

Heritability and responses to high fat diet of plasma lipidomics in a twin study.

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Structural equation model

Structural equations models (including ACE model) are used in epidemiology and (behavior) genetic research to reveal the importance for environmental and genetic effects on phenotypes in health and disease. They are used in Twin studies but were also generalized to Case-Control Family Data^{1,2}.

In Twin studies, the models are mainly based on three assumptions:

1. Monozygotic twins (MZ) develop from a single zygote and share all of their alleles. Therefore they are nearly genetically identical.
2. Dizygotic twins (DZ) develop from two zygotes and share on average 50% of their alleles like non-twin siblings.
3. MZ and DZ share mainly the same environment.

These assumptions lead to the ability to separate genetic and environmental effects by comparing the within-pair (dis-)concordance between monozygotic and dizygotic twin pairs. For example, if monozygotic twins show a high concordance (or only small within-pair variance/variation) in a trait, whereas dizygotic twins vary much more, it is more likely that this trait is driven by genetic effects. In contrast, if monozygotic and dizygotic twins only show slight variance within the pairs for the same trait, it is most likely, that the trait is mostly driven by a within-pair shared environment of the twins.

Usually the structural equation models are able to identify one of two genetic factors:

- Additive genetic effects (A),
- Dominant or non-additive genetic effects (D),

and up to two environmental factors:

- The shared environment or common environment (C), that have the effect of making siblings more similar to one another (e.g. shared family structure, place of birth/living, nutrition in childhood),
- The individual environment (E), that have the effect of making siblings unique (e.g. smoker status, nutrition in adulthood).

Nevertheless, the discrimination between shared and individual environment effectors in terms of biology is difficult.

- 1 Javaras, K. N., Hudson, J. I. & Laird, N. M. Fitting ACE structural equation models to case-control family data. *Genet Epidemiol* **34**, 238-245, doi:10.1002/gepi.20454 (2010).
- 2 Maes, H. H. in *Encyclopedia of Statistics in Behavioral Science* (John Wiley & Sons, Ltd, 2005).

Supplementary figures

Supplementary Figure S1: Plasma concentration of the stable lipid classes after LF. In contrast to the concentrations of the other classes, the concentrations of TAG and LPC did not change significantly.

(rep.M. ANOVA + Bonferroni adjustment; n.s. – not significant, mean \pm SEM)

Supplementary Figure S2: Pie charts of class dependent species changes after normalization (LF, HF1, HF6). Although the overall concentration of some classes (like LPC and TAG) did not change, single species reacted to the nutritional challenge of the HFD. Moreover the single species showed an obviously more complex reaction pattern than the overall concentration, which necessitates the distinction of species. (rep.M. ANOVA + Bonferroni adjustment)

Supplementary Figure S3: Flexibility of lipid species (n=150). The flexibility of the lipidome depicted the ability of the participants to adapt to the HFD. The increase after one week HFD vanished completely after additional five weeks and the participants were synchronized again by lowering the variability within the mostly young cohort. The flexibility is shown as the quartiles dispersion coefficient for each CID and each lipid species. The triangles represented the arithmetic mean of the lipid species. (rep.M. ANOVA + Bonferroni adjustment)

Supplementary Figure S4: Flow chart for the analysis of lipid species. We first excluded the samples, which did not pass the quality control (n=30), then the lipid species, which were only measurable in < 80% of the remaining samples. We included 150 lipid species measured in 246 samples in the analysis.

Media S1: Interactive 3D bubble plot (Fig.5) with R script and data. (3DBubble_small.mov, Bubbleplot.R, Lipidomics_150_corrected_diagonale.csv)

Supplementary Table S1: Absolute amount of variance contribution determined by a linear mixed model based on the repeated measured ACE model (LF, HF1, HF6) for lipid classes. The classes showed a high variability for additive genetic effects (heritability). Only SM were highly heritable with A-values greater than 0.40 (= 40%). The parameters – except Total concentration - were sorted/ranked by the rounded values for heritability (A), common environment (C), individual environment (E) and unknown effects (U).

	A	C	E	U
Total	0.005	0.444	0.442	0.108
SM	0.650	0.063	0.282	0.004
PE	0.353	0.000	0.084	0.562
LPC	0.250	0.000	0.301	0.449
TAG	0.180	0.053	0.664	0.103
LPE	0.144	0.000	0.283	0.574
PE-O	0.014	0.259	0.661	0.067
PC	0.011	0.406	0.504	0.079
PI	0.007	0.268	0.713	0.011
ST	0.005	0.197	0.652	0.146
DAG	0.002	0.390	0.401	0.207
CER	0.000	0.621	0.268	0.111
SE	0.000	0.460	0.448	0.092
PC-O	0.000	0.354	0.475	0.171

Supplementary Table S2: Absolute amount of variance contribution determined by a linear mixed model based on the repeated measured ACE model (LF, HF1, HF6) for lipid species. The species showed a high variability for additive genetic effects (heritability) with values between 0 and 62 %. The parameters were sorted/ranked by the rounded values for heritability (A), common environment (C), individual environment (E) and unknown effects (U).

	A	C	E	U
PI [34:2, (18:2, 16:0)]	0.621	0.000	0.058	0.321
PE [36:2, (18:2, 18:0)]	0.594	0.000	0.275	0.131
PC-O [32:0, (16:0, 16:0)]	0.575	0.000	0.423	0.003
PC-O [34:3, (16:1, 18:2)]	0.567	0.008	0.338	0.087
PE-O [36:5, (16:1, 20:4)]	0.561	0.035	0.295	0.109
PC [33:1, (17:1, 16:0)]	0.552	0.000	0.368	0.081
SM [36:1]	0.514	0.014	0.408	0.064
PE [38:4, (20:4, 18:0)]	0.511	0.000	0.068	0.421
PI [36:2, (18:0, 18:2)]	0.510	0.019	0.467	0.003
PC-O [36:3, (18:1, 18:2)]	0.508	0.007	0.419	0.066
PC-O [34:1, (18:1, 16:0)]	0.504	0.000	0.210	0.287
SE [47:4, (27:1, 20:3)]	0.490	0.091	0.283	0.136
LPE [16:0]	0.483	0.000	0.384	0.133
PC-O [34:1, (16:0, 18:1)]	0.483	0.000	0.302	0.215
LPC [18:1]	0.478	0.000	0.355	0.166
SM [40:1]	0.477	0.000	0.257	0.266
LPE [18:1]	0.424	0.000	0.115	0.461
PC [38:4, (20:3, 18:1)]	0.423	0.000	0.303	0.274
LPC [20:4]	0.413	0.000	0.330	0.257

TAG [52:2]	0.389	0.202	0.296	0.113
LPC [18:0]	0.389	0.000	0.286	0.325
PI [36:1, (18:0, 18:1)]	0.386	0.000	0.108	0.507
PC [38:3, (18:0, 20:3)]	0.358	0.000	0.352	0.291
LPE [18:0]	0.344	0.000	0.227	0.428
PC [36:3, (20:3, 16:0)]	0.337	0.000	0.407	0.256
SM [38:1]	0.333	0.029	0.502	0.136
SM [36:2:b]	0.328	0.132	0.466	0.074
PI [38:3, (18:0, 20:3)]	0.320	0.000	0.483	0.197
PC [36:1, (18:0, 18:1)]	0.290	0.000	0.260	0.450
TAG [49:2]	0.285	0.180	0.375	0.160
PC [36:2, (20:2, 16:0)]	0.285	0.058	0.616	0.042
TAG [56:6]	0.279	0.321	0.263	0.136
LPE [20:4]	0.278	0.000	0.166	0.555
PC [33:2, (18:2, 15:0)]	0.276	0.078	0.631	0.015
SM [36:2:a]	0.274	0.189	0.397	0.139
DAG [34:1, (16:0, 18:1)]	0.274	0.000	0.301	0.425
PC [38:6, (22:6, 16:0)]	0.262	0.132	0.599	0.007
TAG [54:6]	0.260	0.181	0.440	0.118
LPC [20:3]	0.245	0.000	0.115	0.640
DAG [36:2, (18:1, 18:1)]	0.230	0.135	0.555	0.079
LPC [18:2]	0.229	0.000	0.381	0.390
LPC [16:1]	0.223	0.000	0.176	0.601
SM [34:1]	0.214	0.089	0.687	0.009
PC [34:1, (18:1, 16:0)]	0.207	0.216	0.483	0.094

PC [32:1, (16:0, 16:1)]	0.205	0.000	0.498	0.296
TAG [52:5]	0.203	0.087	0.597	0.113
LPC [16:0]	0.197	0.000	0.157	0.646
CER [40:2]	0.193	0.051	0.691	0.065
TAG [56:5]	0.190	0.100	0.627	0.083
PC [33:1, (18:1, 15:0)]	0.188	0.000	0.653	0.159
PE-O [38:6, (18:2, 20:4)]	0.187	0.000	0.130	0.684
PC [36:4, (20:4, 16:0)]	0.180	0.000	0.477	0.343
PC-O [34:2, (16:1, 18:1)]	0.175	0.074	0.563	0.188
PE-O [36:4, (18:2, 18:2)]	0.165	0.280	0.438	0.117
TAG [54:3]	0.157	0.205	0.635	0.003
SE [43:2, (27:1, 16:1)]	0.155	0.000	0.261	0.584
TAG [54:4]	0.149	0.122	0.622	0.107
CER [40:1]	0.147	0.239	0.544	0.071
SM [40:2]	0.138	0.000	0.313	0.549
PC [36:5, (16:0, 20:5)]	0.136	0.000	0.278	0.587
PC-O [34:1, (17:0, 17:1)]	0.133	0.000	0.191	0.676
LPE [22:6]	0.126	0.000	0.492	0.382
PC [37:3, (20:3, 17:0)]	0.122	0.000	0.296	0.583
SM [42:2]	0.113	0.237	0.536	0.114
PC-O [34:2, (18:2, 16:0)]	0.113	0.263	0.460	0.165
PE-O [36:3, (18:1, 18:2)]	0.111	0.470	0.263	0.155
SM [32:1]	0.110	0.000	0.342	0.548
TAG [54:2]	0.108	0.008	0.705	0.179
PC-O [32:1, (16:1, 16:0)]	0.095	0.000	0.369	0.535

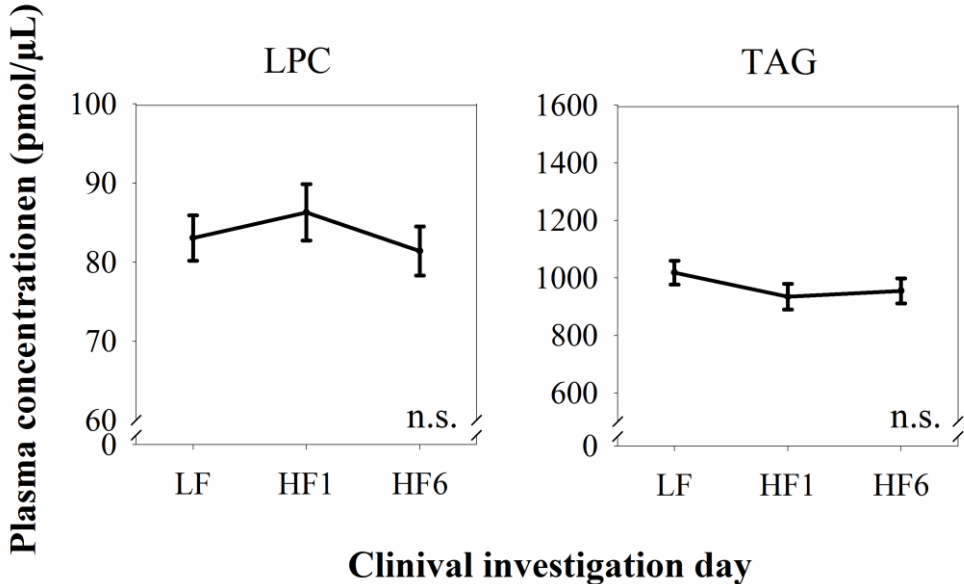
PC [38:5, (18:1, 20:4)]	0.095	0.231	0.673	0.001
SM [34:2]	0.085	0.308	0.467	0.140
PC-O [36:4, (16:0, 20:4)]	0.084	0.222	0.661	0.033
TAG [51:1]	0.084	0.006	0.738	0.172
PI [36:2, (18:1, 18:1)]	0.077	0.000	0.311	0.612
PC-O [36:3, (16:0, 20:3)]	0.067	0.000	0.337	0.597
PC [37:4, (17:0, 20:4)]	0.066	0.417	0.472	0.045
PC-O [34:2, (16:0, 18:2)]	0.065	0.372	0.542	0.021
PE-O [34:3, (16:1, 18:2)]	0.063	0.506	0.282	0.149
PC [36:2, (18:1, 18:1)]	0.062	0.182	0.610	0.146
SM [34:0]	0.061	0.078	0.655	0.205
PC [38:5, (22:5, 16:0)]	0.057	0.105	0.745	0.094
PC-O [32:0, (18:0, 14:0)]	0.050	0.000	0.123	0.827
LPE [18:2]	0.035	0.000	0.399	0.566
PC [38:6, (20:4, 18:2)]	0.032	0.133	0.778	0.057
SE [42:1, (27:1, 15:0)]	0.031	0.377	0.519	0.072
TAG [50:1]	0.030	0.000	0.354	0.615
TAG [49:1]	0.027	0.080	0.681	0.212
LPC [14:0]	0.027	0.000	0.356	0.617
PC [32:0, (16:0, 16:0)]	0.025	0.348	0.510	0.117
SE [45:4, (27:1, 18:3)]	0.021	0.365	0.426	0.188
CER [42:2]	0.020	0.486	0.383	0.111
PC [32:1, (18:1, 14:0)]	0.014	0.000	0.378	0.608
SE [45:3, (27:1, 18:2)]	0.013	0.497	0.415	0.075
PC [38:4, (22:4, 16:0)]	0.010	0.000	0.413	0.576

PI [34:1, (18:1, 16:0)]	0.010	0.000	0.224	0.765
PC-O [32:0, (17:0, 15:0)]	0.009	0.000	0.232	0.759
TAG [50:2]	0.008	0.006	0.470	0.517
PC [34:2, (18:1, 16:1)]	0.007	0.379	0.565	0.049
SE [45:2, (27:1, 18:1)]	0.007	0.428	0.565	0.000
TAG [48:3]	0.006	0.218	0.649	0.126
SE [45:1, (27:1, 18:0)]	0.006	0.311	0.619	0.064
SM [38:2]	0.006	0.366	0.527	0.102
ST [27:1]	0.005	0.197	0.652	0.146
PC [36:4, (18:2, 18:2)]	0.005	0.274	0.590	0.131
PC [34:2, (18:2, 16:0)]	0.004	0.250	0.678	0.067
PC-O [38:4, (18:1, 20:3)]	0.004	0.084	0.660	0.253
TAG [48:1]	0.003	0.527	0.326	0.144
TAG [52:3]	0.002	0.292	0.617	0.088
PC [30:0, (16:0, 14:0)]	0.002	0.000	0.381	0.617
PC-O [36:4, (18:2, 18:2)]	0.001	0.001	0.535	0.464
TAG [53:2]	0.001	0.468	0.403	0.128
LPC [22:6]	0.001	0.544	0.363	0.093
TAG [52:4]	0.000	0.565	0.391	0.044
PI [38:4, (18:0, 20:4)]	0.000	0.500	0.418	0.082
PC [36:2, (18:0, 18:2)]	0.000	0.252	0.627	0.121
TAG [50:3]	0.000	0.504	0.489	0.007
TAG [54:5]	0.000	0.437	0.512	0.051
SE [47:5, (27:1, 20:4)]	0.000	0.369	0.564	0.067
CER [38:1]	0.000	0.370	0.431	0.199

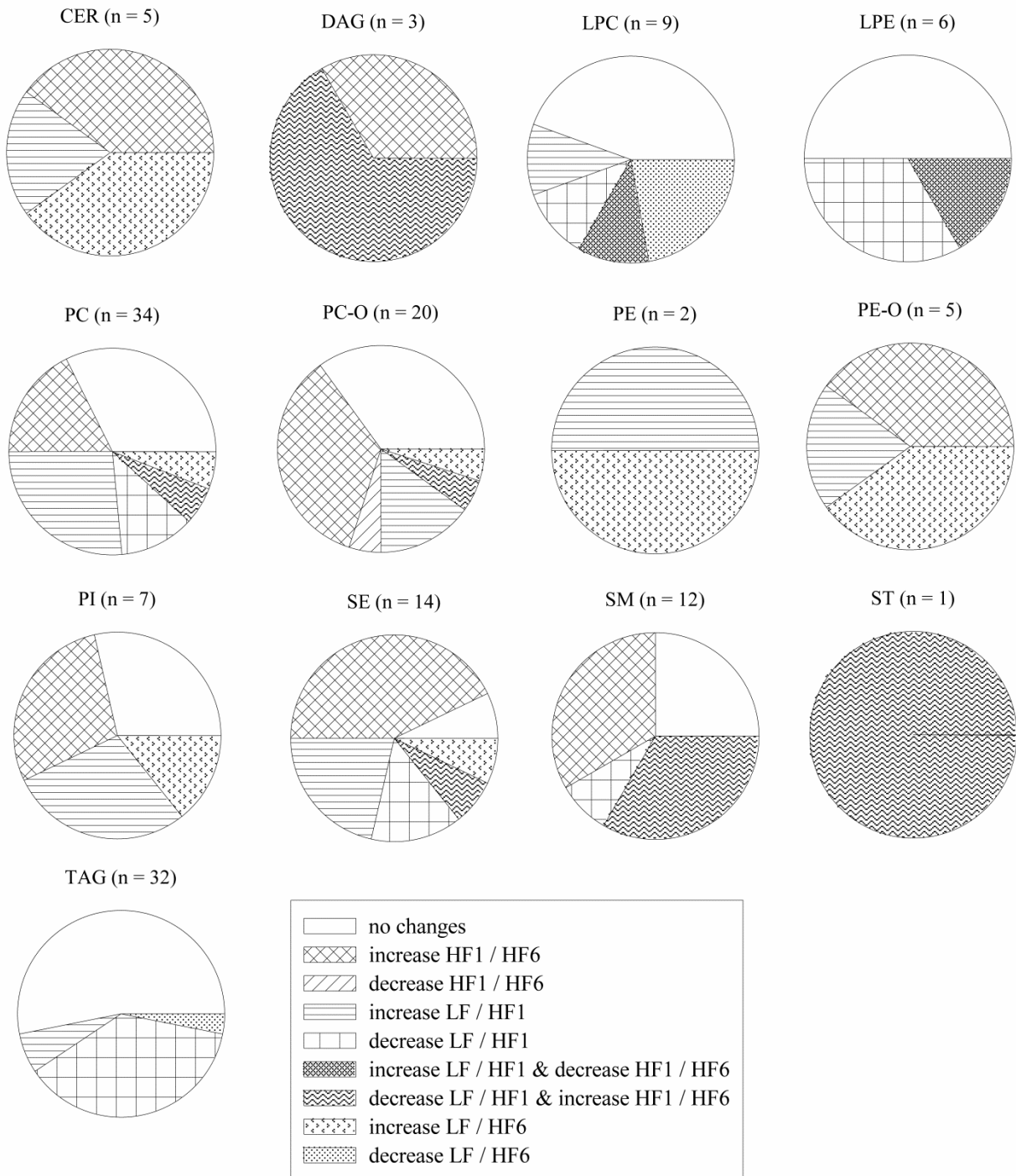
TAG [56:3]	0.000	0.190	0.784	0.026
SE [43:1, (27:1, 16:0)]	0.000	0.348	0.607	0.045
SE [44:1, (27:1, 17:0)]	0.000	0.029	0.321	0.650
TAG [48:2]	0.000	0.517	0.340	0.143
PC-O [38:4, (18:0, 20:4)]	0.000	0.419	0.495	0.085
TAG [56:4]	0.000	0.504	0.415	0.081
SE [49:7, (27:1, 22:6)]	0.000	0.535	0.460	0.006
PC-O [38:5, (18:1, 20:4)]	0.000	0.450	0.430	0.120
PC [34:3, (16:0, 18:3)]	0.000	0.372	0.546	0.082
TAG [50:4]	0.000	0.399	0.521	0.079
PC [38:4, (18:0, 20:4)]	0.000	0.467	0.437	0.096
SE [47:6, (27:1, 20:5)]	0.000	0.453	0.454	0.093
TAG [53:4]	0.000	0.432	0.434	0.133
PC [35:2, (17:0, 18:2)]	0.000	0.310	0.496	0.195
PC [36:3, (18:1, 18:2)]	0.000	0.435	0.557	0.008
DAG [36:3, (18:2, 18:1)]	0.000	0.518	0.433	0.048
SE [44:2, (27:1, 17:1)]	0.000	0.374	0.548	0.078
PC-O [36:3, (18:2, 18:1)]	0.000	0.372	0.574	0.053
TAG [51:2]	0.000	0.554	0.353	0.093
TAG [48:0]	0.000	0.492	0.319	0.189
TAG [54:7]	0.000	0.260	0.648	0.092
PC [32:2, (18:2, 14:0)]	0.000	0.013	0.441	0.546
PC [34:0, (18:0, 16:0)]	0.000	0.507	0.443	0.050
TAG [51:3]	0.000	0.449	0.527	0.024
PC-O [36:5, (16:1, 20:4)]	0.000	0.352	0.485	0.163

TAG [46:1]	0.000	0.413	0.580	0.007
CER [42:1]	0.000	0.430	0.398	0.171
PC [34:3, (18:2, 16:1)]	0.000	0.502	0.471	0.027
TAG [56:7]	0.000	0.101	0.747	0.152
SE [41:1, (27:1, 14:0)]	0.000	0.393	0.426	0.181
TAG [53:3]	0.000	0.262	0.610	0.127

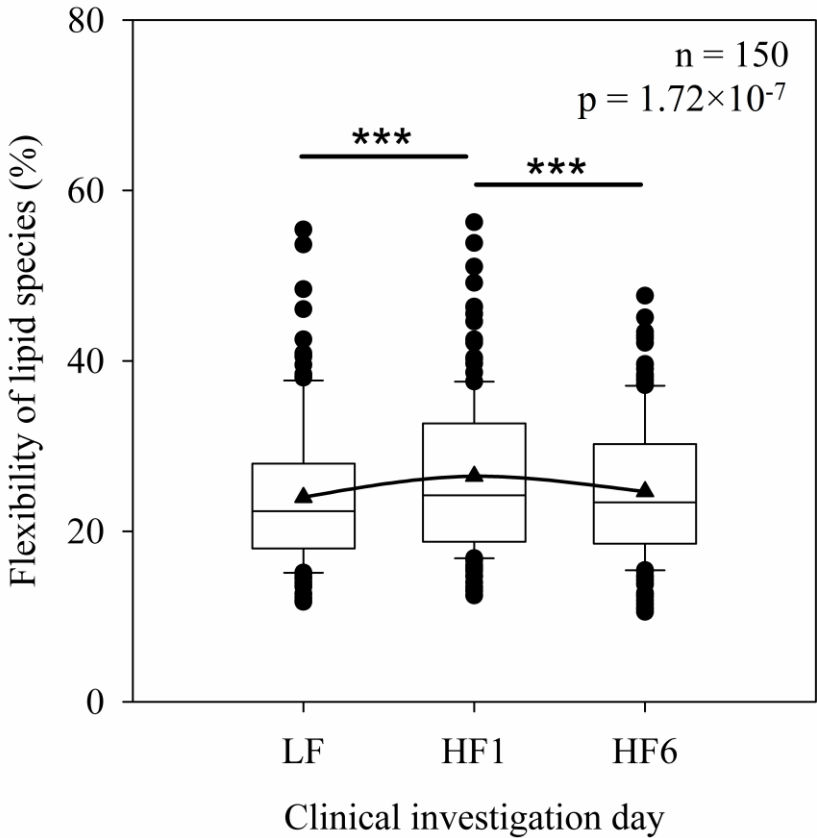
Supplementary Figure S1: Plasma concentration of the stable lipid classes after LF.



Supplementary Figure S2: Pie charts of class dependent species changes after normalization (LF, HF1, HF6).



Supplementary Figure S3: Flexibility of lipid species (n=150).



Supplementary Figure S4: Flow chart for the analysis of lipid species.

