 \pm 0.45	6.46 \pm 1.23	0.03**	0.13	2.07	1.35
TG 50:0	0.42 \pm 0.03	0.74 \pm 0.12	0.03**	0.13	1.77	1.34
PC 35:2	0.35 \pm 0.02	0.42 \pm 0.02	0.03**	0.13	1.19	1.31
TG 52:2	10.05 \pm 1.59	20.73 \pm 4.05	0.03**	0.13	2.06	1.31
TG 52:5	8.05 \pm 1.17	16.74 \pm 3.57	0.04**	0.15	2.08	1.30
TG 51:2	0.76 \pm 0.07	1.34 \pm 0.24	0.04**	0.15	1.77	1.29
ChoE (22:4)	3.88 \pm 0.24	4.49 \pm 0.17	0.06*	0.17	1.16	1.27
TG 50:4	1.7 \pm 0.27	3.21 \pm 0.61	0.04**	0.15	1.89	1.26

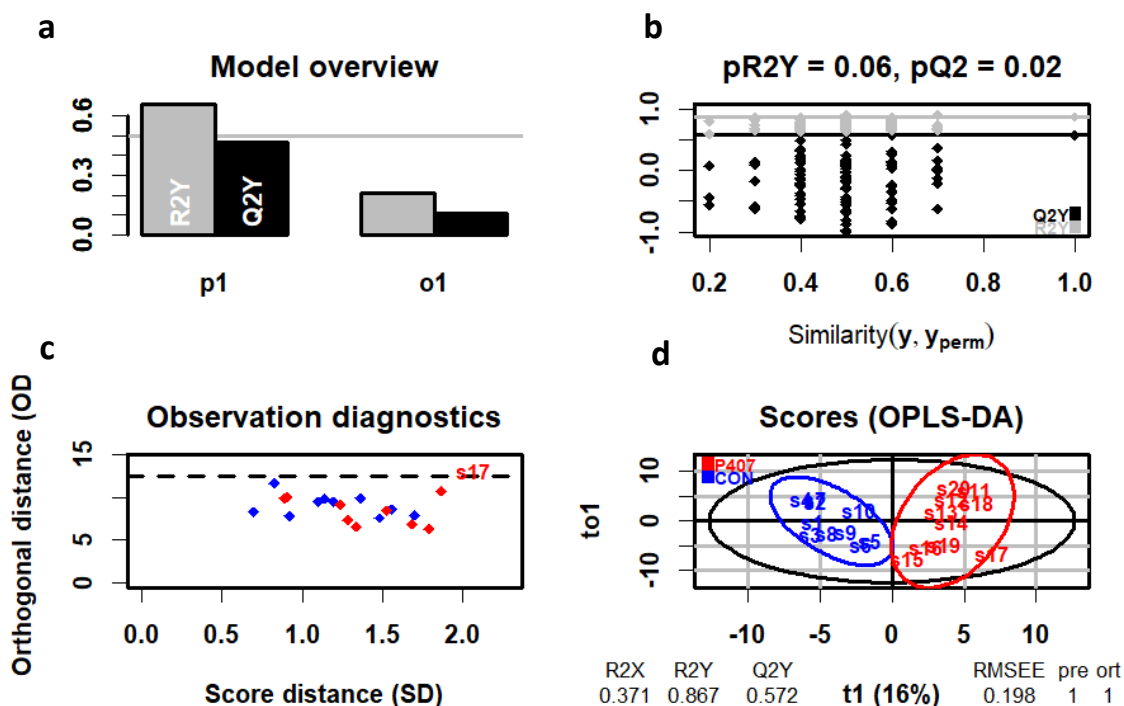
Lactic acid	7.79 ± 0.31	6.92 ± 0.39	0.09*	0.25	0.89	1.26
TG 52:6	1.25 ± 0.2	2.32 ± 0.45	0.05*	0.16	1.87	1.26
Lysine	0.66 ± 0.04	0.76 ± 0.05	0.14	0.29	1.15	1.23
Hydroxyproline	0.87 ± 0.08	1.1 ± 0.1	0.09*	0.24	1.27	1.22
Malic acid	0.38 ± 0.05	0.28 ± 0.02	0.07*	0.19	0.74	1.22
Alanine	0.31 ± 0.04	0.39 ± 0.05	0.22	0.37	1.25	1.19
TG 46:0	0.84 ± 0.05	1.16 ± 0.07	<0.01***	0.04**	1.37	1.17
TG 48:2	1.4 ± 0.15	2.18 ± 0.33	0.05*	0.16	1.56	1.16
TG 50:3	5.61 ± 0.98	10 ± 1.87	0.06*	0.17	1.78	1.16
Alpha-ketoglutarate	1.12 ± 0.05	1 ± 0.06	0.15	0.31	0.90	1.11
ChoE (22:5)	0.58 ± 0.07	0.71 ± 0.03	0.11	0.27	1.23	1.11
Glucose	0.71 ± 0.01	0.75 ± 0.03	0.26	0.41	1.06	1.07
PC 38:3	0.78 ± 0.09	0.97 ± 0.08	0.13	0.29	1.24	1.04
TG 48:3	0.48 ± 0.05	0.68 ± 0.09	0.08*	0.22	1.42	1.03
LPC 18:2	33.17 ± 1.34	29.66 ± 0.86	0.04**	0.15	0.89	1.03
Glycine	2.02 ± 0.07	2.16 ± 0.09	0.22	0.37	1.07	1.00
2-hydroxyglutaric	0.54 ± 0.05	0.44 ± 0.03	0.11	0.27	0.82	0.98
Alpha-tocopherol	0.66 ± 0.05	0.55 ± 0.05	0.14	0.29	0.84	0.98
Beta-alanine	0.05 ± 0	0.06 ± 0.01	0.11	0.27	1.24	0.96
Glycerol	3.68 ± 0.22	4.2 ± 0.32	0.20	0.35	1.14	0.94
Methionine	0.1 ± 0.01	0.12 ± 0.01	0.18	0.34	1.15	0.94
Isoleucine	0.12 ± 0.01	0.12 ± 0.01	0.94	0.97	1.01	0.93
Leucine	0.05 ± 0	0.04 ± 0	0.69	0.77	0.96	0.92
TG 46:1	0.68 ± 0.07	0.84 ± 0.07	0.14	0.29	1.23	0.91
LPC 18:0 e	0.1 ± 0	0.09 ± 0	0.14	0.30	0.92	0.91
LPC 20:0	0.29 ± 0.02	0.33 ± 0.02	0.15	0.31	1.12	0.91
SM 36:1	1.09 ± 0.05	0.93 ± 0.05	0.04**	0.15	0.85	0.90
Tryptophan	1.24 ± 0.06	1.29 ± 0.05	0.59	0.71	1.04	0.90
TG 48:1	1.63 ± 0.16	2.18 ± 0.3	0.12	0.28	1.34	0.89
LPC 16:0 e	0.51 ± 0.02	0.47 ± 0.01	0.06*	0.17	0.91	0.88
PC 30:0	0.04 ± 0	0.04 ± 0	0.31	0.45	1.07	0.87
Glyceric acid	1.15 ± 0.1	0.96 ± 0.08	0.16	0.32	0.84	0.87
LPC 16:1 e	0.14 ± 0.01	0.13 ± 0	0.11	0.27	0.89	0.86
PC 32:0	0.59 ± 0.02	0.62 ± 0.01	0.25	0.41	1.06	0.86
PC 31:0	0.03 ± 0	0.04 ± 0	0.01**	0.06*	1.19	0.86
Valine	0.48 ± 0.02	0.46 ± 0.03	0.65	0.75	0.97	0.85
3-hydroxybutiric acid	1.61 ± 0.08	1.44 ± 0.08	0.17	0.32	0.90	0.84
Tyrosine	0.59 ± 0.04	0.61 ± 0.03	0.68	0.76	1.03	0.84

Fructose	0.4 ± 0.02	0.34 ± 0.01	0.02**	0.13	0.86	0.83
ChoE (18:2)	16.99 ± 0.99	18.25 ± 0.4	0.26	0.41	1.07	0.82
Asparagine	0.15 ± 0.02	0.18 ± 0.01	0.27	0.41	1.18	0.81
TG 46:2	0.37 ± 0.03	0.5 ± 0.04	0.02**	0.13	1.34	0.81
LPC 18:1	13.89 ± 0.48	13.02 ± 0.42	0.19	0.35	0.94	0.80
DG 34:1	1.02 ± 0.04	1.11 ± 0.06	0.22	0.37	1.09	0.80
PC 33:0	0.03 ± 0	0.03 ± 0	1.00	1.00	1.00	0.66
PC 40:5	0.16 ± 0.02	0.19 ± 0.02	0.41	0.57	1.15	0.66
SM 39:1	0.14 ± 0.01	0.11 ± 0.01	0.08*	0.23	0.78	0.66
DG 36:2	1.26 ± 0.09	1.31 ± 0.05	0.69	0.77	1.03	0.65
Ornithine	2.4 ± 0.22	2.55 ± 0.21	0.64	0.75	1.06	0.65
Glycolic acid	2.99 ± 0.13	2.68 ± 0.16	0.14	0.30	0.90	0.64
Pyruvic acid	15.87 ± 1.01	14.88 ± 1.19	0.53	0.67	0.94	0.62
SM 42:3	4.71 ± 0.28	4.15 ± 0.19	0.12	0.27	0.88	0.60
Threonic acid	2.08 ± 0.13	2.07 ± 0.08	0.93	0.97	0.99	0.57
ChoE (20:2)	0.79 ± 0.05	0.93 ± 0.06	0.08*	0.23	1.18	0.57
Glutamic acid	0.1 ± 0.01	0.11 ± 0	0.30	0.44	1.09	0.56
Histidine	0.12 ± 0.01	0.14 ± 0.03	0.47	0.61	1.18	0.56
Oleic acid	1.6 ± 0.12	1.6 ± 0.08	0.97	0.98	1.00	0.55
LPC 15:0	0.91 ± 0.04	0.87 ± 0.02	0.43	0.58	0.96	0.55
ChoE (18:3)	1.32 ± 0.08	1.4 ± 0.06	0.41	0.57	1.06	0.52
Succinic acid	0.64 ± 0.03	0.62 ± 0.03	0.60	0.71	0.97	0.51
Serine	0.26 ± 0.01	0.29 ± 0.03	0.29	0.44	1.13	0.49
SM 35:1	0.16 ± 0.01	0.15 ± 0.01	0.21	0.36	0.90	0.45
PC 33:1	0.06 ± 0	0.07 ± 0	0.20	0.36	1.13	0.45
SM 36:2	0.4 ± 0.02	0.38 ± 0.02	0.49	0.63	0.96	0.44
Proline	0.24 ± 0.01	0.27 ± 0.01	0.19	0.35	1.09	0.40
Urea	2.18 ± 0.1	2.11 ± 0.1	0.60	0.71	0.96	0.40
SM 38:1	0.47 ± 0.02	0.44 ± 0.02	0.29	0.44	0.93	0.40
SM 32:1	0.22 ± 0.01	0.2 ± 0.01	0.30	0.44	0.94	0.38
PC 32:2	0.19 ± 0.01	0.2 ± 0.01	0.46	0.61	1.06	0.37
PC 34:1	3.59 ± 0.21	3.78 ± 0.18	0.51	0.65	1.05	0.36
ChoE (16:1)	0.56 ± 0.05	0.52 ± 0.05	0.56	0.69	0.93	0.36
SM 42:2	9.81 ± 0.63	8.8 ± 0.46	0.21	0.37	0.90	0.35
Ribose	3.69 ± 0.23	4.03 ± 0.56	0.59	0.71	1.09	0.35
SM 42:1	13.11 ± 0.53	12.31 ± 0.41	0.25	0.41	0.94	0.34
SM 43:1	0.97 ± 0.04	0.92 ± 0.04	0.32	0.46	0.94	0.33
PC 32:1	0.29 ± 0.03	0.26 ± 0.01	0.36	0.51	0.89	0.29

SM 41:2	0.56 ± 0.03	0.58 ± 0.03	0.65	0.75	1.04	0.27
LPC 16:0	78.98 ± 1.7	79.45 ± 1.23	0.83	0.88	1.01	0.26
SM 33:1	0.31 ± 0.01	0.31 ± 0.01	0.95	0.97	1.00	0.26
SM 41:1	3.54 ± 0.17	3.37 ± 0.13	0.46	0.61	0.95	0.23
Citric acid	3.87 ± 0.11	3.75 ± 0.12	0.48	0.62	0.97	0.20
Cholesterol	0.33 ± 0.01	0.3 ± 0.02	0.19	0.35	0.91	0.20
SM 34:2	1.53 ± 0.08	1.44 ± 0.02	0.30	0.44	0.94	0.19
PC 38:2	0.11 ± 0.01	0.12 ± 0.02	0.63	0.74	1.10	0.19
SM 34:1	15.83 ± 0.76	15.09 ± 0.48	0.42	0.58	0.95	0.17
ChoE (17:1)	0.09 ± 0.01	0.1 ± 0.01	0.67	0.76	1.04	0.16
Threonine	1.18 ± 0.08	1.01 ± 0.05	0.11	0.27	0.86	0.15
SM 40:1	3.3 ± 0.16	3.16 ± 0.13	0.52	0.65	0.96	0.14
Fumaric acid	0.86 ± 0.09	0.84 ± 0.1	0.92	0.97	0.98	0.14
Aconitic acid	0.01 ± 0	0.01 ± 0	1.00	1.00	1.00	0.11
Phenylalanine	0.58 ± 0.04	0.44 ± 0.04	0.03**	0.14	0.77	0.10
Aspartic acid	0.55 ± 0.04	0.57 ± 0.04	0.73	0.80	1.04	0.07
Glutamine	1.19 ± 0.22	1.14 ± 0.2	0.85	0.90	0.95	0.06
SM 40:2	0.66 ± 0.04	0.68 ± 0.03	0.76	0.82	1.02	0.04
ChoE (22:6)	2.03 ± 0.14	1.97 ± 0.12	0.74	0.80	0.97	0.01



Supplementary Figure 1. PCA summary plot for the plasma of the preclinical model in Wistar male rats. (a) Explained variance. The scree plot suggests that 3 components may be sufficient to capture most of the variance. (b) Observation diagnostics. This plot shows the distances within and orthogonal to the projection plane; the names of the samples with a high value for at least one of the distances are given. (c) Score plot (PCA). The total variance explained is 40%: PC1 explains the 27% and the PC2 explains the 13%. (d) The variables with the most extreme values (positive and negative) for each loading are coloured black and labelled. Legend: blue, CON group; red, P407 group.



Supplementary Figure 2. OPLS-DA summary plot for plasma of the preclinical model in Wistar male rats.

(a) Model overview. The plot here suggests that 2 components may be sufficient to capture most of the inertia (b) Significance diagnostics. The R2Y and Q2Y of the model are compared with the corresponding values obtained after random permutation of the y response. (c) Observation diagnostics. Indicates possible outliers. (d) X-score plot (OPLS-DA). The graph shows the number of components, the cumulative explained variance in X (R2X), in Y (R2Y), and the cumulative prediction power (Q2Y), the root mean square error of estimation (RMSEE), the predicted variation in Y (pre), and the orthogonal variance in Y (ort). Legend: Blue represents the CON group and red the P407 group.

Supplementary Table 2. Coefficients of the predictor variables (OLPS-DA model for plasma in Wistar male rats).

Predictor variables (I)	Coefficients (I)	Predictor variables (II)	Coefficients (II)
Alanine	0.0139117028	LPC 16:1 e	-0.0190946569
Proline	0.0057509122	LPC 18:0	0.0319320995
Valine	0.0105542989	LPC 18:0 e	-0.0200474328
Serine	0.0130068319	LPC 18:1	-0.0149469051
Leucine	0.0108759464	LPC 18:2	-0.0225170149
Threonine	-0.0043935920	LPC 20:0	0.0167937361
Isoleucine	0.0112872433	PC 30:0	0.0160511513
Glycine	0.0134374147	PC 31:0	0.0178124534
Beta-alanine	0.0198563491	PC 32:0	0.0137691700
Aspartic acid	0.0044092255	PC 32:1	-0.0043098115
Methionine	0.0147474134	PC 32:2	0.0082117366
Hydroxyproline	0.0189918620	PC 33:0	0.0087741095
Phenylalanine	-0.0055752569	PC 33:1	0.0097059786
Glutamic acid	0.0117628177	PC 34:0	0.0222891315

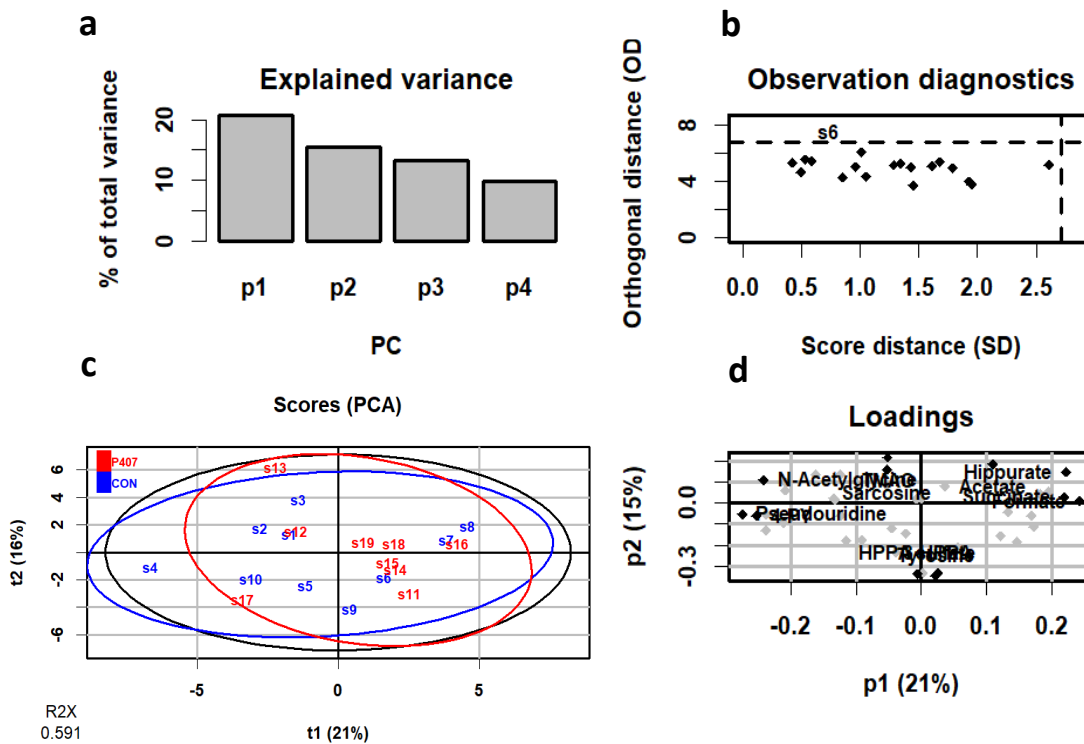
Asparagine	0.0130216778	PC 34:1	0.0076614845
Glutamine	-0.0021464986	PC 35:2	0.0237579685
Ornithine	0.0054485618	PC 36:2	0.0292554316
Histidine	0.0088270784	PC 36:4	0.0345699669
Lysine	0.0198816383	PC 38:2	0.0057213366
Tyrosine	0.0113656621	PC 38:3	0.0171346190
Tryptophan	0.0129384059	PC 38:4	0.0396757665
Pyruvic acid	-0.0072002721	PC 40:4	0.0221817932
Lactic acid	-0.0188417503	PC 40:5	0.0093300734
Glycolic acid	-0.0163933058	SM 32:1	-0.0140149957
3-hydroxybutiric acid	-0.0157332056	SM 33:1	0.0022460412
Urea	-0.0060925404	SM 34:1	-0.0093152394
Glycerol	0.0147598941	SM 34:2	-0.0080030301
Succinic acid	-0.0062096638	SM 35:1	-0.0128520525
Glyceric acid	-0.0161067668	SM 36:1	-0.0221983042
Fumaric acid	-0.0011932335	SM 36:2	-0.0085789191
Malic acid	-0.0208742547	SM 38:1	0.0029028960
Threonic acid	-0.0092229822	SM 39:1	-0.0181507338
Alpha-ketoglutarate	-0.0192362949	SM 40:1	-0.0074965633
2-hydroxyglutaric	-0.0182715323	SM 40:2	0.0032310267
Ribose	-0.0009574493	SM 41:1	-0.0086907206
Aconitic acid	-0.0024919480	SM 41:2	0.0048742838
Citric acid	-0.0081094713	SM 42:1	-0.0131354080
Fructose	-0.0139930938	SM 42:2	-0.0142754758
Glucose	0.0133656925	SM 42:3	-0.0177680716
Oleic acid	0.0086625096	SM 43:1	-0.0111253129
Alpha-tocopherol	-0.0166679209	TG 46:0	0.0220737853
Cholesterol	0.0027644096	TG 46:1	0.0168926176
ChoE (16:0)	0.0304155229	TG 46:2	0.0154115186
ChoE (16:1)	-0.0065143167	TG 48:0	0.0270948726
ChoE (17:0)	0.0338773402	TG 48:1	0.0176241688
ChoE (17:1)	0.0046717433	TG 48:2	0.0221310976
ChoE (18:0)	0.0326773079	TG 48:3	0.0197446743
ChoE (18:1)	0.0322216753	TG 50:0	0.0248579545
ChoE (18:2)	0.0131756227	TG 50:1	0.0251593493
ChoE (18:3)	0.0096585823	TG 50:2	0.0252330213
ChoE (20:2)	0.0060455052	TG 50:3	0.0214235561
ChoE (20:4)	0.0286036539	TG 50:4	0.0229288540
ChoE (22:4)	0.0232762740	TG 51:2	0.0237015174
ChoE (22:5)	0.0181531774	TG 52:1	0.0254514819
ChoE (22:6)	-0.0040345050	TG 52:2	0.0243881888
DG 34:1	0.0139497662	TG 52:3	0.0247693779
DG 34:2	0.0315234375	TG 52:5	0.0233217450
DG 34:3	0.0351110810	TG 52:6	0.0223093304
DG 36:2	0.0048063896	TG 54:2	0.0257023998

DG 36:4	0.0397463320	TG 54:3	0.0250637844
LPC 15:0	-0.0091158438	TG 54:4	0.0260663582
LPC 16:0	0.0025775299	TG 54:6	0.0294310174
LPC 16:0 e	-0.0211248353	TG 54:7	0.0245195758

Supplementary Table 3. Urine univariate analysis of the preclinical model in Wistar male rats. 43 metabolites are shown as mean \pm SEM per group ($n = 10$, group). Summary of the univariate analysis includes p -value, q -value (pFDR) and FC (P407/CON). Metabolites are listed according to q -value. * Denotes $p < 0.1$ (trend), ** $p < 0.05$ (significantly different) and *** $p < 0.01$ (highly significantly different). Groups: CON, control HTG; P407, Poloxamer 407 induced HTG. Abbreviations: TMAO, trimethylamine N-oxide; PAG, phenylacetyl glycine; DG, diacylglycerol; PC, phosphatidylcholine; ChoE, cholesteryl ester; LPC, lysophospholipid; TG, triglyceride; sphingomyelin, SM.

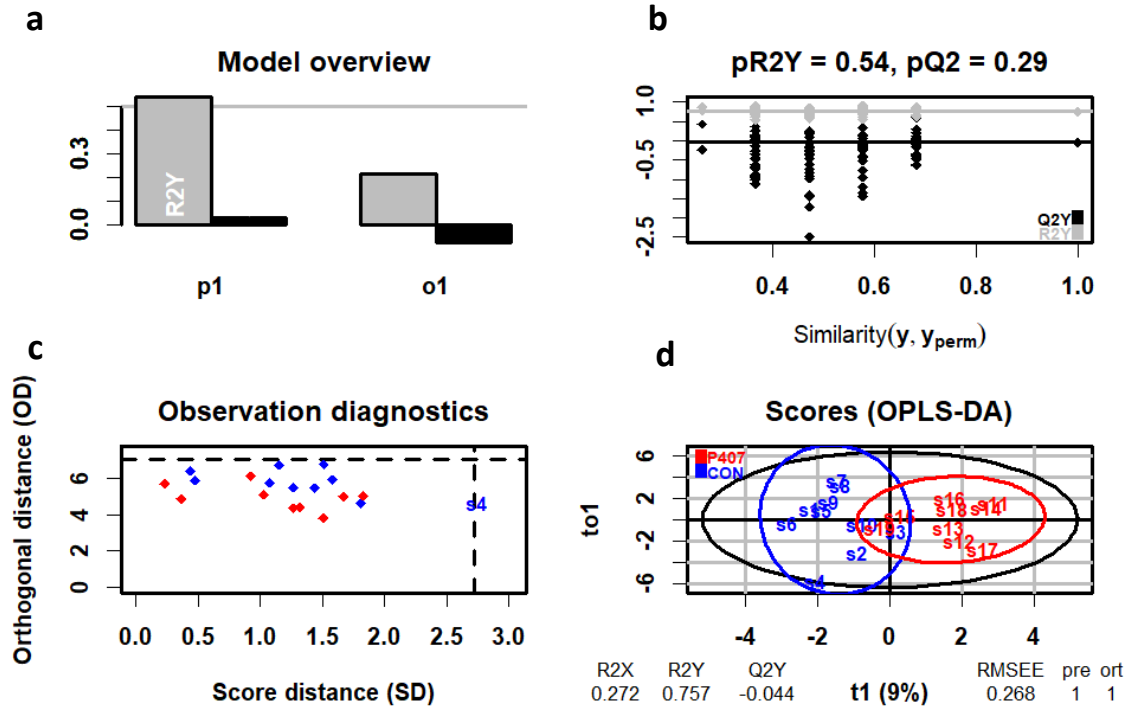
Metabolite	CON	P407	p -value	q -value	FC
TMAO	2.31 \pm 0.26	1.28 \pm 0.09	<0.01***	0.15	0.55
PAG	39.07 \pm 3.42	63.78 \pm 7.31	0.01**	0.23	1.63
2-deoxycytidine	1.89 \pm 0.19	1.36 \pm 0.11	0.03**	0.35	0.72
Leucine	11.97 \pm 1.03	9.23 \pm 0.38	0.03**	0.35	0.77
3-hydroxyisovalerate	3.38 \pm 0.15	2.90 \pm 0.16	0.06*	0.55	0.86
Betaine	25.78 \pm 2.25	21.36 \pm 0.62	0.09*	0.62	0.83
HPPA sulfate	6.98 \pm 1.77	14.91 \pm 3.68	0.10*	0.62	2.14
o-Coumaric acid	3.48 \pm 0.58	4.99 \pm 0.75	0.13	0.67	1.44
Creatinine	126.44 \pm 6.22	114.02 \pm 4.64	0.13	0.67	0.90
Trimethylamine	0.91 \pm 0.12	1.37 \pm 0.26	0.18	0.79	1.50
Malate	1.92 \pm 0.12	2.84 \pm 0.65	0.20	0.79	1.48
Tyrosine	14.15 \pm 3.39	21.75 \pm 4.56	0.21	0.79	1.54
N,N-Dimethylglycine	6.09 \pm 1.19	4.53 \pm 0.52	0.26	0.79	0.74
2-Hydroxyisobutyrate	0.004 \pm 0.001	0.003 \pm 0.0007	0.27	0.79	0.62
Formate	1.60 \pm 0.25	2.14 \pm 0.39	0.27	0.79	1.34
Glycine	10.24 \pm 0.78	9.21 \pm 0.50	0.28	0.79	0.90
4-PY	2.98 \pm 0.55	2.31 \pm 0.34	0.32	0.81	0.78
3-HPPA	9.90 \pm 2.38	14.22 \pm 3.47	0.35	0.81	1.44
Fumarate	3.78 \pm 0.52	3.10 \pm 0.39	0.36	0.81	0.82
Allantoin	230.44 \pm 5.54	222.16 \pm 7.86	0.41	0.81	0.96
Sarcosine	3.99 \pm 0.36	4.36 \pm 0.26	0.43	0.87	1.09
Indoxyl Sulphate	7.50 \pm 0.73	8.39 \pm 1.01	0.48	0.87	1.12
Tryptophan	7.52 \pm 0.74	8.40 \pm 1.02	0.49	0.87	1.12
Alanine	3.97 \pm 0.28	3.74 \pm 0.16	0.50	0.87	0.94
Methylamine	5.17 \pm 0.21	4.97 \pm 0.20	0.52	0.87	0.96

N-acetylglycoproteins	73.29 ± 8.32	66.48 ± 5.35	0.54	0.87	0.91
2-Oxoglutarate	142.06 ± 13.08	129.55 ± 15.72	0.56	0.87	0.91
3-methyl-2-oxovalerate	4.20 ± 0.39	3.95 ± 0.20	0.59	0.87	0.94
Hippurate	267.88 ± 27.15	245.29 ± 32.31	0.60	0.87	0.92
Acetate	4.74 ± 0.58	5.07 ± 0.39	0.64	0.87	1.07
1-methylnicotinamide	0.02 ± 0.01	0.03 ± 0.01	0.65	0.87	1.24
Pseudouridine	10.38 ± 0.73	10.14 ± 0.50	0.79	0.88	0.98
α-hydroxyhippurate	1.09 ± 0.11	1.12 ± 0.09	0.82	0.88	1.03
Succinate	43.05 ± 3.57	43.96 ± 2.80	0.84	0.95	1.02
Taurine	417.08 ± 39.53	428.39 ± 40.02	0.84	0.95	1.03
Dimethylamine	49.30 ± 2.54	48.57 ± 2.33	0.86	0.95	0.99
N-Acetylglycine	29.61 ± 2.69	29.02 ± 1.87	0.87	0.95	0.98
Citrate	252.17 ± 20.74	258.04 ± 28.6	0.88	0.95	1.02
Fucose	10.19 ± 0.38	10.26 ± 0.54	0.92	0.95	1.01
NAD+	0.30 ± 0.04	0.30 ± 0.04	0.92	0.95	0.98
Valine	1.11 ± 0.12	1.10 ± 0.02	0.93	0.95	0.99
N6-Acetyllysine	16.84 ± 0.91	16.72 ± 1.02	0.93	0.95	0.99
Lactate	10.19 ± 0.97	10.17 ± 0.76	0.99	0.95	1.00



Supplementary Figure 3. PCA summary plot for the urine of the preclinical model in Wistar male rats.
 (a) Explained variance. The scree plot suggests that 4 components may be sufficient to capture most of

the variance. (b) Observation diagnostics. This plot shows the distances within and orthogonal to the projection plane; the names of the samples with a high value for at least one of the distances are given. (c) Score plot (PCA). The total variance explained is 37%: PC1 explains the 21% and the PC2 explains the 16%. (d) The variables with the most extreme values (positive and negative) for each loading are coloured black and labelled. Legend: blue, CON group; red, P407 group.



Supplementary Figure 4. OPLS-DA summary plot for the urine of the preclinical model in Wistar male rats. (a) Model overview. The plot here suggests that 2 components may be sufficient to capture most of the inertia (b) Diagnostic significance. The R2Y and Q2Y of the model are compared with the corresponding values obtained after random permutation of the y-response. (c) Observation diagnostics. Indicates possible outliers. (d) X-score plot (OPLS-DA). The graph shows the number of components, the cumulative explained variance in X (R2X), in Y (R2Y), and the cumulative prediction power (Q2Y), the root mean square error of estimation (RMSEE), the predicted variation in Y (pre), and the orthogonal variance in Y (ort). Legend: blue, CON group; red, P407 group.

Supplementary Table 4. Characteristics of the human population classified by the preclinical predictive model. Results are presented as the mean \pm SEM. Statistical comparisons between groups were performed using *t*-student. * Denotes $p < 0.1$ (trend), ** $p < 0.05$ (significantly different) and *** $p < 0.01$ (highly significantly different). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; APOB, apolipoprotein B-100; LPL activity, lipoprotein lipase activity (Δ nmol/mL·min).

Prediction	Healthy (n = 69)	At-risk of LPL-mediated HTG (n = 71)	p-value
Age	51.84 \pm 1.73	50.15 \pm 1.67	0.48
BMI	26.33 \pm 0.35	26.69 \pm 0.27	0.43
SBP (mmHg)	137.68 \pm 1.9	133.27 \pm 2	0.11
DBP (mmHg)	84.01 \pm 1.2	83.18 \pm 1.12	0.61
FPG (mM)	5.42 \pm 0.07	5.57 \pm 0.1	0.24
TG (mM)	1.04 \pm 0.06	1.67 \pm 0.1	<0.01***
TC (mM)	5.37 \pm 0.11	5.95 \pm 0.09	<0.01***
LDL (mM)	3.42 \pm 0.1	3.8 \pm 0.09	0.01**

HDL (mM)	1.36 ± 0.05	1.27 ± 0.04	0.10*
APOB (mM)	0.98 ± 0.03	1.14 ± 0.02	<0.01***
LPL activity (Δ)	1.46 ± 0.01	1.45 ± 0.01	0.29

Supplementary Table 5. Characteristics of the human population classified by TG levels (according to guidelines). Results are presented as the mean ± SEM. Statistical comparisons between groups were performed using *t*-student. * Denotes $p < 0.1$ (trend), ** $p < 0.05$ (significantly different) and *** $p < 0.01$ (highly significantly different). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; APOB, apolipoprotein B-100; LPL activity, lipoprotein lipase activity (Δ nmol/mL·min).

TG levels	Healthy ($n = 106$)	At-risk TG levels ($n = 34$)	<i>p</i> -value
Age	50.04 ± 1.43	53.94 ± 2.07	0.13
BMI	26.44 ± 0.25	26.76 ± 0.46	0.55
SBP (mmHg)	135.79 ± 1.59	134.35 ± 2.92	0.67
DBP (mmHg)	83.35 ± 0.96	84.31 ± 1.53	0.60
FPG (mM)	5.42 ± 0.05	5.73 ± 0.19	0.11
TG (mM)	1.03 ± 0.03	2.39 ± 0.12	<0.01***
TC (mM)	5.61 ± 0.09	5.81 ± 0.09	0.13
LDL (mM)	3.64 ± 0.09	3.53 ± 0.11	0.46
HDL (mM)	1.38 ± 0.04	1.1 ± 0.05	<0.01***
APOB (mM)	1.03 ± 0.02	1.16 ± 0.03	<0.01***
LPL activity (Δ)	1.45 ± 0.01	1.45 ± 0.01	0.67

Supplementary Table 6. Characteristics of the healthy human population (according to TG guidelines) classified as healthy and at-risk of LPL-mediated HTG (predictive model). Results are presented as the mean ± SEM. Statistical comparisons between groups were performed using *t*-student. * Denotes $p < 0.1$ (tendency), ** $p < 0.05$ (significantly different) and *** $p < 0.01$ (high significantly different). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; APOB, apolipoprotein B-100; LPL activity, lipoprotein lipase activity (Δ nmol/mL·min).

	Predicted healthy ($n = 62$)	Predicted at-risk of LPL-mediated HTG ($n = 44$)	<i>p</i> -value
Age	51.02 ± 1.84	48.66 ± 2.27	0.42
BMI	26.4 ± 0.38	26.5 ± 0.29	0.83
SBP (mmHg)	136.95 ± 2.03	134.16 ± 2.55	0.39
DBP (mmHg)	83.06 ± 1.27	83.77 ± 1.49	0.72
FPG (mM)	5.38 ± 0.07	5.46 ± 0.09	0.49
TG (mM)	0.92 ± 0.04	1.19 ± 0.05	<0.01***
TC (mM)	5.34 ± 0.12	6 ± 0.13	<0.01***
LDL (mM)	3.42 ± 0.1	3.94 ± 0.13	<0.01***

HDL (mM)	1.4 ± 0.05	1.36 ± 0.05	0.65
APOB (mM)	0.97 ± 0.03	1.11 ± 0.03	<0.01***
LPL activity (Δ)	4.37 ± 0.17	4.35 ± 0.15	0.61

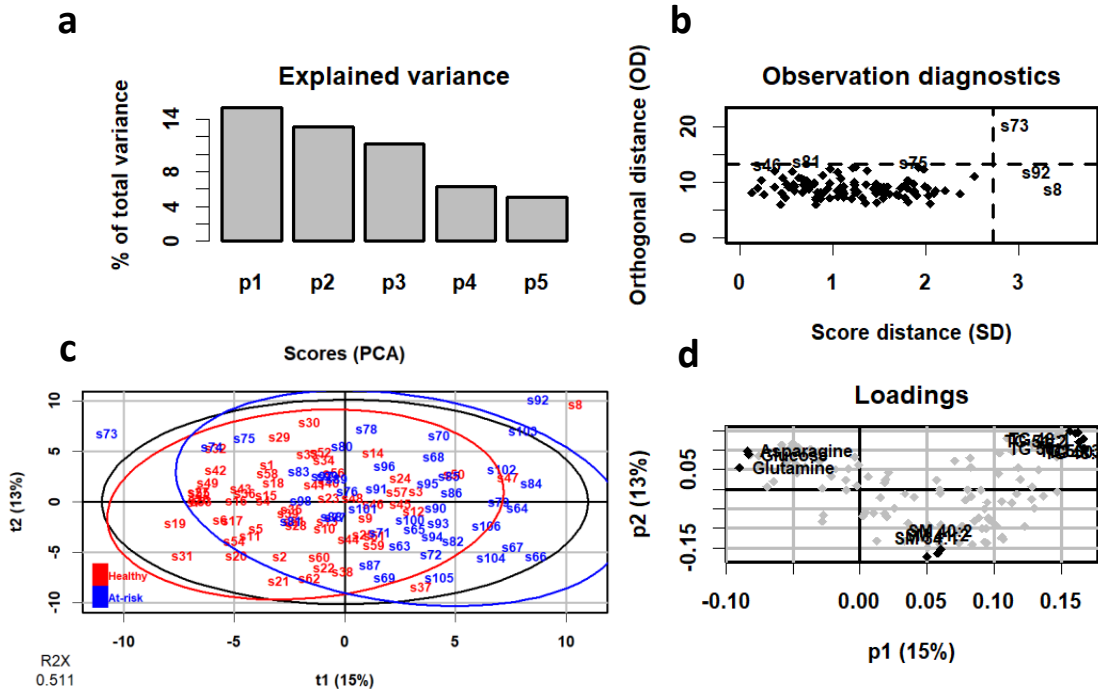
Supplementary Table 7. Summary of univariate/multivariate plasma analysis of the healthy human population (according to TG guidelines) classified as healthy and at-risk of LPL-mediated HTG (predictive model). 126 metabolites are shown as the mean ± SEM ($n = 10$, group). Summary of univariate analysis includes p -value, q -value (pFDR) and FC (at-risk of LPL-mediated HTG /healthy). Summary of the multivariate analysis is presented by VIP values of OPLS-DA. Metabolites are listed according to VIP values. * Denotes $p < 0.1$ (trend), ** $p < 0.05$ (significantly different) and *** $p < 0.01$ (highly significantly different). Abbreviations: DG, diacylglycerol; PC, phosphatidylcholine; ChoE, cholesteryl ester; LPC, lysophospholipid; TG, triglyceride; SM, sphingomyelin.

Metabolites	Predicted healthy ($n = 62$)	Predicted at-risk of LPL-mediated HTG ($n = 44$)	p -value	q -value	VIP
LPC 16:0	42.34 ± 0.8	50 ± 1.3	<0.01***	<0.01***	1.91
LPC 18:0	12.59 ± 0.25	15.93 ± 0.58	<0.01***	<0.01***	1.84
TG 52:3	55.19 ± 2.86	74.16 ± 3.42	<0.01***	<0.01***	1.68
TG 51:2	1.49 ± 0.09	1.94 ± 0.1	<0.01***	0.01**	1.59
ChoE (20:4)	61.88 ± 1.78	77.05 ± 2.4	<0.01***	<0.01***	1.56
ChoE (18:2)	122.82 ± 2.51	139.24 ± 2.5	<0.01***	<0.01***	1.55
PC 36:2	30.74 ± 0.79	35.39 ± 0.97	<0.01***	<0.01***	1.51
TG 50:3	5.44 ± 0.44	7.65 ± 0.45	<0.01***	<0.01***	1.50
TG 52:5	2.53 ± 0.17	3.58 ± 0.23	<0.01***	<0.01***	1.49
TG 50:2	17.82 ± 1.3	23.57 ± 1.39	<0.01***	0.01**	1.49
TG 52:1	3.41 ± 0.31	5.61 ± 0.4	<0.01***	<0.01***	1.47
TG 52:2	58.28 ± 3.28	74.84 ± 3.53	<0.01***	0.01**	1.45
PC 38:4	10.95 ± 0.35	14.12 ± 0.56	<0.01***	<0.01***	1.45
PC 40:5	0.54 ± 0.02	0.64 ± 0.02	<0.01***	<0.01***	1.41
ChoE (16:0)	6.26 ± 0.14	7.23 ± 0.15	<0.01***	<0.01***	1.41
Valine	3.29 ± 0.37	7.56 ± 2.88	0.15	0.20	1.41
TG 54:4	23 ± 1.1	29.46 ± 1.39	<0.01***	<0.01***	1.40
PC 36:4	17.59 ± 0.52	21.87 ± 0.73	<0.01***	<0.01***	1.39
PC 40:4	0.23 ± 0.01	0.29 ± 0.02	<0.01***	0.01**	1.37
Ornithine	10.62 ± 0.76	27.15 ± 8.09	0.05*	0.09*	1.37
TG 54:2	5.6 ± 0.3	7.58 ± 0.39	<0.01***	<0.01***	1.34
TG 50:4	1.02 ± 0.08	1.38 ± 0.09	<0.01***	0.02**	1.34
TG 54:6	2.12 ± 0.14	2.99 ± 0.2	<0.01***	<0.01***	1.33
TG 50:1	14.15 ± 1.08	19.17 ± 1.26	<0.01***	0.01**	1.32
LPC 16:1 e	0.29 ± 0.01	0.33 ± 0.01	<0.01***	0.01**	1.32

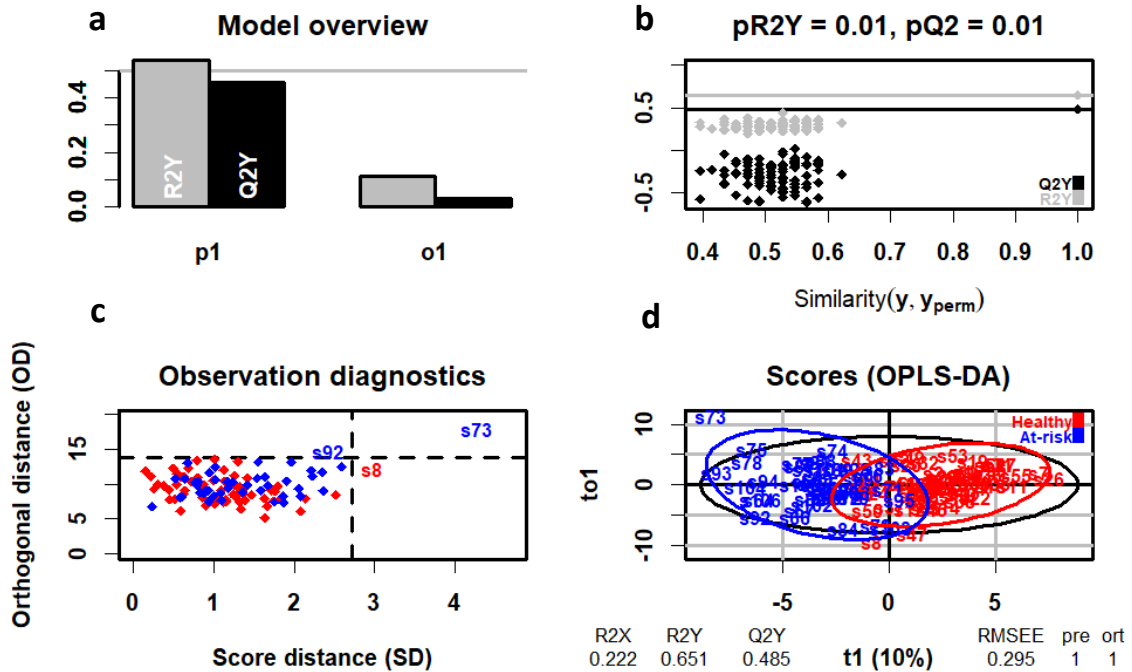
PC 32:0	1.32 ± 0.03	1.46 ± 0.03	<0.01***	0.01**	1.31
PC 38:3	4.23 ± 0.14	5.17 ± 0.22	<0.01***	<0.01***	1.30
DG 34:2	1.91 ± 0.05	2.12 ± 0.04	<0.01***	0.01**	1.28
Lysine	2.23 ± 0.31	4.93 ± 1.44	0.07*	0.12	1.28
SM 42:1	17.04 ± 0.45	20.19 ± 0.8	<0.01***	0.01**	1.25
Glutamic acid	0.09 ± 0.01	0.24 ± 0.06	0.02**	0.06*	1.25
TG 48:2	1.72 ± 0.19	2.49 ± 0.24	0.01**	0.04**	1.21
TG 48:1	3.43 ± 0.38	5.09 ± 0.49	0.01**	0.03**	1.20
PC 34:0	0.34 ± 0.07	0.32 ± 0.01	0.82	0.83	1.18
SM 40:1	28.54 ± 0.84	33.15 ± 1.27	<0.01***	0.01**	1.17
Tyrosine	2.13 ± 0.2	3.52 ± 0.56	0.02**	0.06*	1.17
TG 48:3	0.46 ± 0.05	0.66 ± 0.07	0.02**	0.06*	1.17
Leucine	0.25 ± 0.03	2.12 ± 1.24	0.14	0.19	1.15
Isoleucine	0.94 ± 0.11	2.1 ± 0.9	0.21	0.27	1.13
DG 34:1	3.04 ± 0.09	3.4 ± 0.08	<0.01***	0.01**	1.12
Threonine	1.55 ± 0.12	2.49 ± 0.43	0.04**	0.08*	1.11
Beta-alanine	0.54 ± 0.04	1.36 ± 0.47	0.09*	0.15	1.08
DG 34:3	0.38 ± 0.02	0.44 ± 0.02	0.01**	0.02**	1.07
Glycolic acid	11.16 ± 2.21	45.36 ± 15.93	0.04**	0.08*	1.06
TG 52:6	0.33 ± 0.03	0.44 ± 0.04	0.01**	0.03**	1.06
ChoE (18:3)	15.96 ± 0.64	20.36 ± 1.06	<0.01***	<0.01***	1.05
LPC 20:0	0.07 ± 0	0.08 ± 0	0.01**	0.03**	1.03
SM 36:2	7.17 ± 0.25	8.15 ± 0.28	0.01**	0.03**	1.03
PC 35:2	1.02 ± 0.03	1.13 ± 0.03	0.02**	0.06*	1.02
Tryptophan	1.41 ± 0.22	2.37 ± 0.38	0.03**	0.07*	1.02
TG 54:3	22.92 ± 1.26	28.55 ± 1.57	0.01**	0.02**	1.02
SM 38:1	10.82 ± 0.32	12.38 ± 0.5	0.01**	0.03**	1.01
PC 34:1	25.06 ± 0.77	26.82 ± 0.67	0.08*	0.14	1.01
ChoE (18:1)	26.27 ± 0.64	28.56 ± 0.58	0.01**	0.03**	1.01
LPC 16:0 e	0.31 ± 0.01	0.34 ± 0.01	0.02**	0.05*	0.99
PC 38:2	0.47 ± 0.01	0.51 ± 0.01	0.03**	0.06*	0.98
ChoE (18:0)	0.58 ± 0.02	0.71 ± 0.03	<0.01***	<0.01***	0.96
SM 35:1	2.38 ± 0.08	2.7 ± 0.1	0.01**	0.04**	0.95
Hydroxyproline	0.49 ± 0.06	2.12 ± 0.94	0.09*	0.15	0.95
SM 34:1	94.82 ± 2.5	103.87 ± 2.79	0.02**	0.05*	0.95
Aspartic acid	0.62 ± 0.13	1.31 ± 0.35	0.07*	0.12	0.95
SM 36:1	14.43 ± 0.46	16.29 ± 0.57	0.01**	0.04**	0.94
SM 43:1	1.01 ± 0.03	1.13 ± 0.04	0.01**	0.04**	0.93

Asparagine	0.15 ± 0.02	0.34 ± 0.09	0.05*	0.09*	0.92
LPC 18:2	18.45 ± 0.68	20.33 ± 0.98	0.12	0.17	0.92
SM 41:1	11.7 ± 0.33	12.95 ± 0.45	0.03**	0.07*	0.91
LPC 18:1	10.3 ± 0.33	10.87 ± 0.44	0.30	0.35	0.91
LPC 18:0 e	0.08 ± 0	0.09 ± 0	0.03**	0.07*	0.88
ChoE (22:6)	15.17 ± 0.57	17.77 ± 0.78	0.01**	0.03**	0.85
SM 40:2	12.51 ± 0.39	13.96 ± 0.54	0.03**	0.07*	0.85
DG 36:4	1.66 ± 0.07	1.89 ± 0.07	0.03**	0.06*	0.84
Cholesterol	0.36 ± 0.05	0.88 ± 0.31	0.11	0.16	0.84
ChoE (22:5)	0.61 ± 0.02	0.68 ± 0.03	0.05*	0.09*	0.84
Glycine	8.95 ± 0.93	29.08 ± 11.8	0.10	0.15	0.83
ChoE (16:1)	3.14 ± 0.17	3.43 ± 0.23	0.31	0.36	0.83
Phenylalanine	1.18 ± 0.08	1.68 ± 0.26	0.06*	0.11	0.83
3-hydroxybutiric acid	1.48 ± 0.11	1.17 ± 0.09	0.03**	0.07*	0.82
PC 32:2	0.37 ± 0.02	0.41 ± 0.02	0.14	0.19	0.81
SM 42:2	44.05 ± 1.4	47.35 ± 1.37	0.10	0.15	0.81
TG 46:1	0.45 ± 0.07	0.66 ± 0.12	0.12	0.17	0.81
Glutamine	1.51 ± 0.1	2.23 ± 0.31	0.03**	0.07*	0.80
TG 46:2	0.23 ± 0.03	0.33 ± 0.05	0.09*	0.15	0.80
PC 32:1	1.49 ± 0.09	1.62 ± 0.11	0.36	0.40	0.80
TG 48:0	1.12 ± 0.1	1.41 ± 0.15	0.11	0.16	0.79
SM 42:3	22.22 ± 0.62	23.64 ± 0.66	0.12	0.17	0.75
ChoE (17:1)	0.17 ± 0.01	0.18 ± 0.01	0.18	0.24	0.75
SM 34:2	10.78 ± 0.3	11.65 ± 0.34	0.06*	0.11	0.75
PC 30:0	0.2 ± 0.01	0.24 ± 0.02	0.09*	0.14	0.75
DG 36:2	6.04 ± 0.18	6.75 ± 0.22	0.01**	0.04**	0.72
ChoE (22:4)	0.15 ± 0.01	0.2 ± 0.02	0.02**	0.06*	0.71
LPC 15:0	0.3 ± 0.01	0.32 ± 0.01	0.22	0.28	0.69
Proline	0.3 ± 0.03	0.59 ± 0.13	0.04**	0.08*	0.65
SM 33:1	2.97 ± 0.09	3.26 ± 0.12	0.05*	0.10	0.64
Alanine	1.48 ± 0.15	3.43 ± 1.36	0.16	0.22	0.63
ChoE (20:2)	0.35 ± 0.02	0.41 ± 0.02	0.05*	0.10	0.63
TG 54:7	0.94 ± 0.08	1.2 ± 0.12	0.08*	0.14	0.62
SM 32:1	5.93 ± 0.2	6.54 ± 0.27	0.07*	0.12	0.61
Serine	0.2 ± 0.02	0.32 ± 0.06	0.05*	0.09*	0.61
Histidine	0.08 ± 0.02	0.3 ± 0.19	0.26	0.32	0.58
Ribose	0.24 ± 0.01	0.22 ± 0.02	0.17	0.23	0.57
TG 46:0	0.59 ± 0.05	0.63 ± 0.08	0.67	0.69	0.57

PC 31:0	0.07 ± 0	0.07 ± 0	0.19	0.25	0.56
SM 39:1	4.15 ± 0.14	4.56 ± 0.21	0.11	0.16	0.55
Methionine	0.17 ± 0.03	0.31 ± 0.11	0.23	0.28	0.55
Malic acid	0.34 ± 0.11	0.49 ± 0.15	0.42	0.46	0.55
Lactic acid	3.9 ± 0.09	4.07 ± 0.12	0.27	0.32	0.54
Glycerol	9.07 ± 5.88	18.93 ± 9.56	0.38	0.43	0.51
Pyruvic acid	16.21 ± 0.84	16.18 ± 0.74	0.98	0.98	0.46
PC 33:1	0.24 ± 0.01	0.25 ± 0.01	0.60	0.63	0.44
PC 33:0	0.05 ± 0	0.05 ± 0	0.26	0.32	0.40
SM 41:2	6.42 ± 0.19	6.76 ± 0.25	0.29	0.35	0.39
Glyceric acid	0.57 ± 0.02	0.56 ± 0.02	0.58	0.62	0.36
Glucose	0.29 ± 0.01	0.32 ± 0.02	0.11	0.16	0.33
TG 50:0	0.38 ± 0.04	0.51 ± 0.06	0.07*	0.12	0.27
Alpha-tocopherol	0.36 ± 0.03	0.42 ± 0.05	0.36	0.40	0.25
Alpha-ketoglutarate	0.5 ± 0.02	0.53 ± 0.03	0.48	0.51	0.24
Threonic acid	1.66 ± 0.06	1.55 ± 0.1	0.38	0.43	0.21
Oleic acid	3.5 ± 0.15	3.9 ± 0.37	0.32	0.37	0.21
Fructose	0.35 ± 0.04	0.32 ± 0.02	0.42	0.46	0.19
Aconitic acid	0.02 ± 0	0.02 ± 0	0.40	0.44	0.18
Urea	1.2 ± 0.04	1.23 ± 0.04	0.64	0.66	0.18
Citric acid	5.84 ± 0.19	5.95 ± 0.25	0.72	0.74	0.16
2-hydroxyglutaric	0.97 ± 0.04	0.89 ± 0.05	0.23	0.28	0.10
Fumaric acid	0.48 ± 0.02	0.46 ± 0.02	0.47	0.51	0.08
ChoE (17:0)	0.07 ± 0.01	0.07 ± 0.02	0.69	0.70	0.04
Succinic acid	0.63 ± 0.03	0.58 ± 0.03	0.21	0.27	0.01



Supplementary Figure 5. PCA summary plot of the plasma metabolome of healthy human population (according to TG guidelines) classified as healthy and at-risk of LPL-mediated HTG (predictive model). (a) Explained variance. The scree plot suggests that 5 components may be sufficient to capture most of the variance. (b) Observation diagnostics. This plot shows the distances within and orthogonal to the projection plane; the names of the samples with a high value for at least one of the distances are given. (c) Score plot (PCA). The total variance explained is 28%. PC1 explains the 15% and the PC2 explains the 13%. (d) The variables with the most extreme values (positive and negative) for each loading are coloured black and labelled. Legend: red, healthy; blue, at-risk of LPL-mediated HTG.



Supplementary Figure 6. OPLS-DA of the plasma metabolome of the human cohort (according to TG guidelines) classified as healthy and at-risk of LPL-mediated HTG (predictive model). (a) Overview of the model. The graph here suggests that 2 components may be sufficient to capture most of the inertia (b) Diagnostic significance. The R2Y and Q2Y of the model are compared with the corresponding values obtained after random permutation of the y-response. (c) Observation diagnostics. Indicates possible outliers. (d) X-score plot (OPLS-DA). The graph shows the number of components, the cumulative explained variance in X (R2X), in Y (R2Y), and the cumulative prediction power (Q2Y), the root mean square error of estimation (RMSEE), the predicted variation in Y (pre), and the orthogonal variance in Y (ort). Legend: red, healthy; blue, at-risk of LPL-mediated HTG.