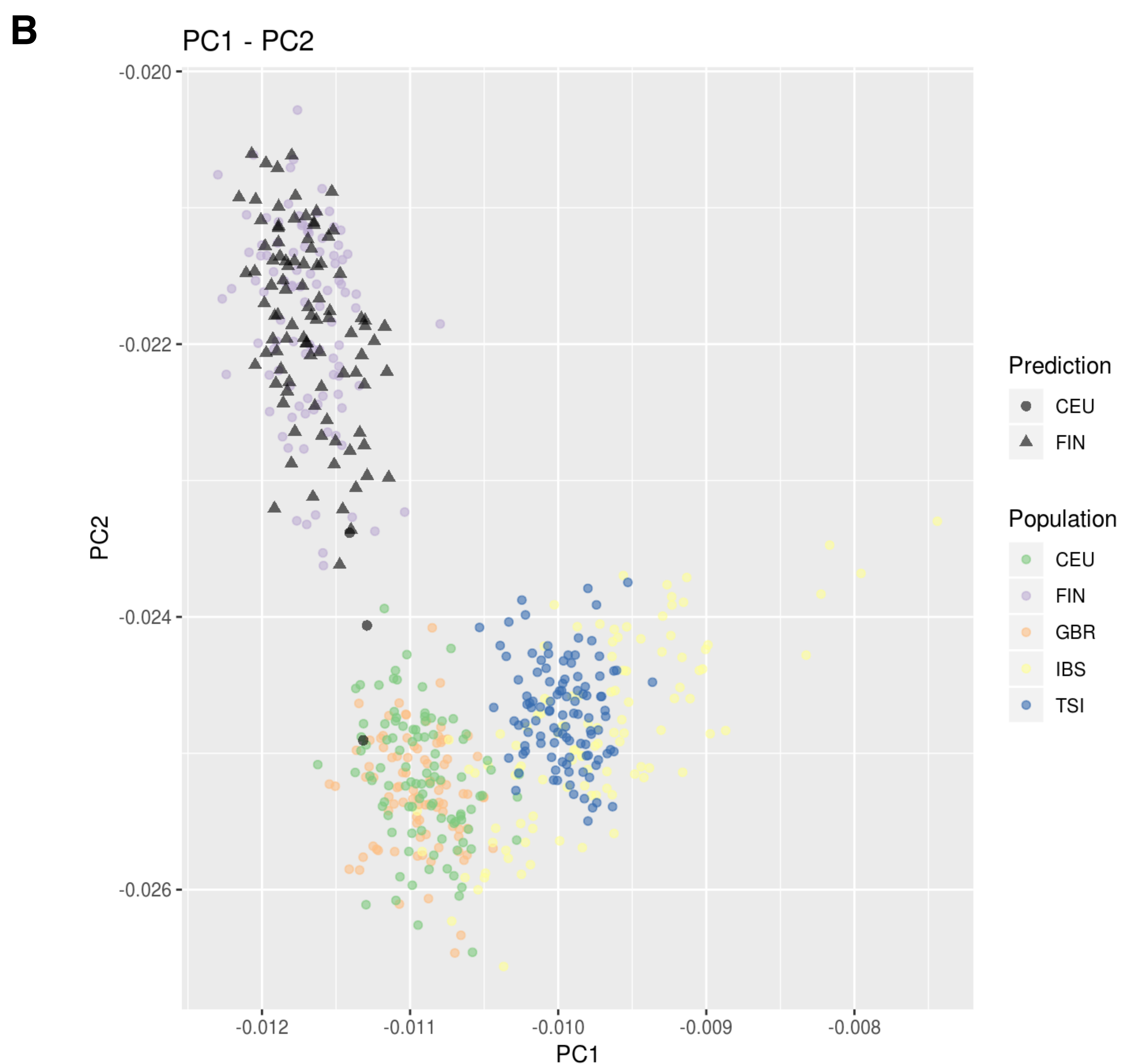
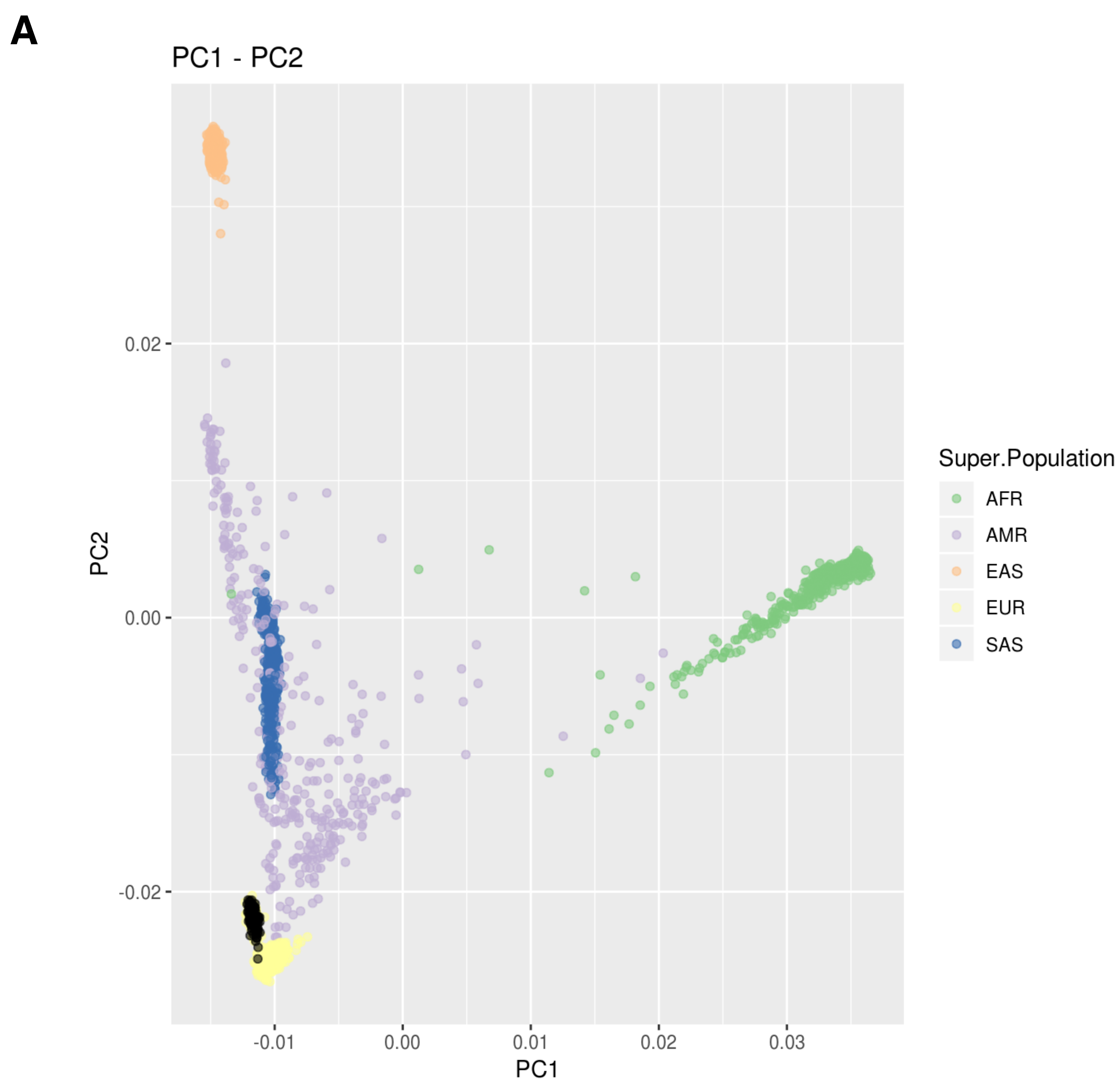
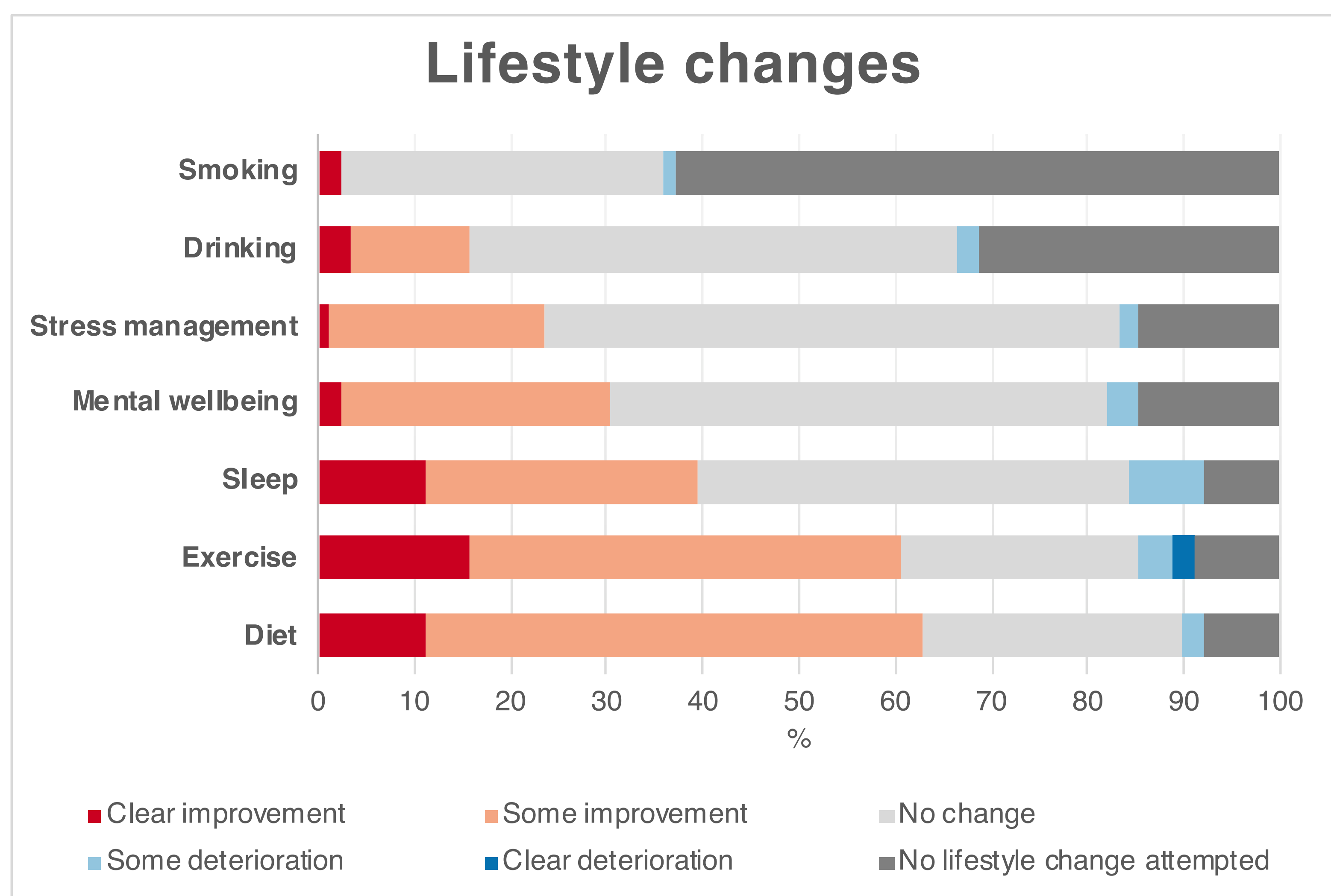
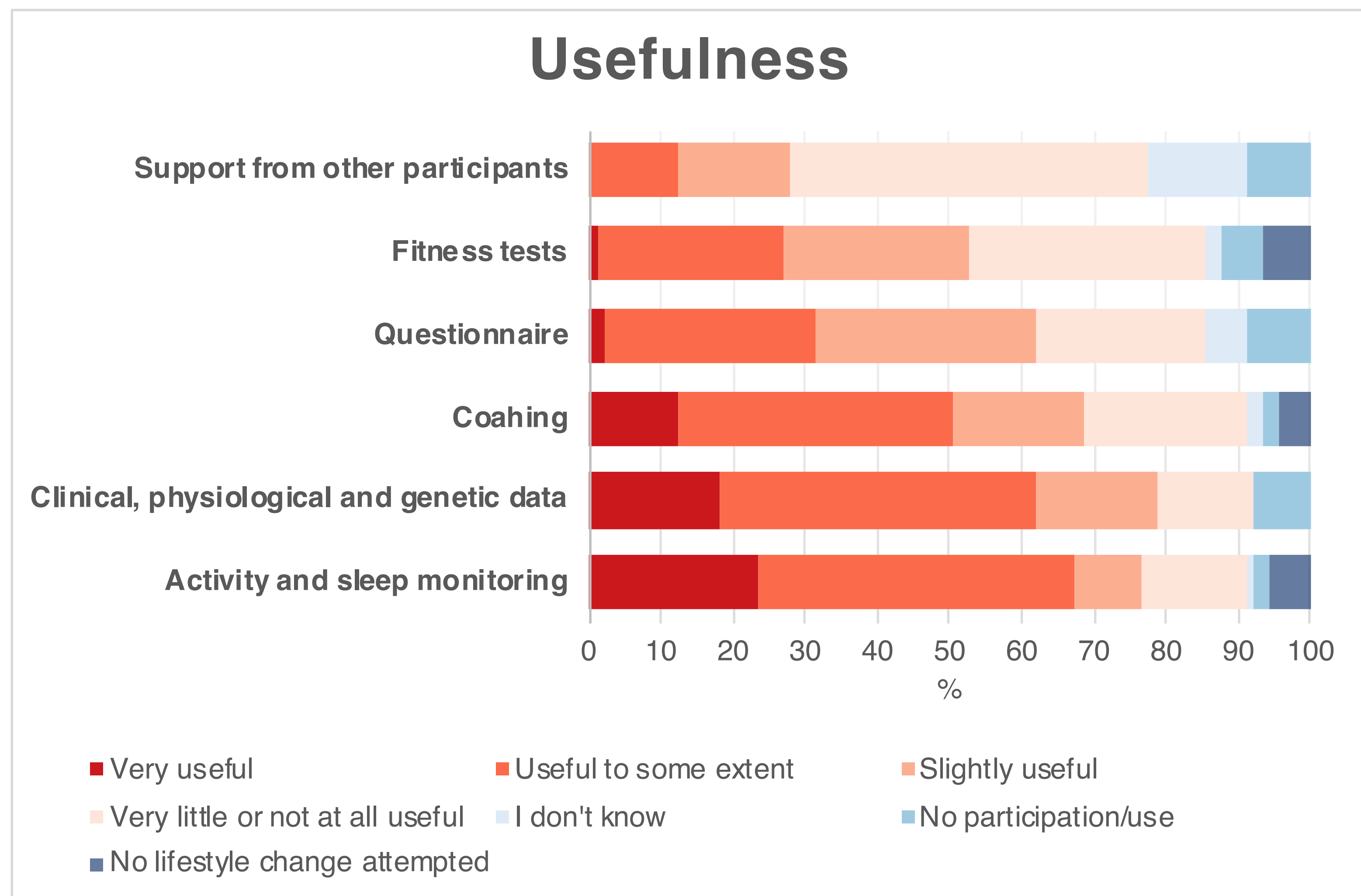
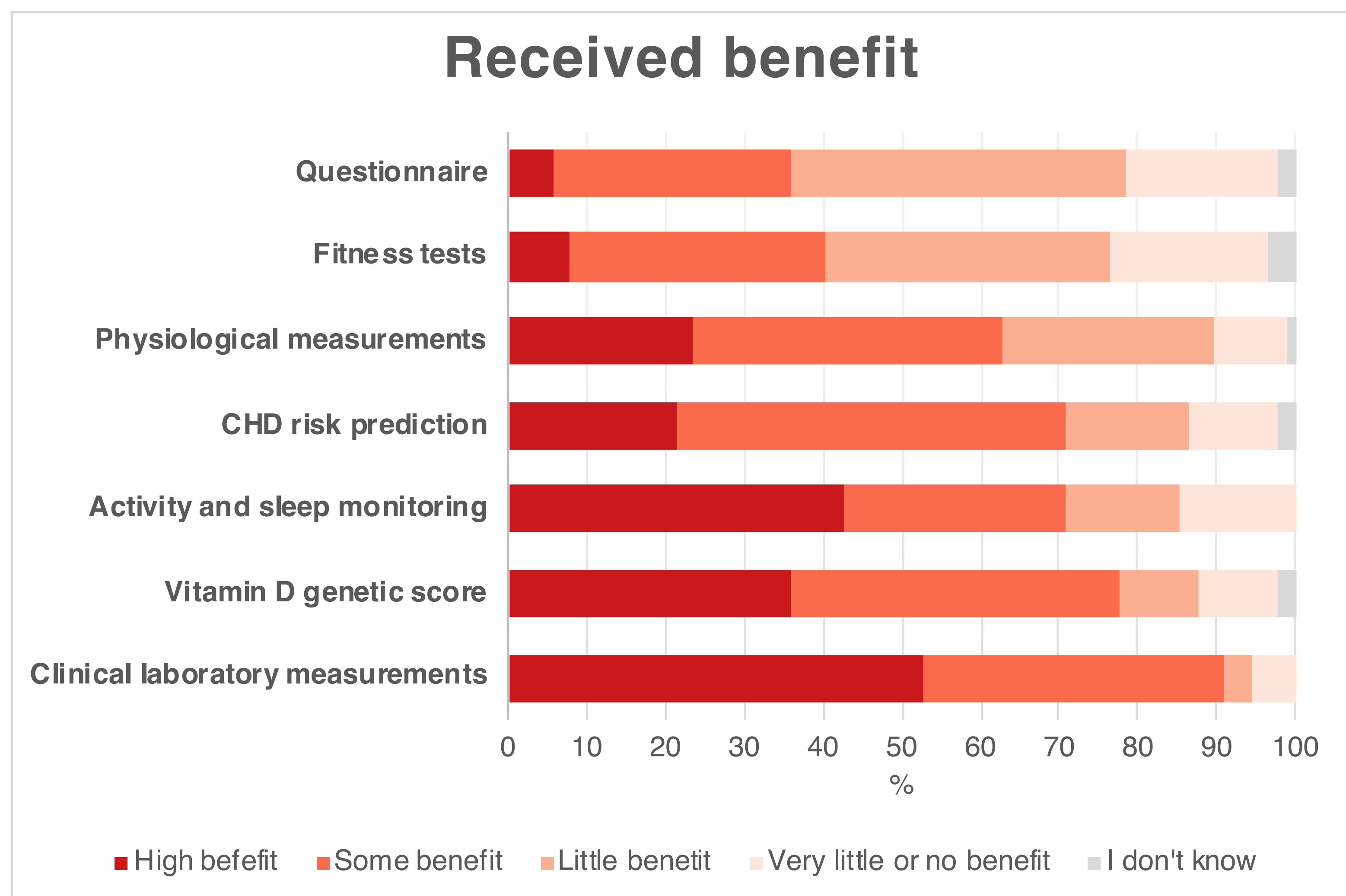


**Supplementary figure 1: A.** Study flowchart showing the number of individuals from the recruitment to the end of the study. **B.** The visit date for each individual is shown. Every row corresponds to an individual and the dots to the corresponding five study visits.

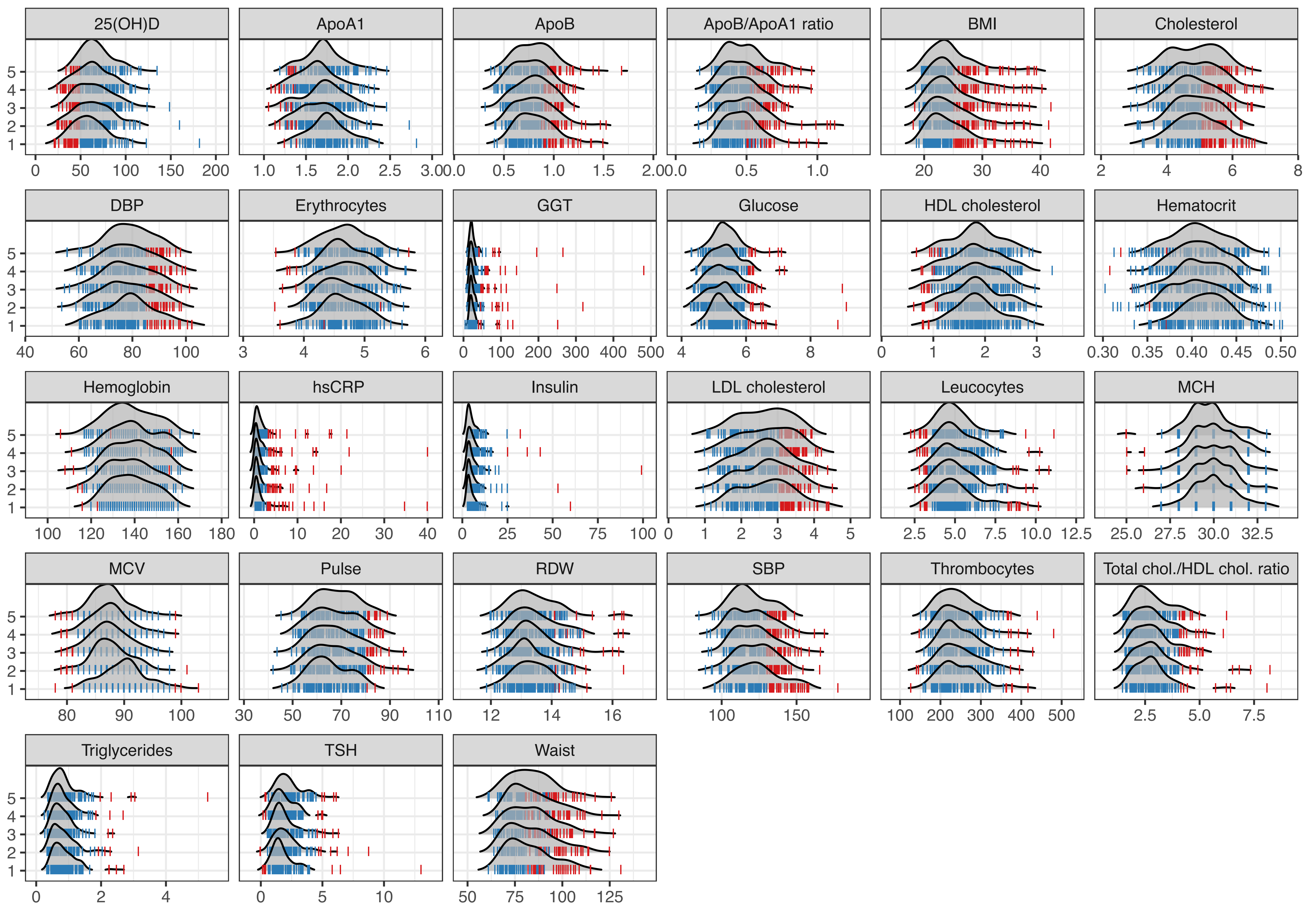


**Supplementary figure 2:** Population stratification plots obtained with PCA analysis using a LD-pruned biallelic set of SNPs. The DHR individuals are shown in black while the other individual from the 1000 Genome phase 3 project are shown in different colors, according to their respective population. **A.** All 1000G samples together with the DHR individuals. **B.** Only the individuals from the EUR super-population are shown with colored points. The DHR individuals are shown in black, while the symbol denotes the predicted population according to a Linear Discriminant Analysis model

**A****B****C**

**Supplementary figure 3. A.** Perceived lifestyle changes. Question: “Do you feel that a change has occurred in the following factors during the study?”. **B.** Usefulness of the data to make lifestyle changes. Question: “Were the following useful to make lifestyle changes?” **C.** Received benefit. Question: “Did you benefit from the following results/information that you received during the study?”

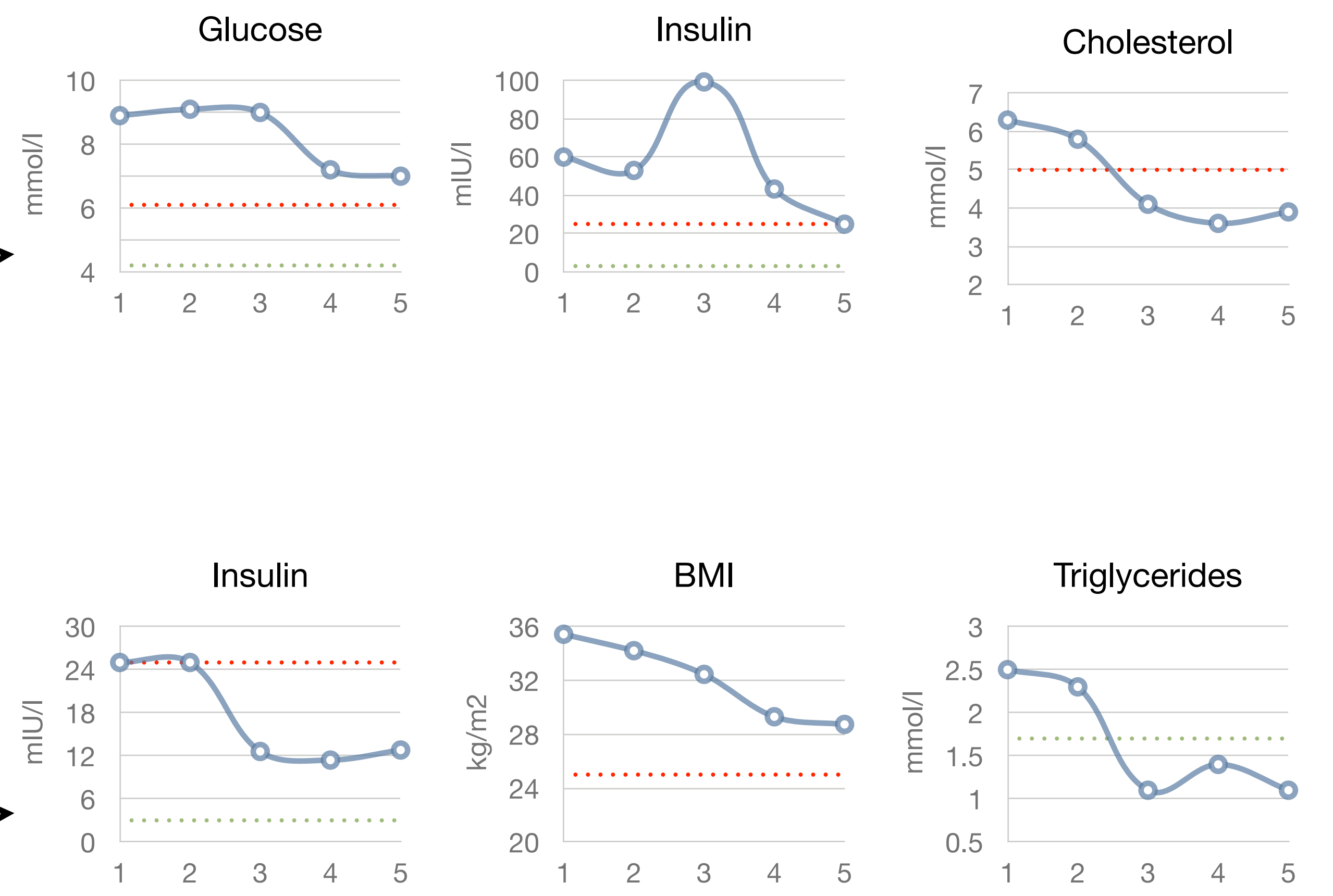
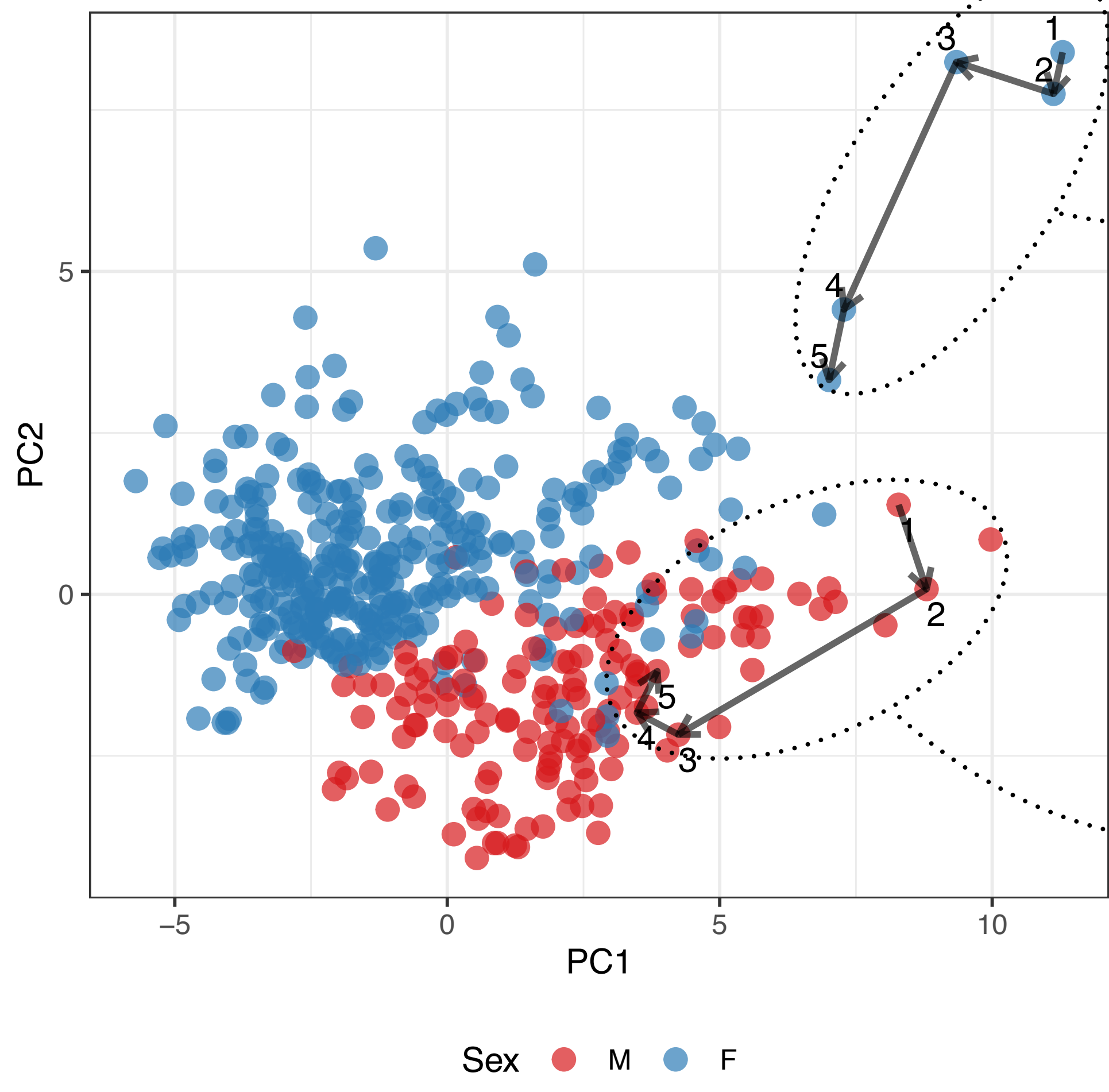




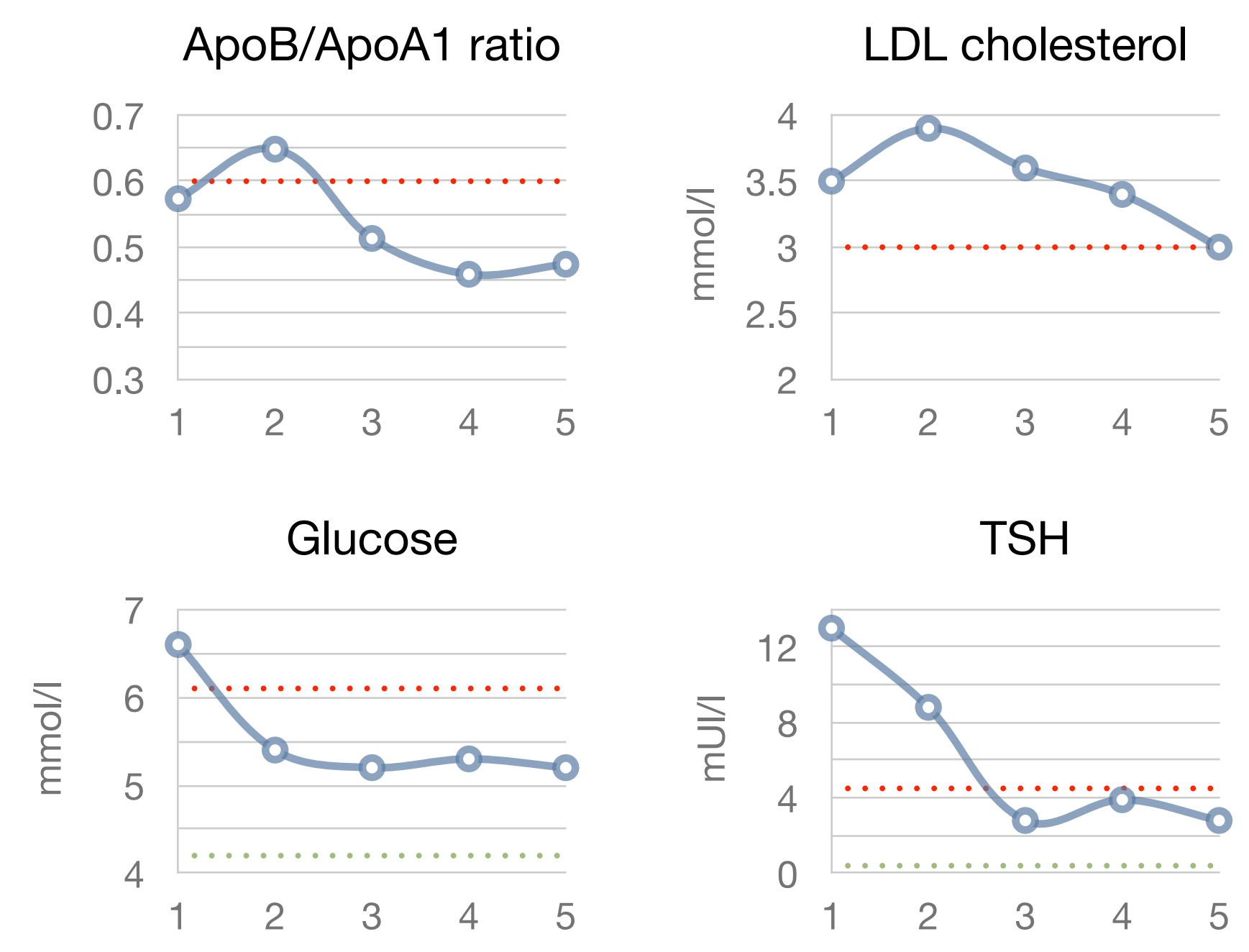
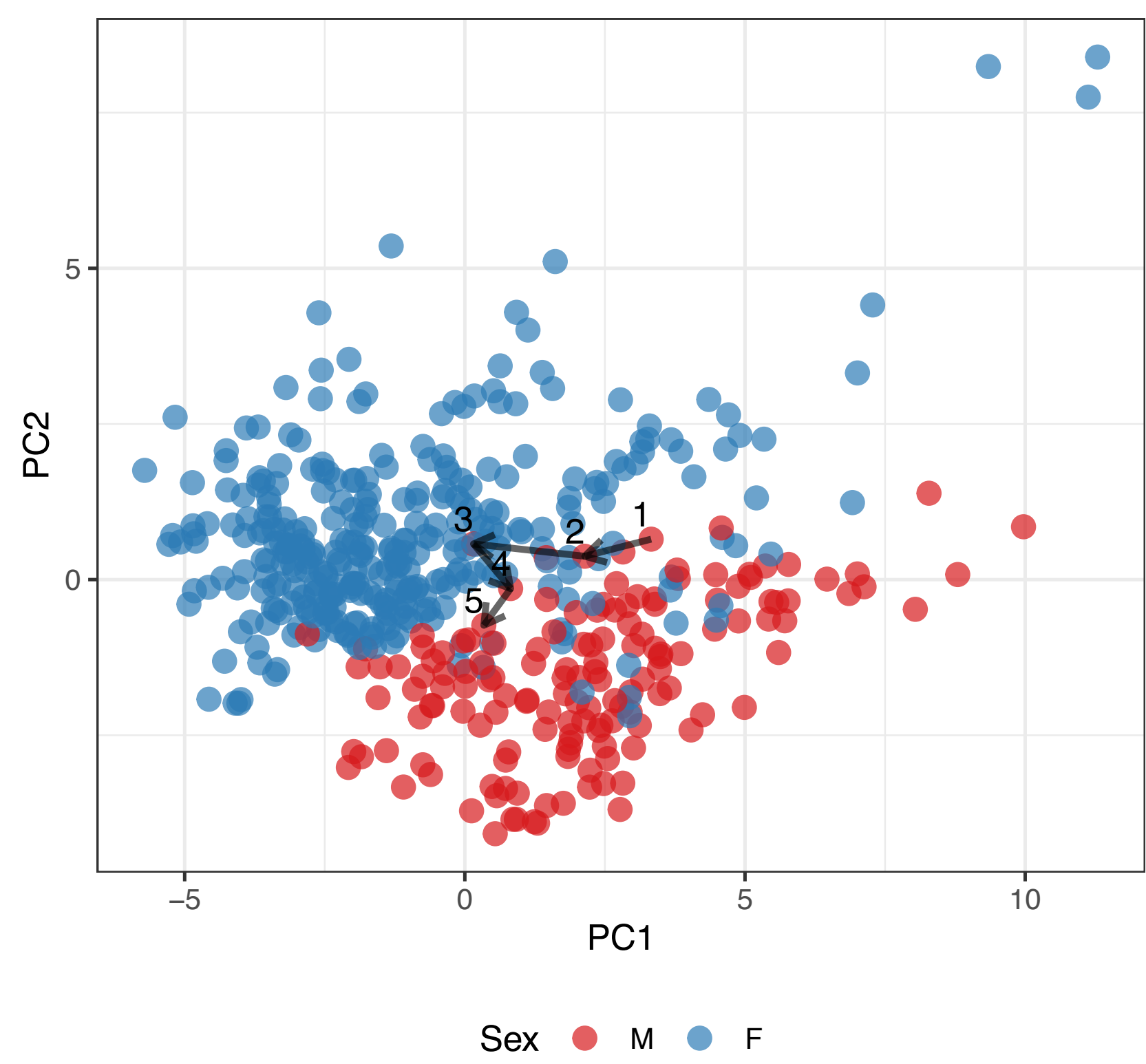
**Supplementary figure 4:** Distribution of the values of the clinical variables. Density distributions were obtained for each visit and variable and shown separately. Vertical lines indicate individual values and are coloured according to their Out-Of-Range status (blue: within range, Red: out of range).



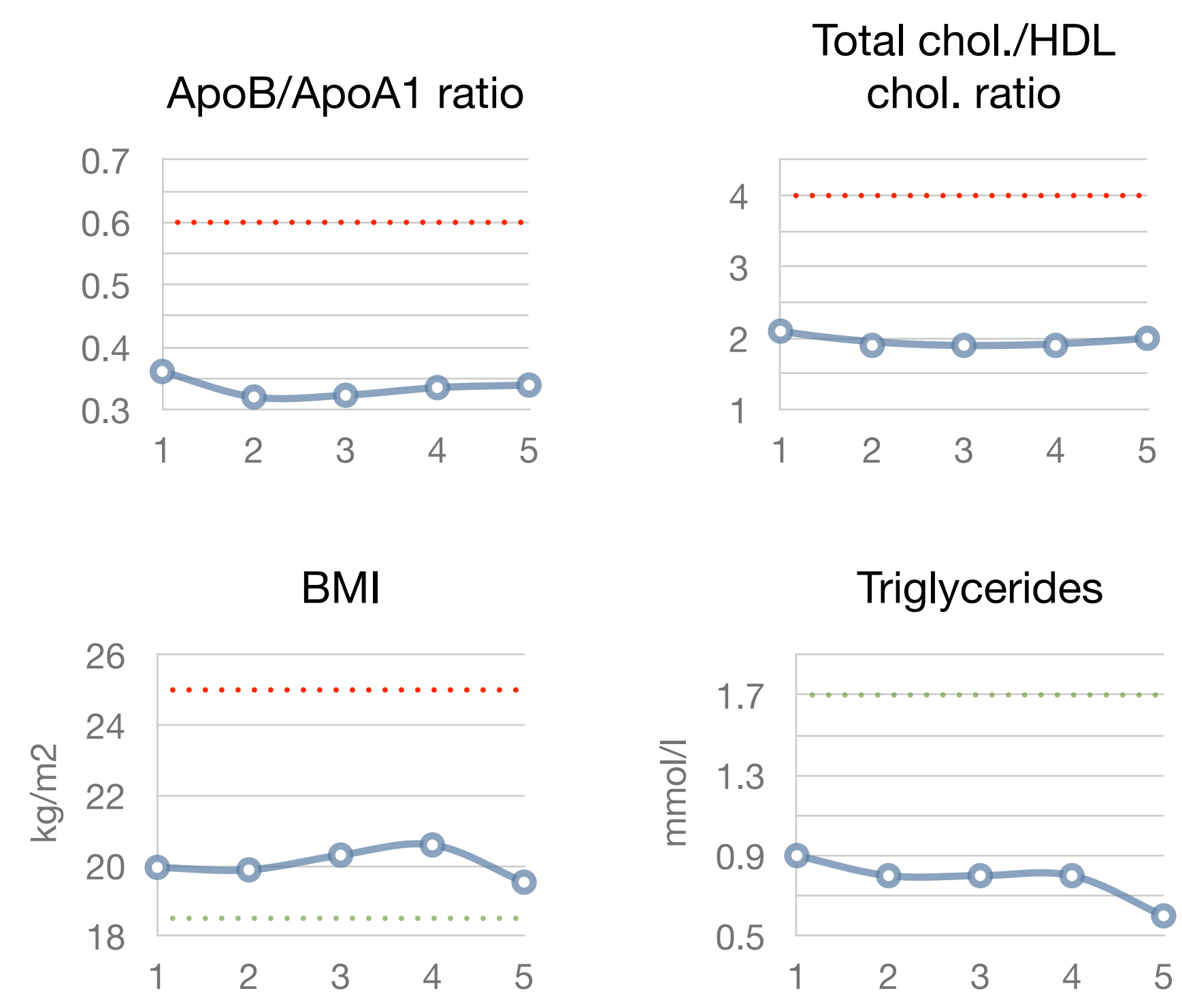
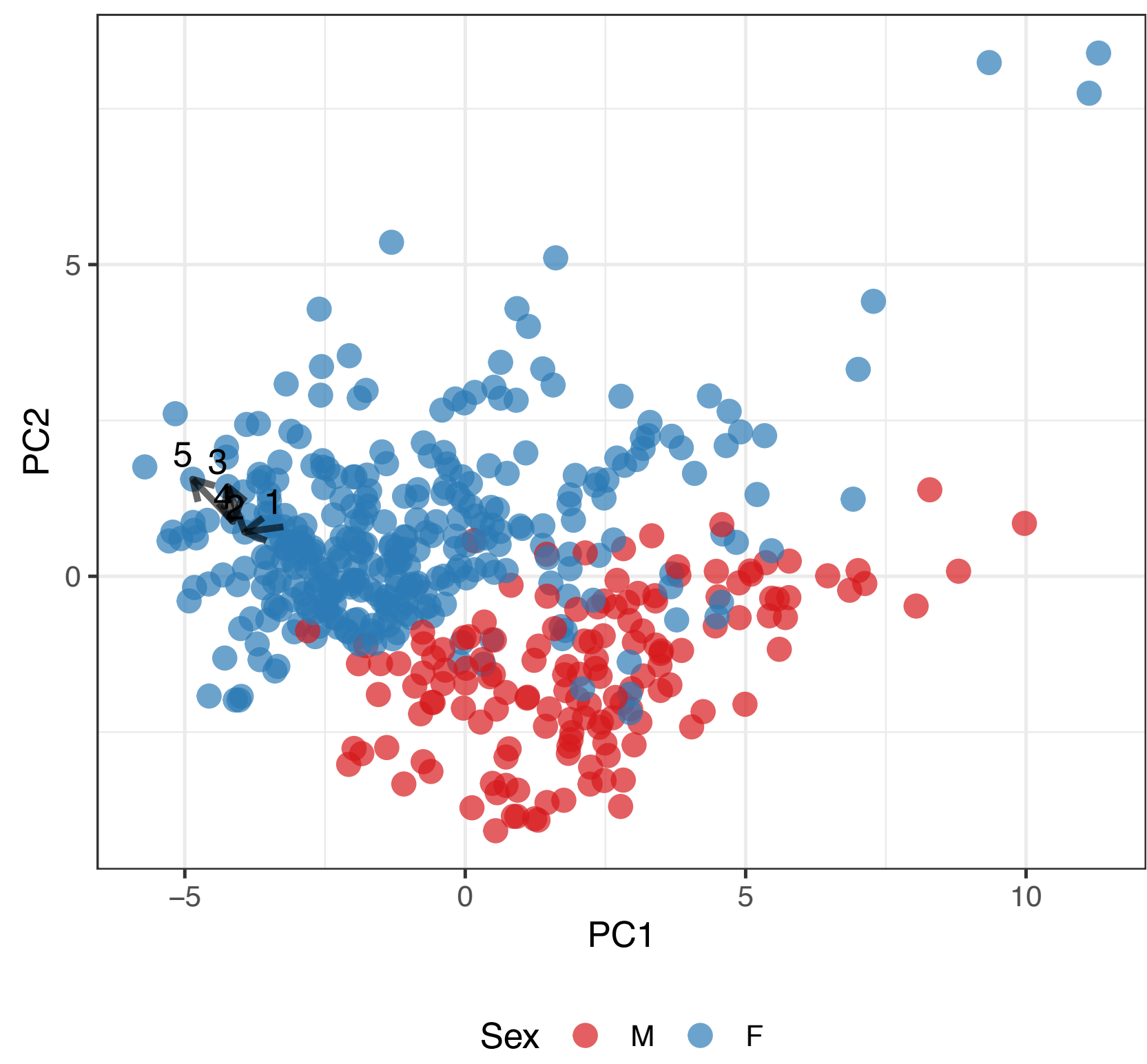
### Longitudinal changes - long trajectory



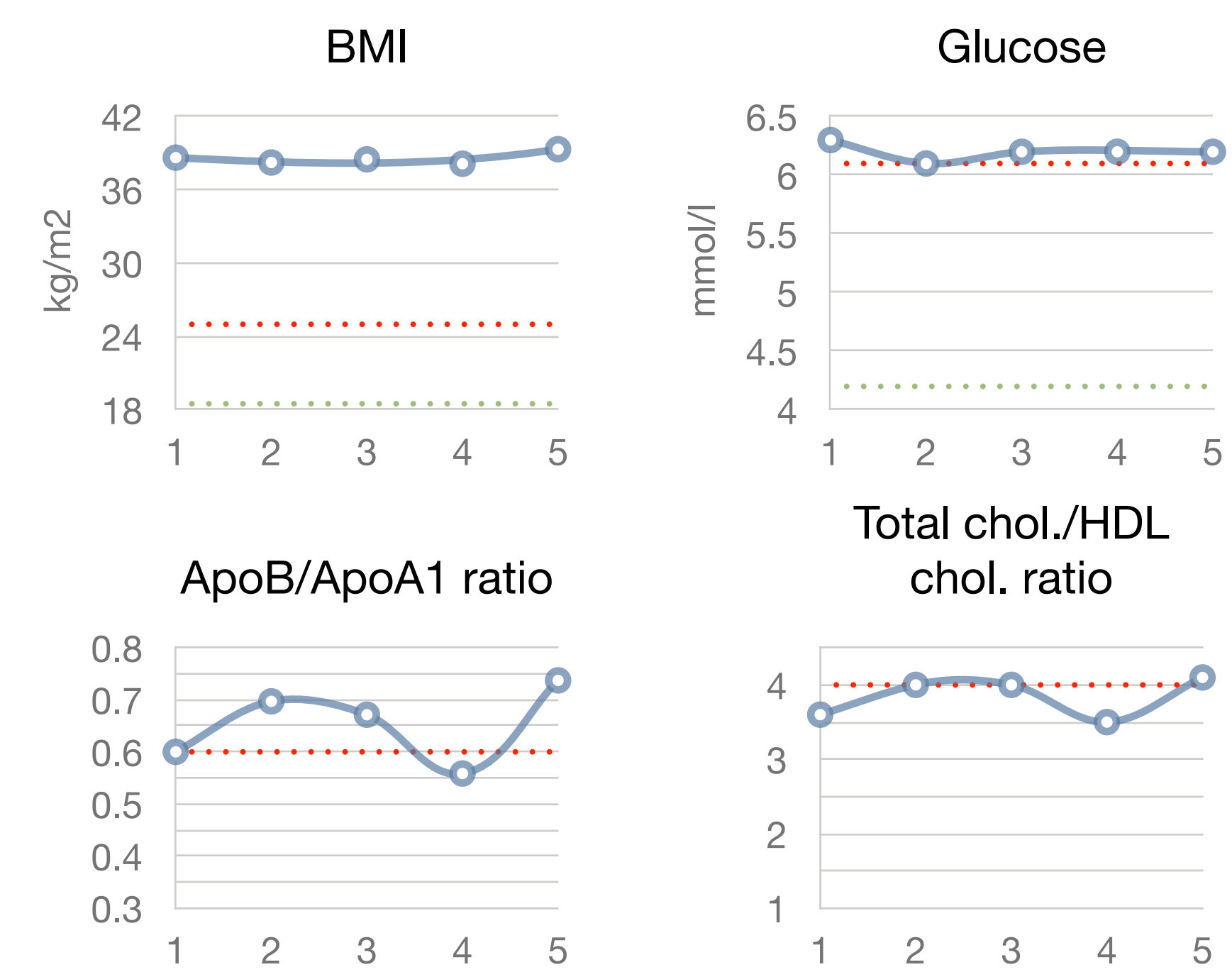
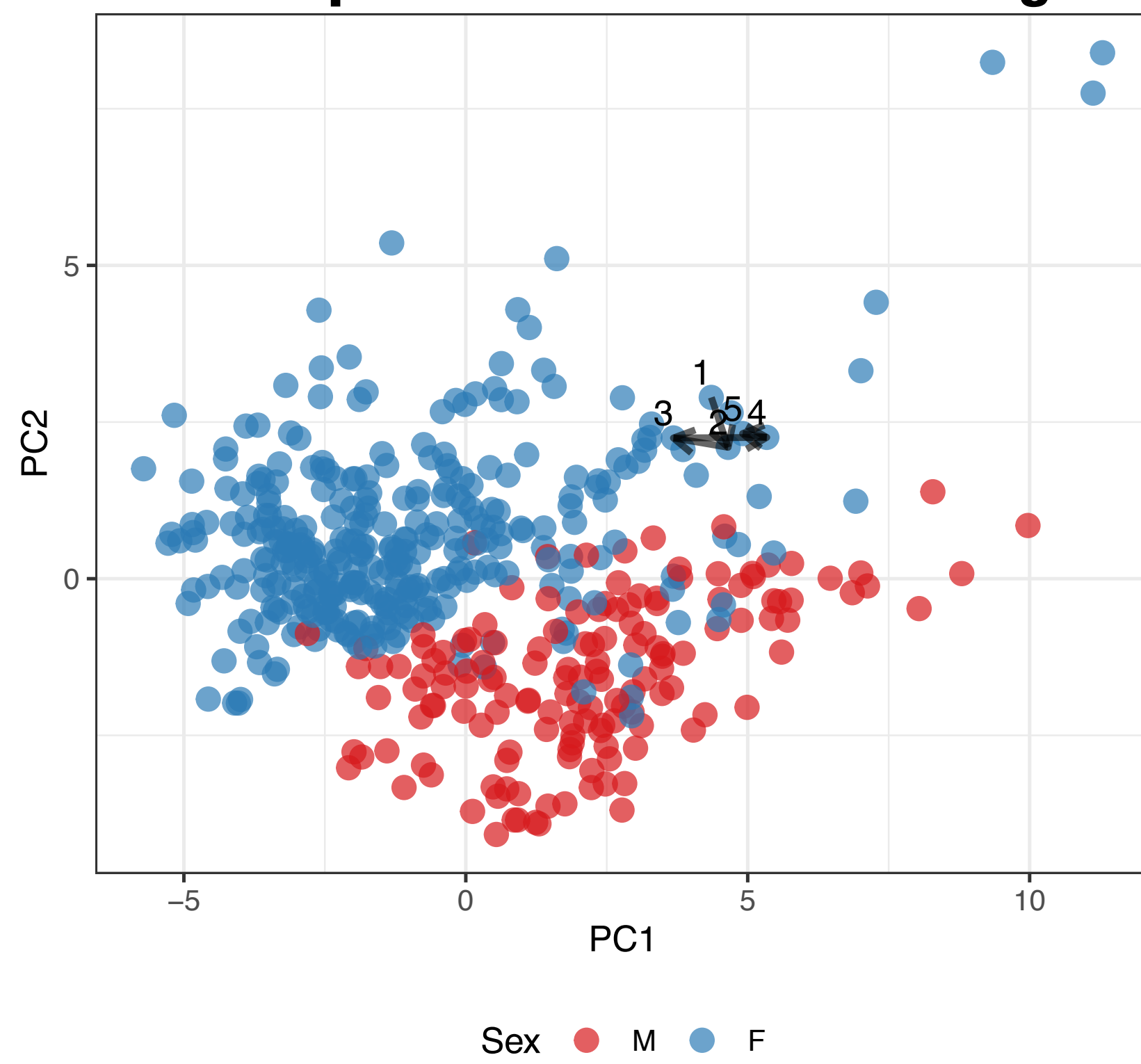
### Longitudinal changes - short trajectory



### Stable profile - values within range

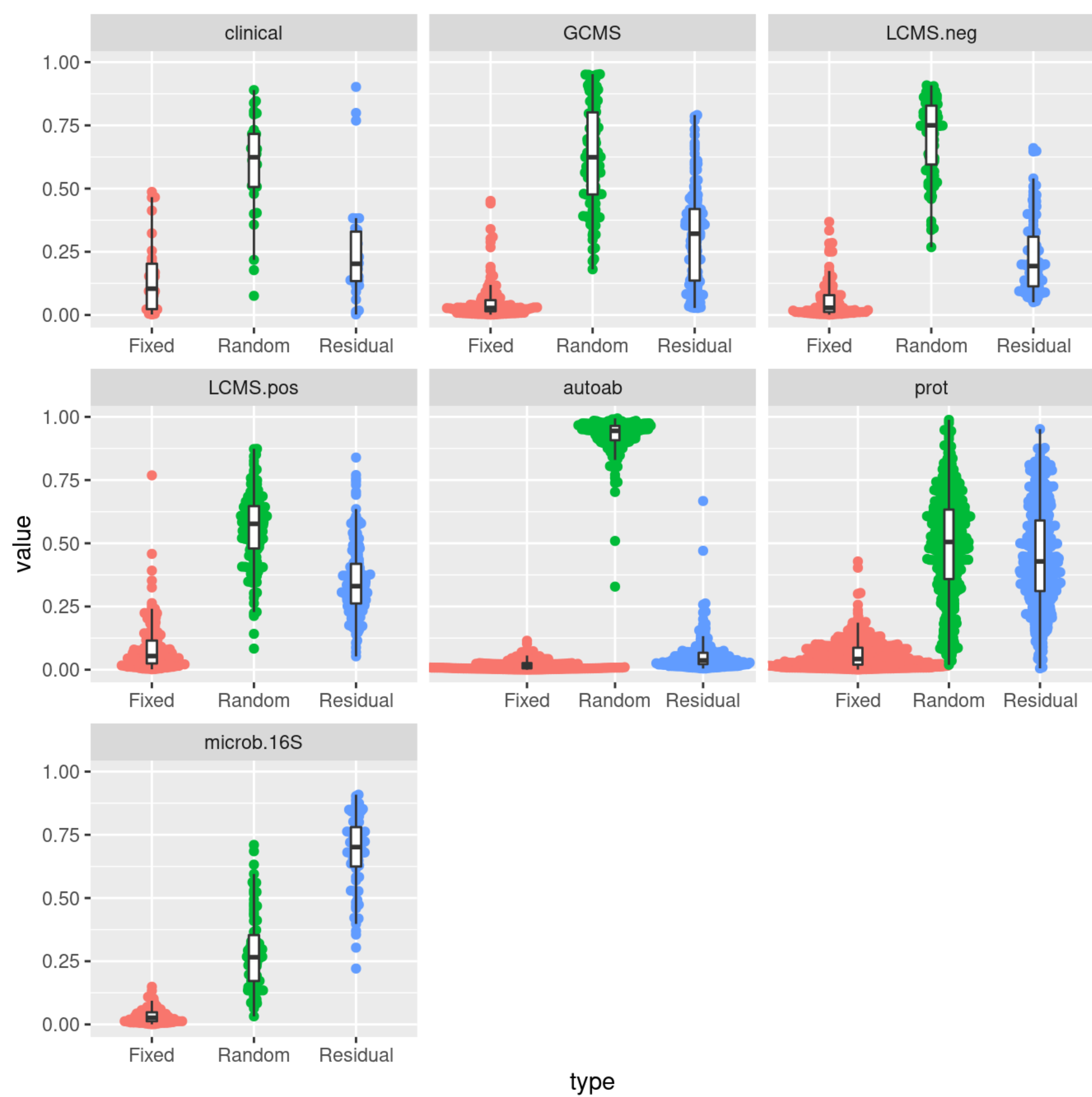


### Stable profile - values out of range



**Supplementary figure 5 (previous page):** Extended main figure 2. **A.** Principal components plot of the individuals obtained using all the numerical clinical variables. The trajectories for five individuals across successive study visits are shown with arrows, along with the corresponding values for selected clinical variables.



**A****B**

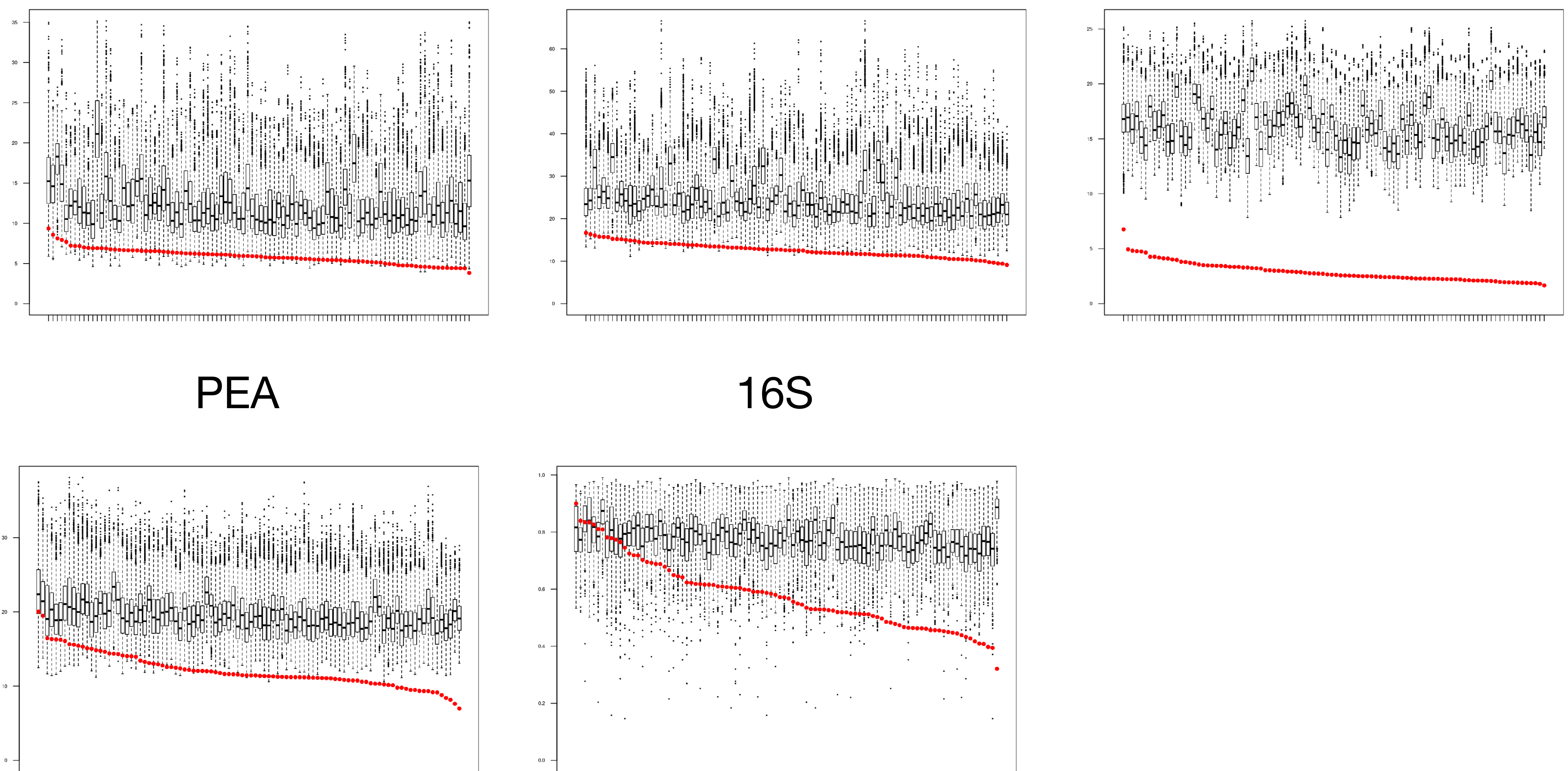
GCMS

LCMS

Autoantibodies

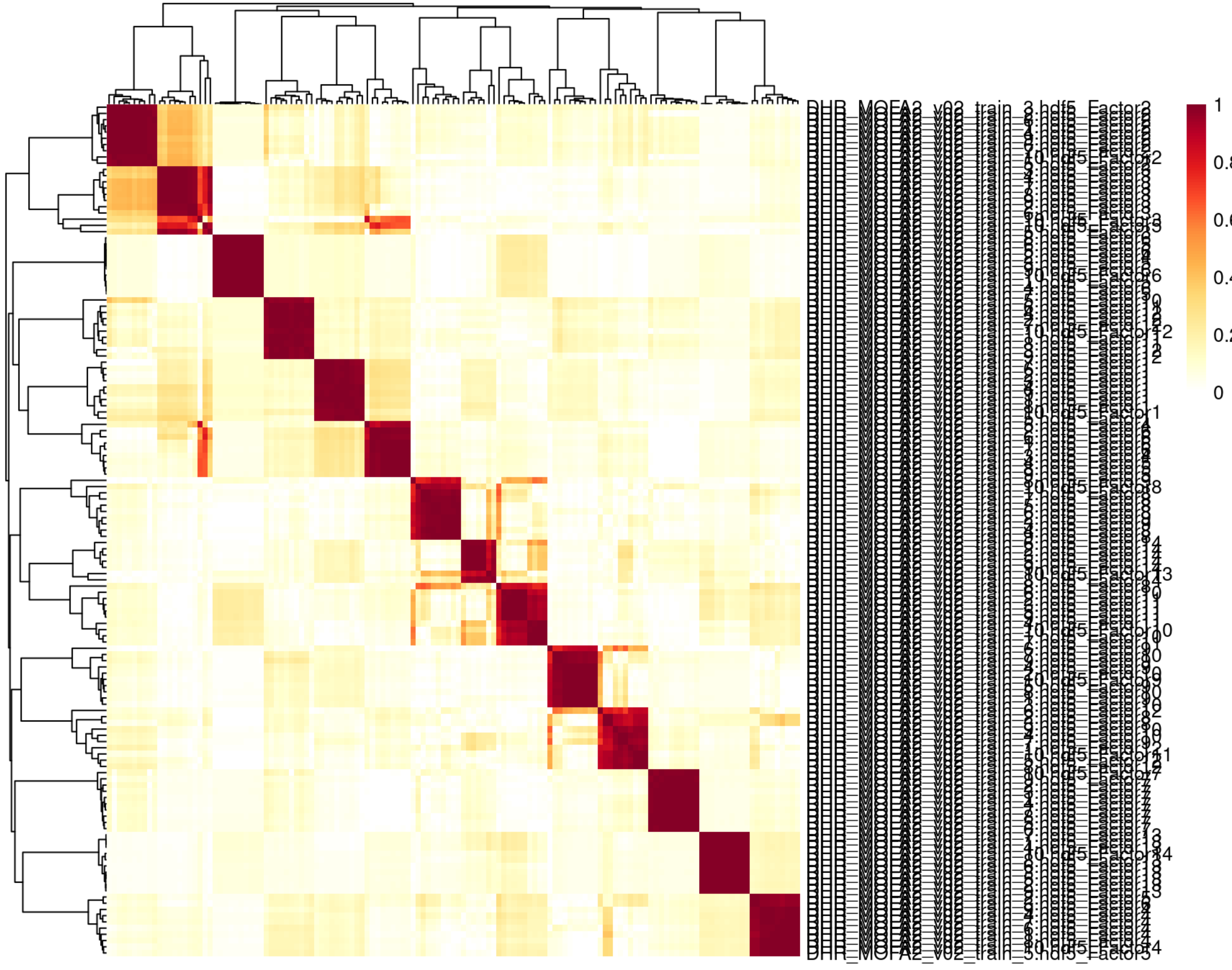
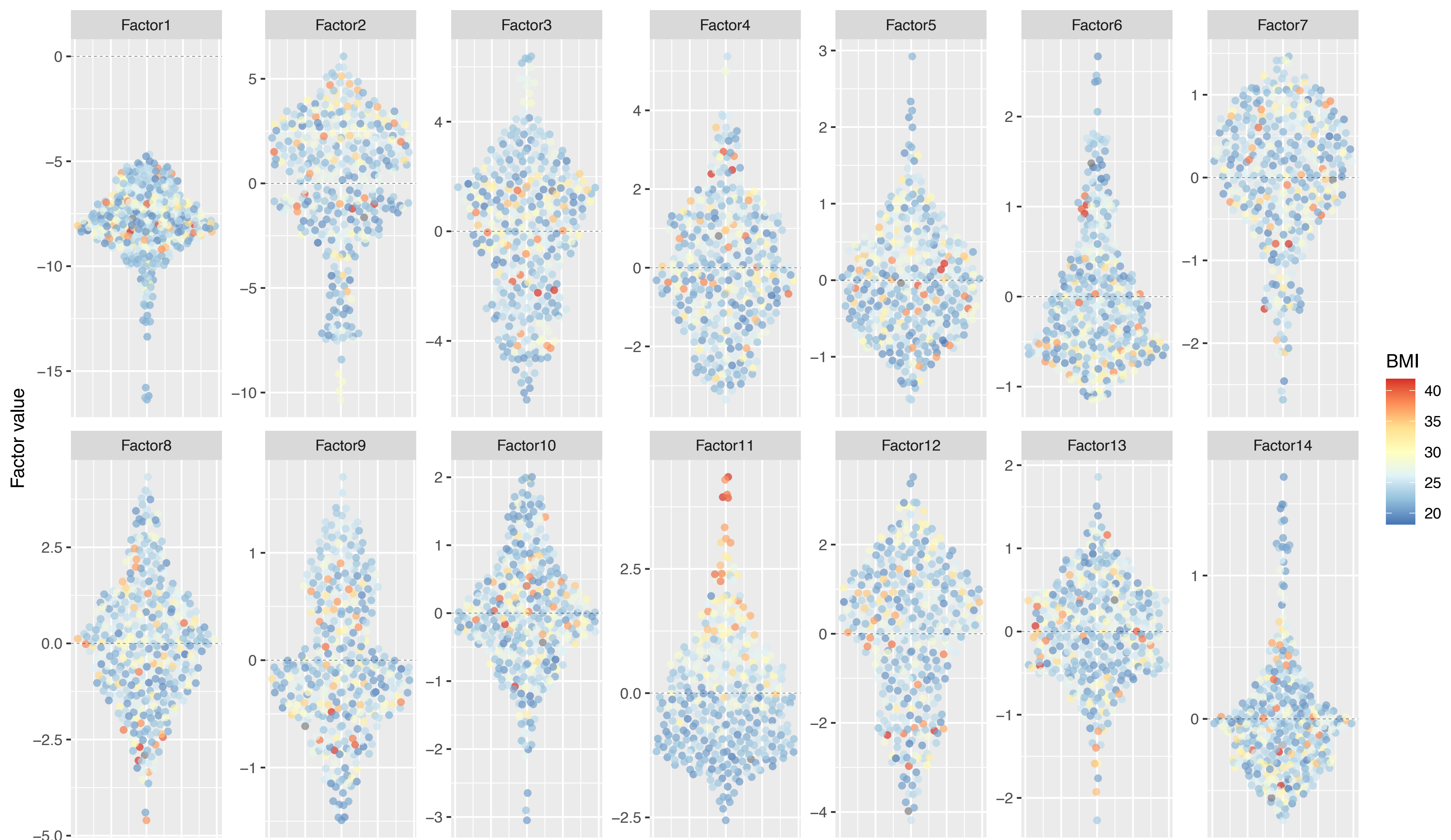
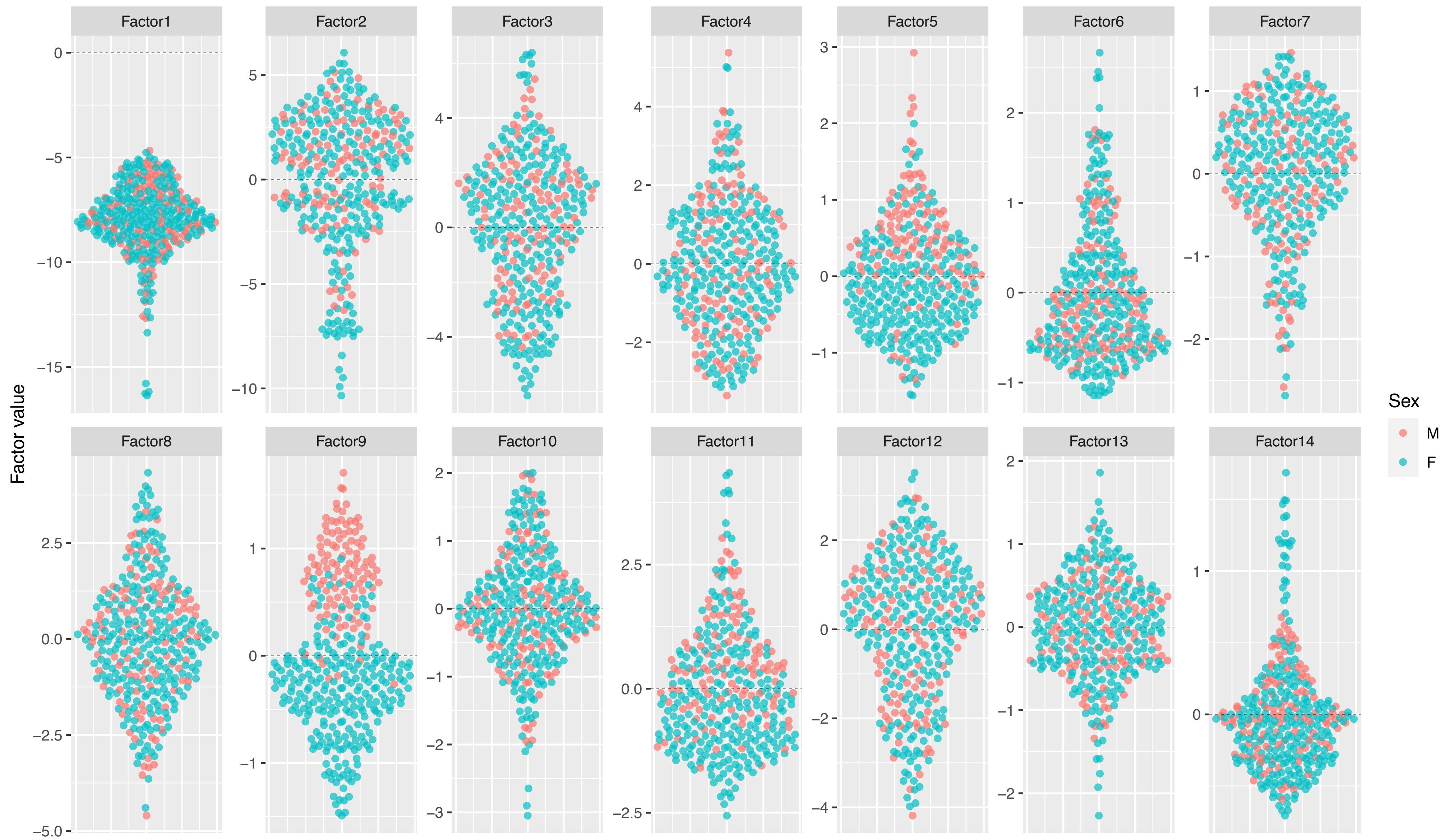
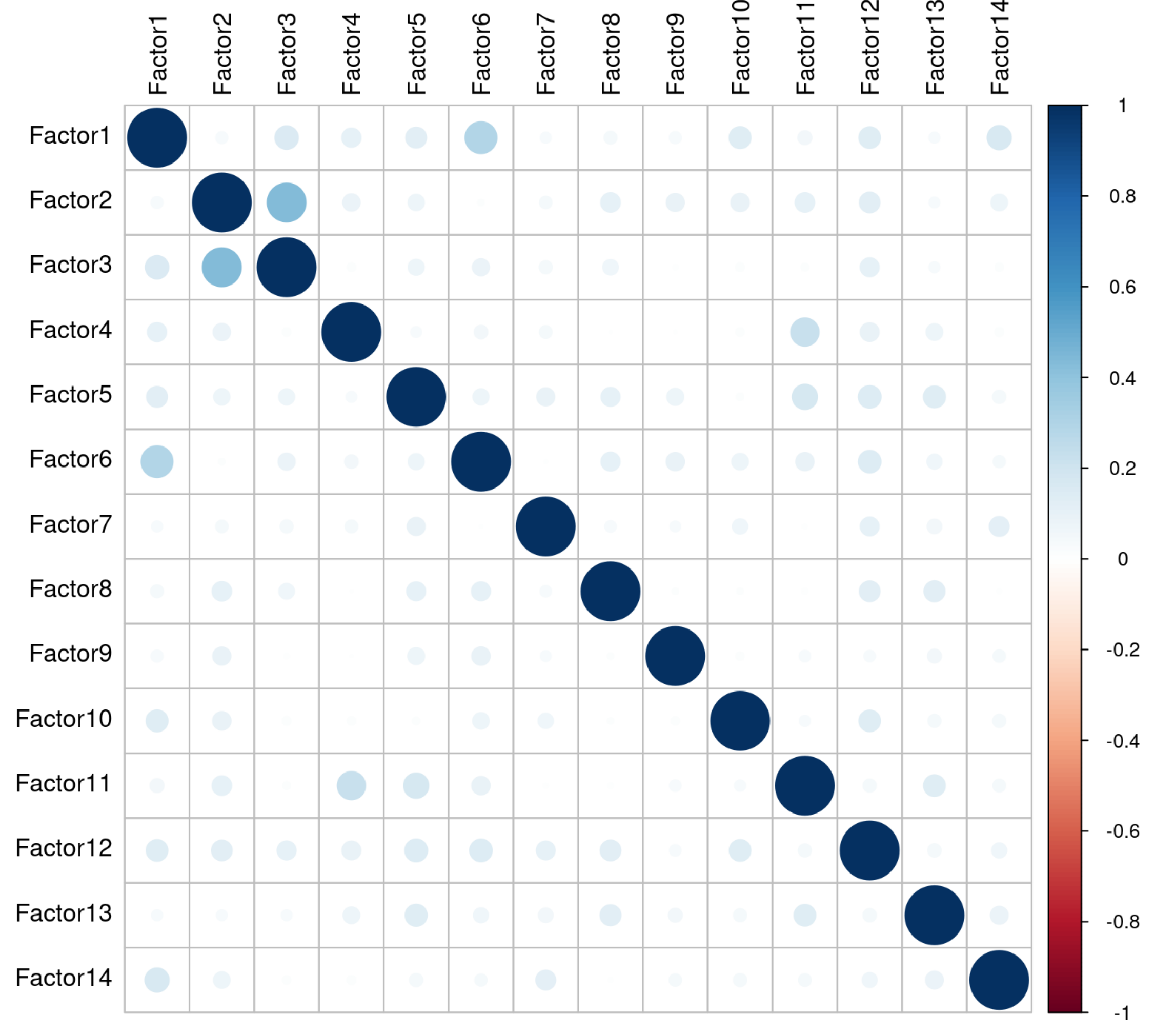
PEA

16S



**Supplementary figure 6: Variance partitioning analysis. A.** A linear mixed model was fitted independently to each feature. We included the individual as a random intercept and age, sex, time point and phenotypic subgroup as fixed effects. The fixed effect variance, random intercept variance and residual variance components were extracted and the relative fraction plotted. **B.** Each column represents an individual and show the distribution of the Euclidean distances between each individual and the rest of the individuals. A red dot indicates the median value of the distances obtained with the pairs of samples from the same individual (within-individual distance).

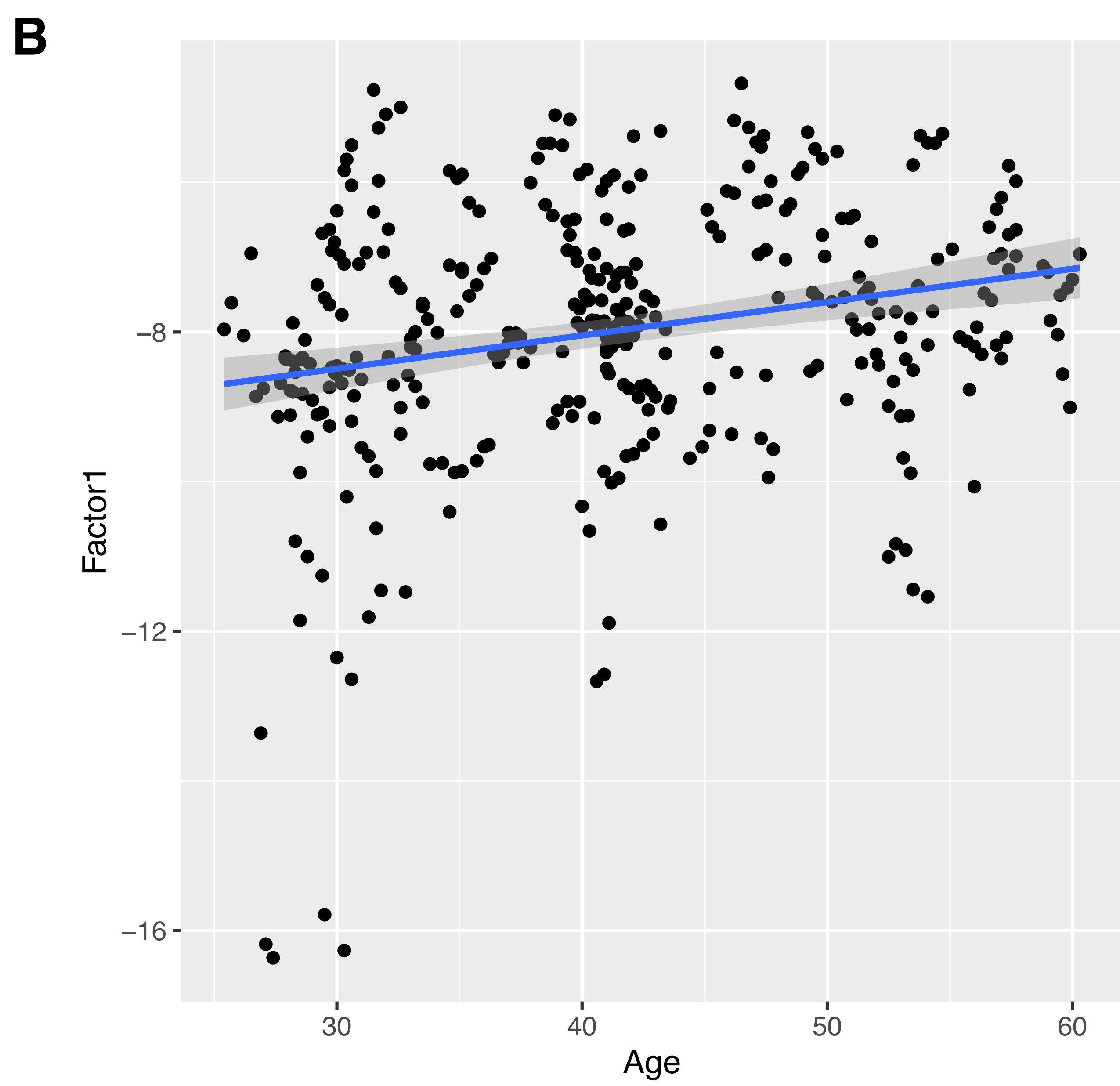
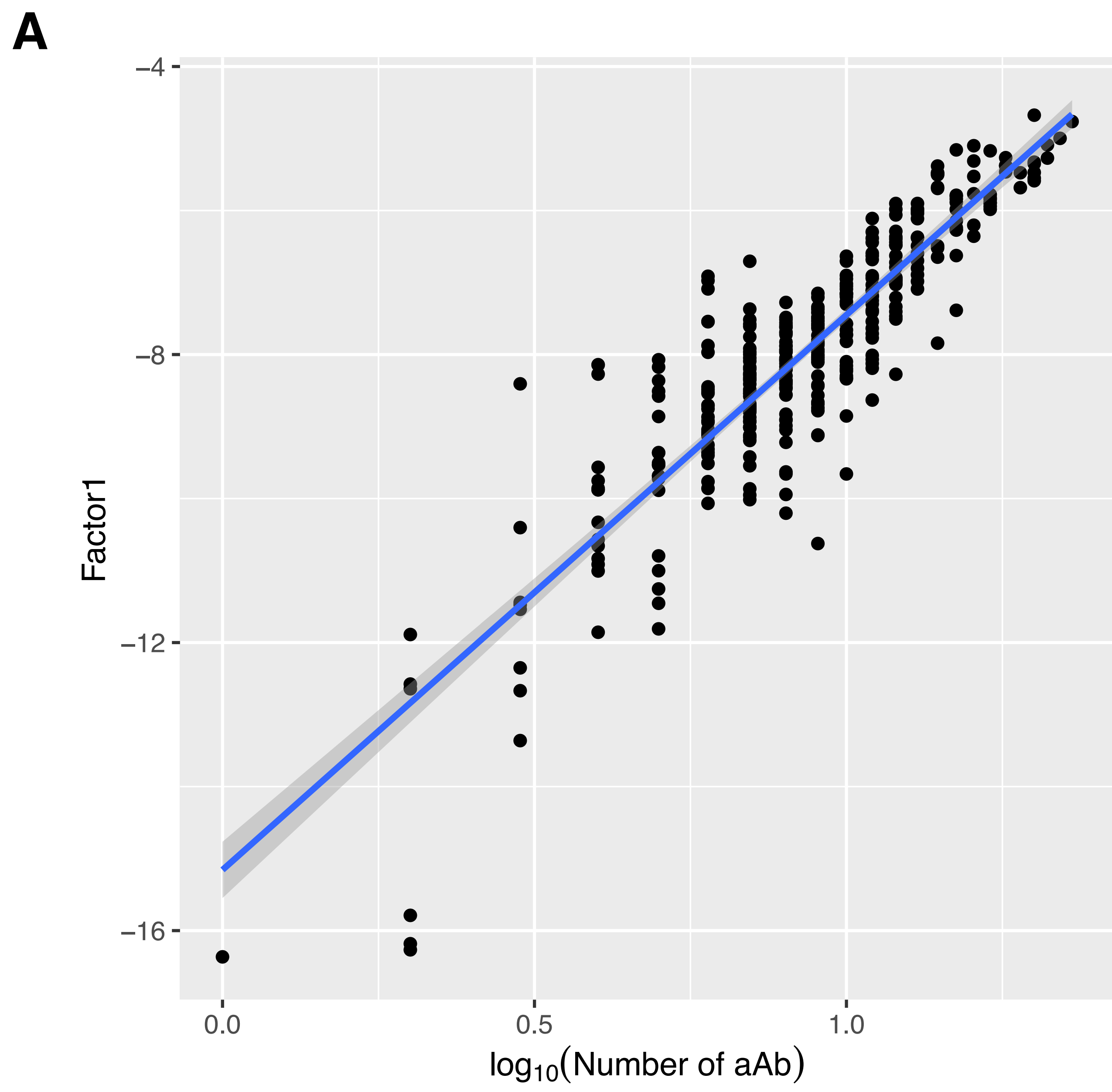


**A****B**



**Supplementary figure 7 (previous page):** **A:** Ten different models were trained with random initialization and then the consistency of the learned factors across multiple runs was assessed with the absolute Pearson correlation coefficients between pairs of factors. **B:** The model with the highest ELBO was selected and the Pearson correlation matrix between the factors is shown. **C:** Factor values are shown for all samples as points and coloured based on sex (upper panel) or BMI (lower panel).



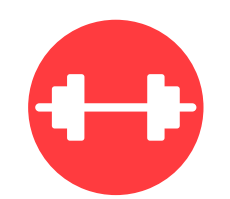
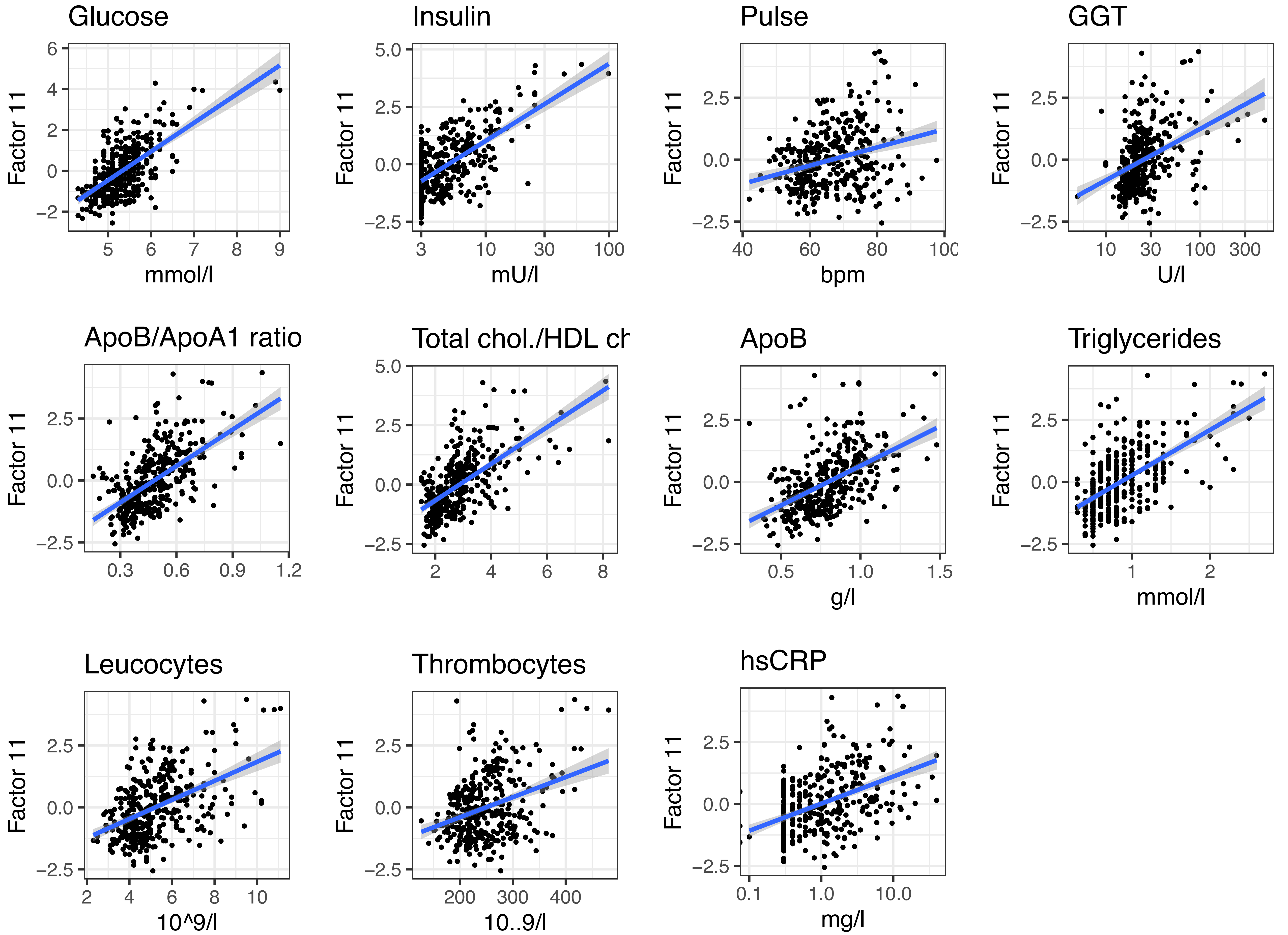


**Supplementary figure 8: A.** Factor 1 is associated with the number of detected autoantibodies. **B.** A scatterplot of the individual's age vs. Factor 1 values. Regression lines are shown with 95% confidence intervals.

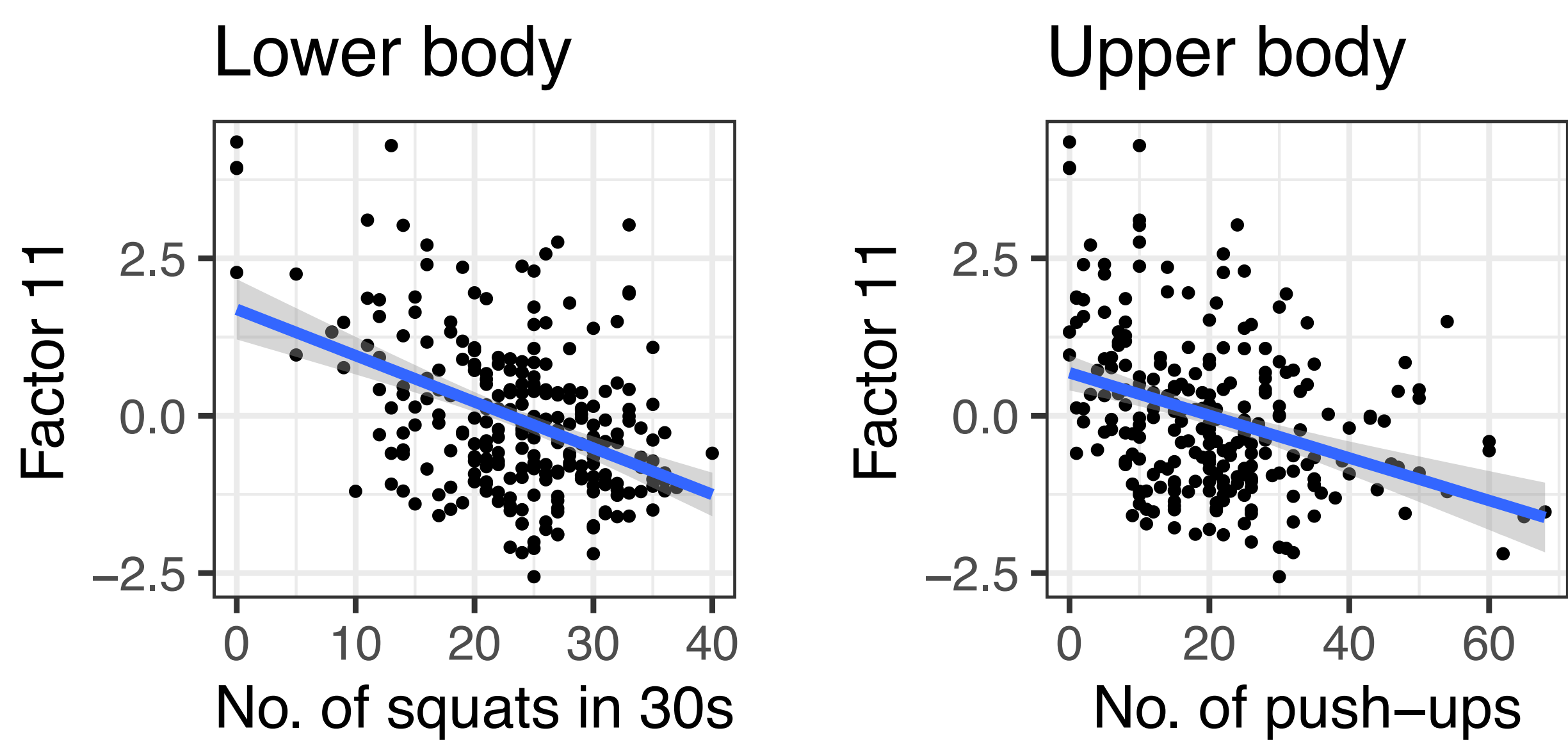




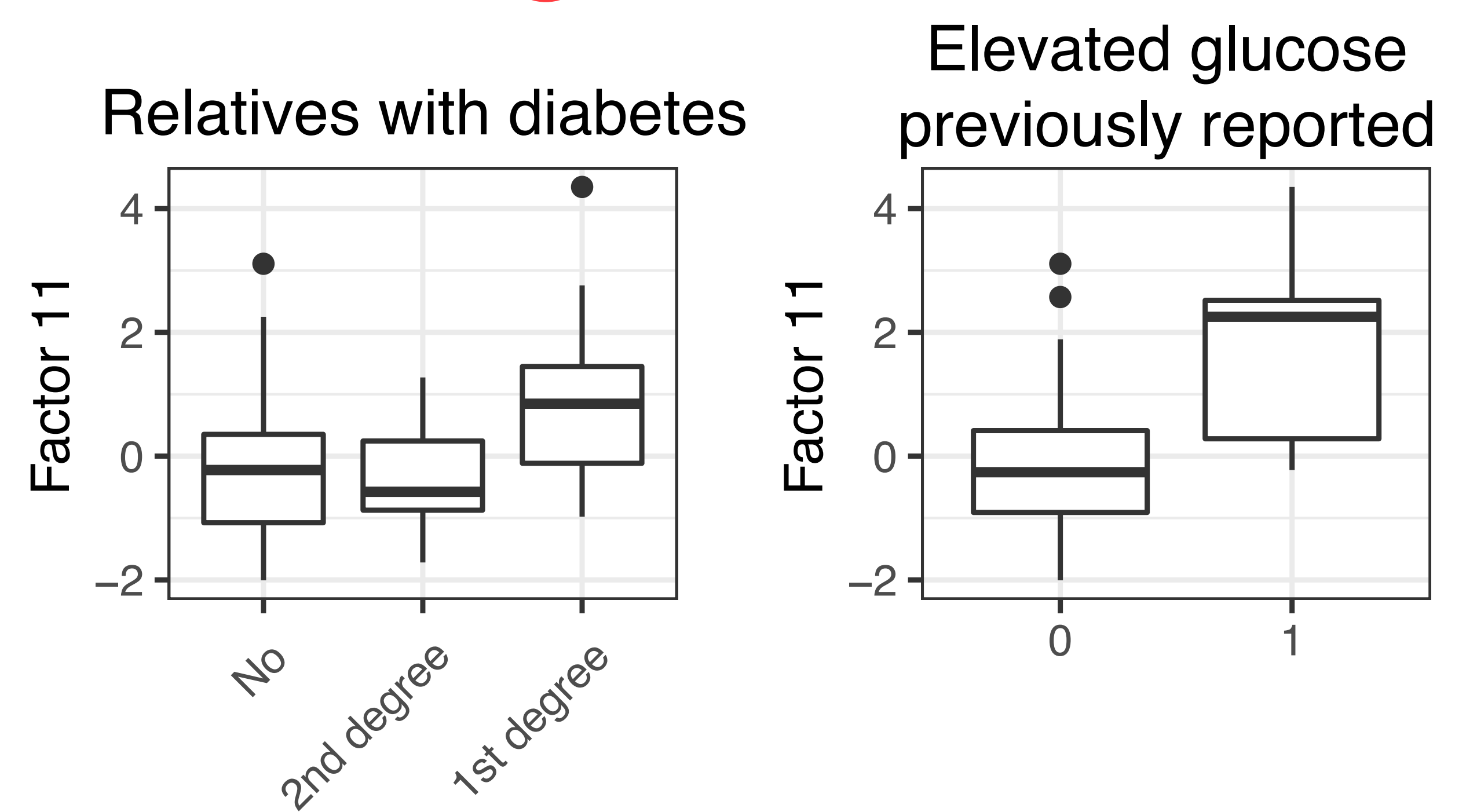
## Clinical variables



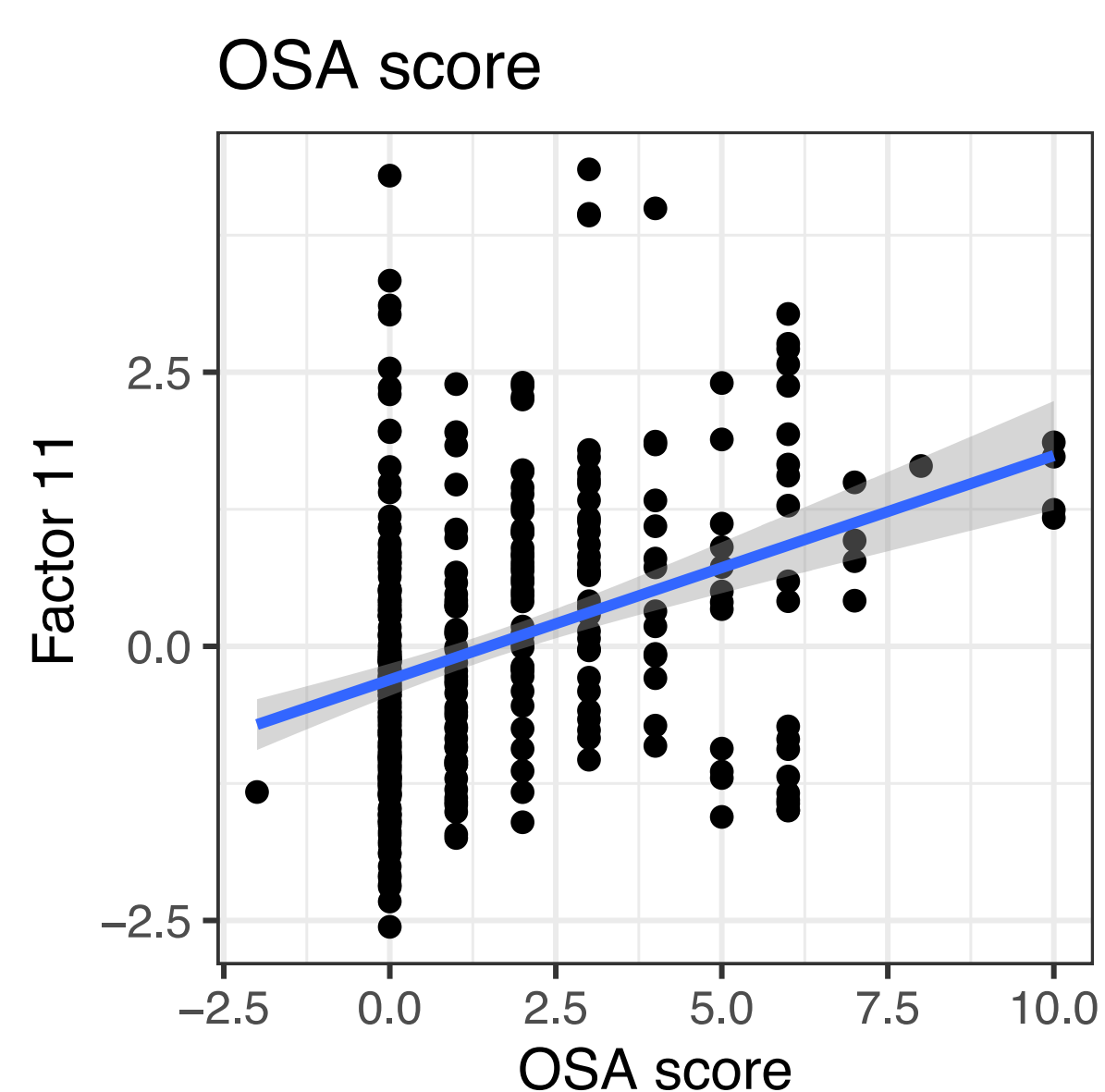
## Fitness tests



## Questionnaire



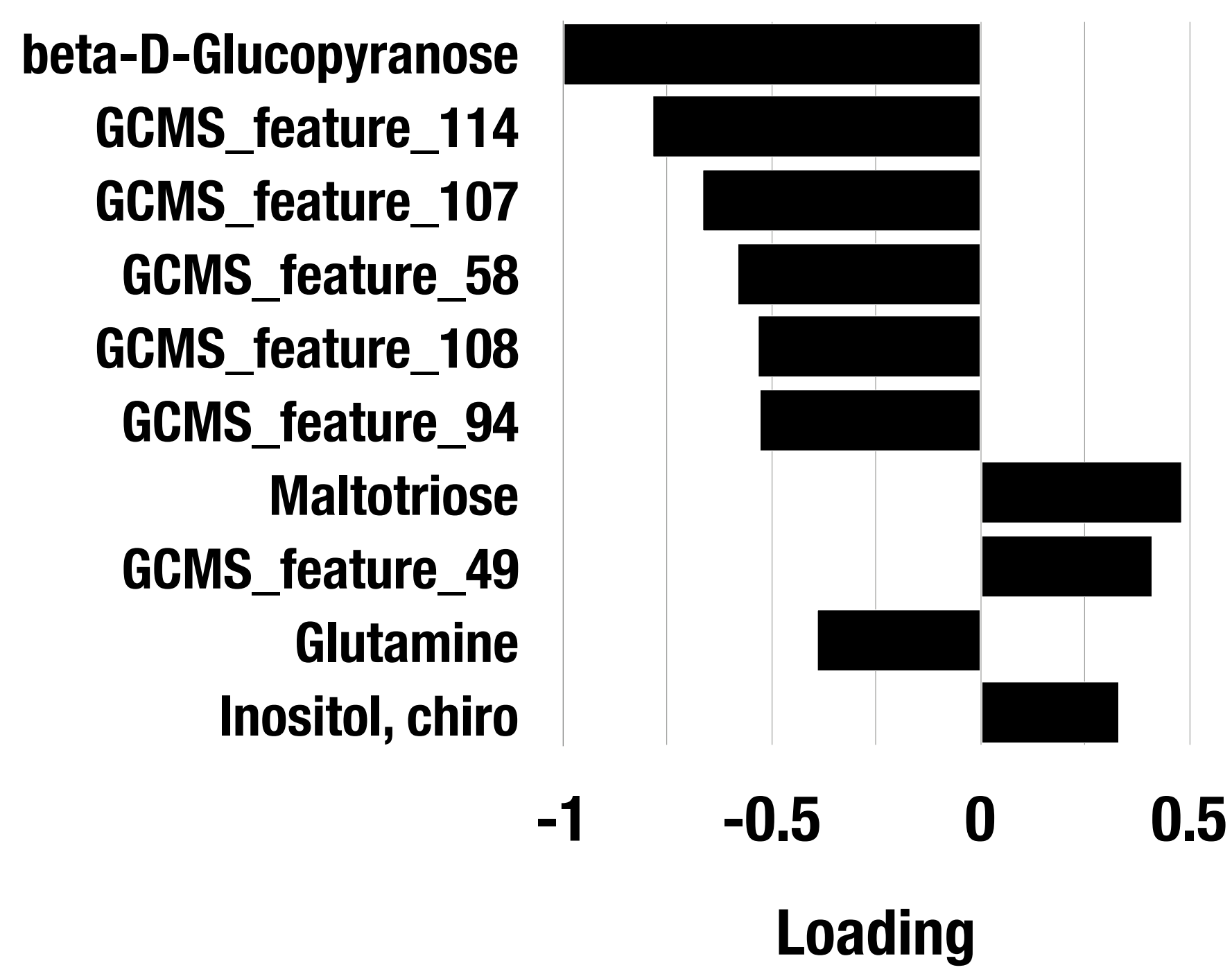
## Other



**Supplementary figure 9:** Additional plots showing the association of Factor11 with phenotypic variables. Regression lines are added when appropriate and 95% confidence intervals are shown. OSA: Obstructive Sleep Apnea

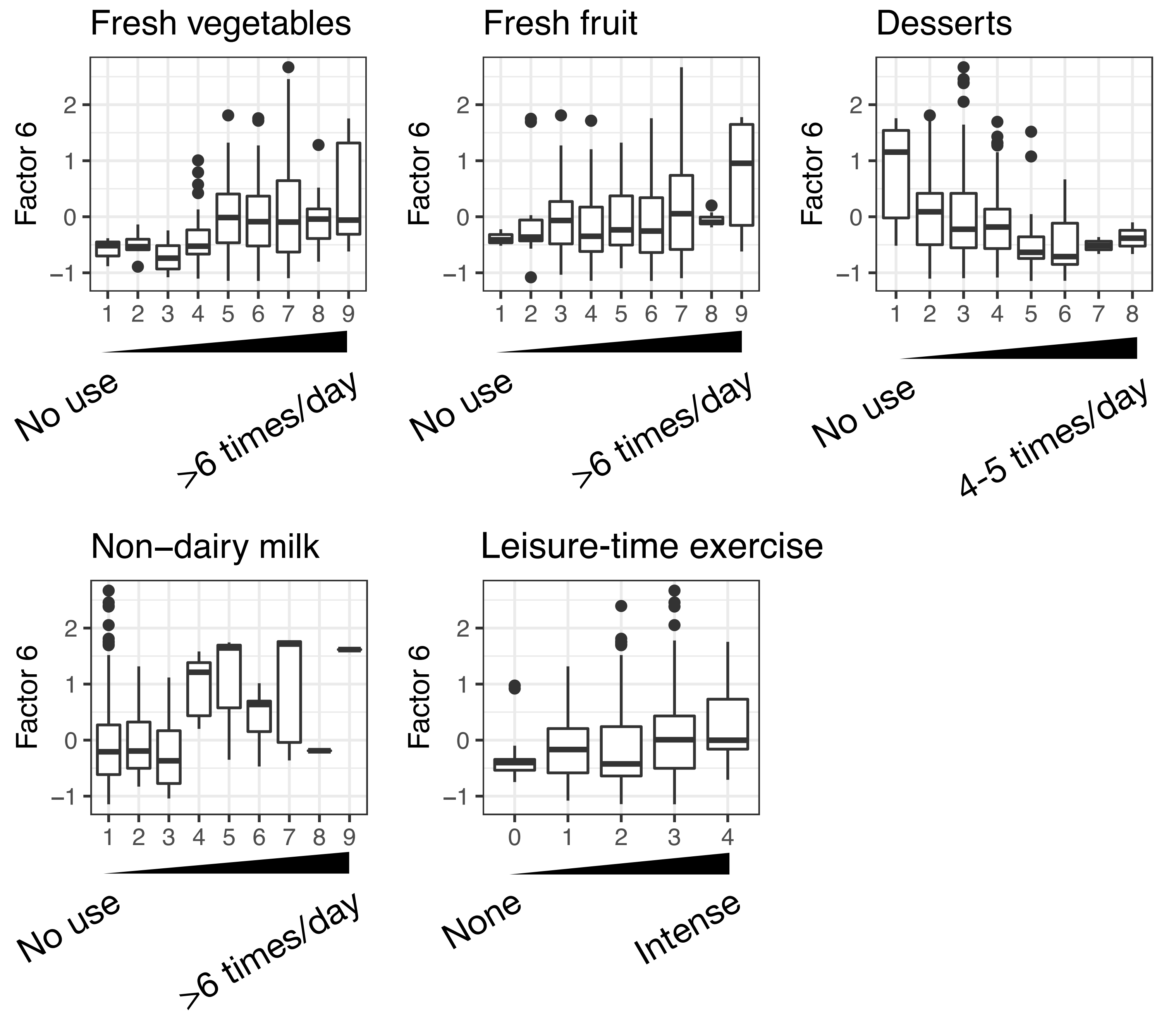


### Feature weights - Factor 6

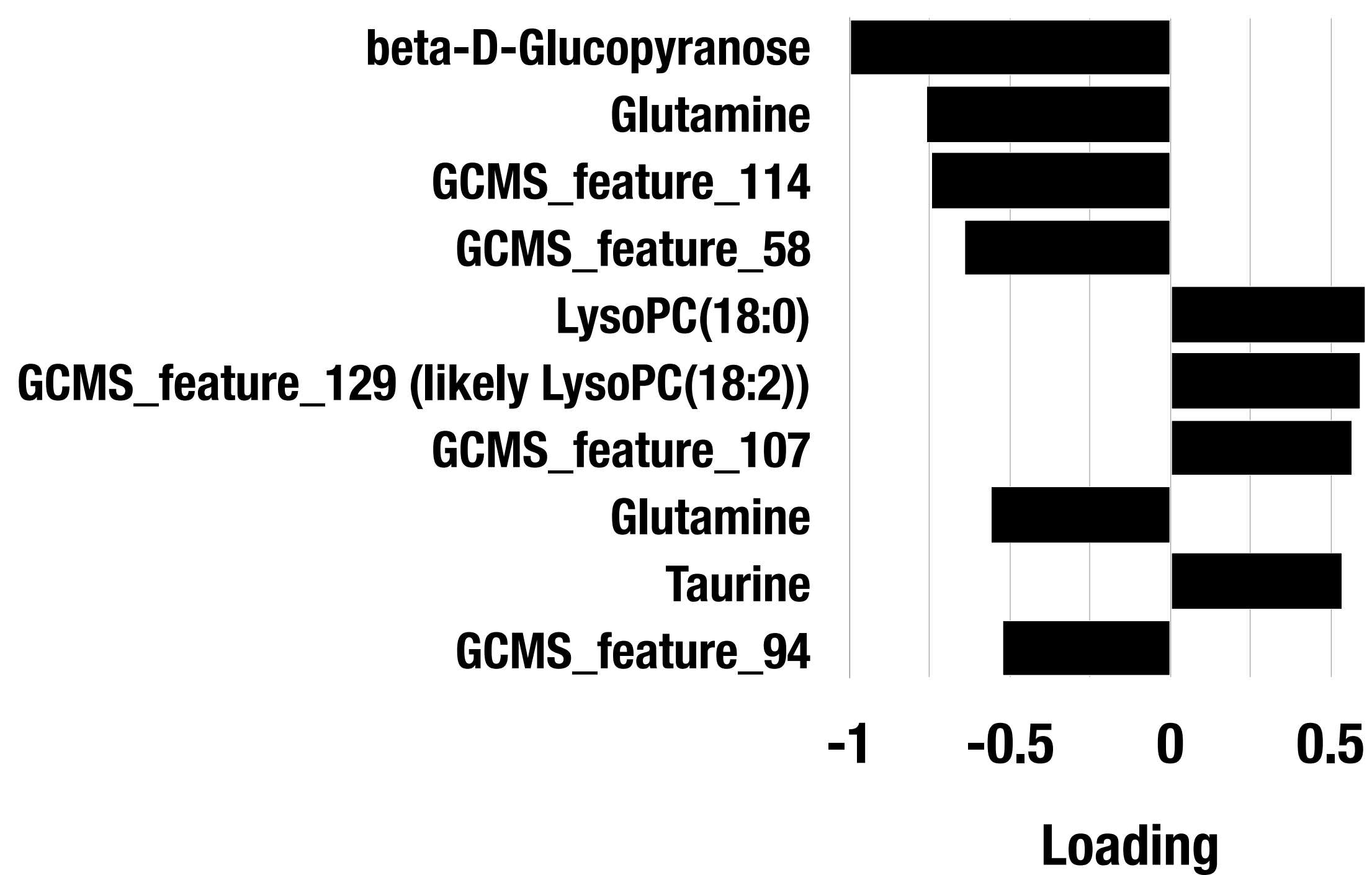


### Factor 6 values

? Questionnaire

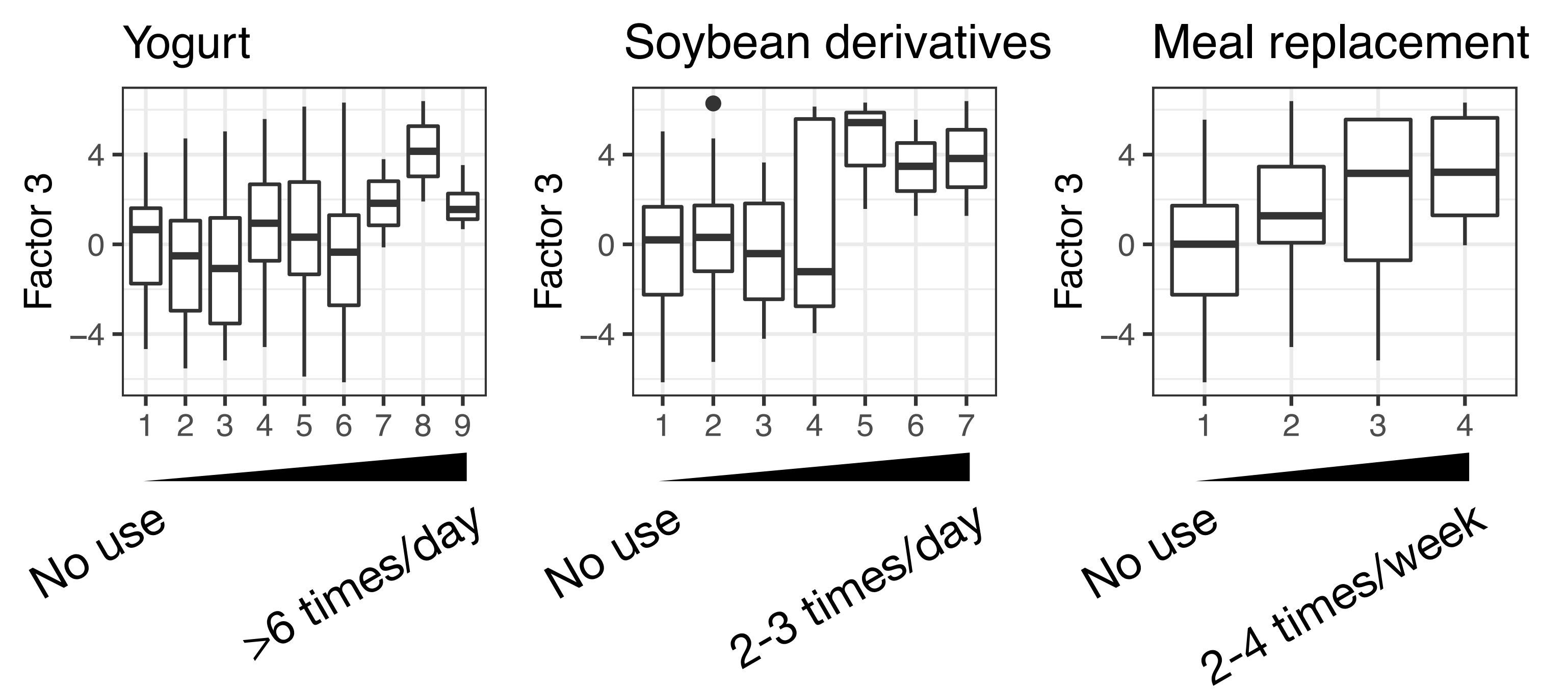


### Feature weights - Factor 3



### Factor 3 values

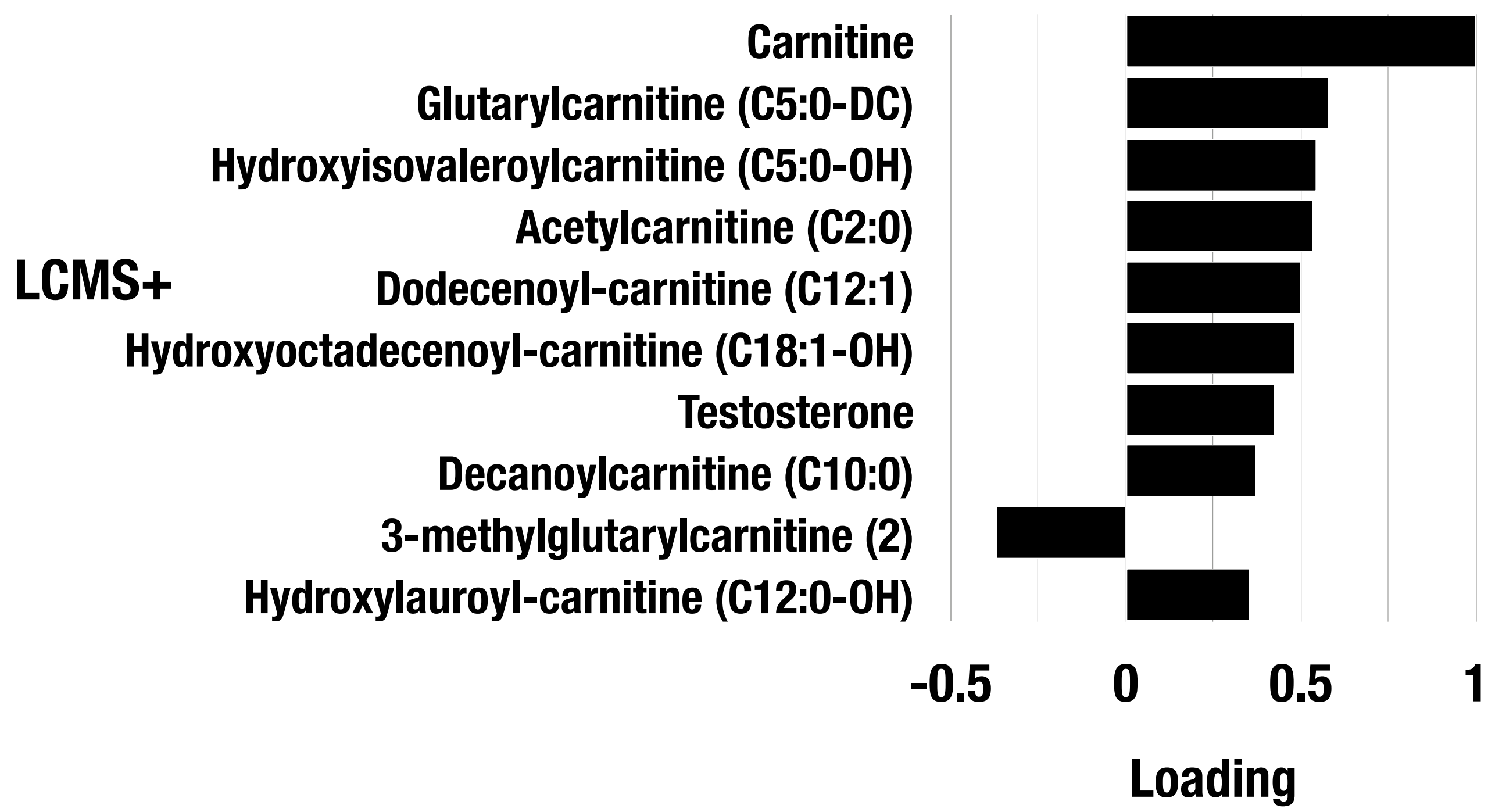
? Questionnaire



**Supplementary figure 10:** Factor 3 and Factor 6 are associated with diet. The top scaled feature weights are shown. The association between the factor values for each sample and the phenotypic variables is shown. A regression line with 95% confidence interval is shown when appropriate.

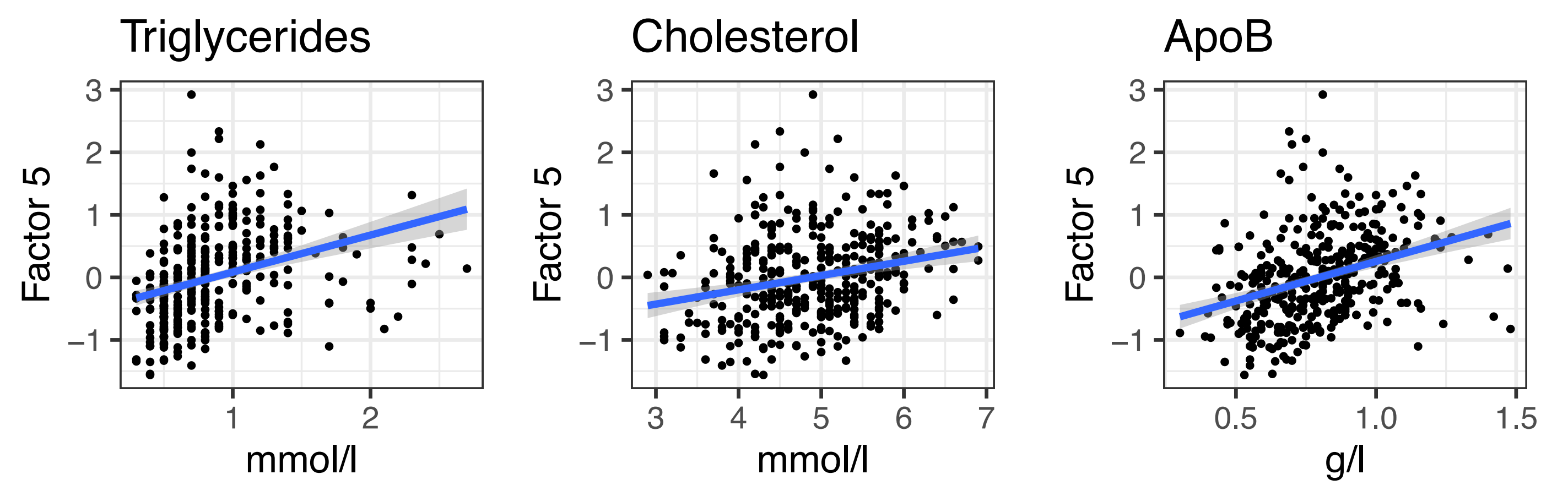


### Feature weights - Factor 5

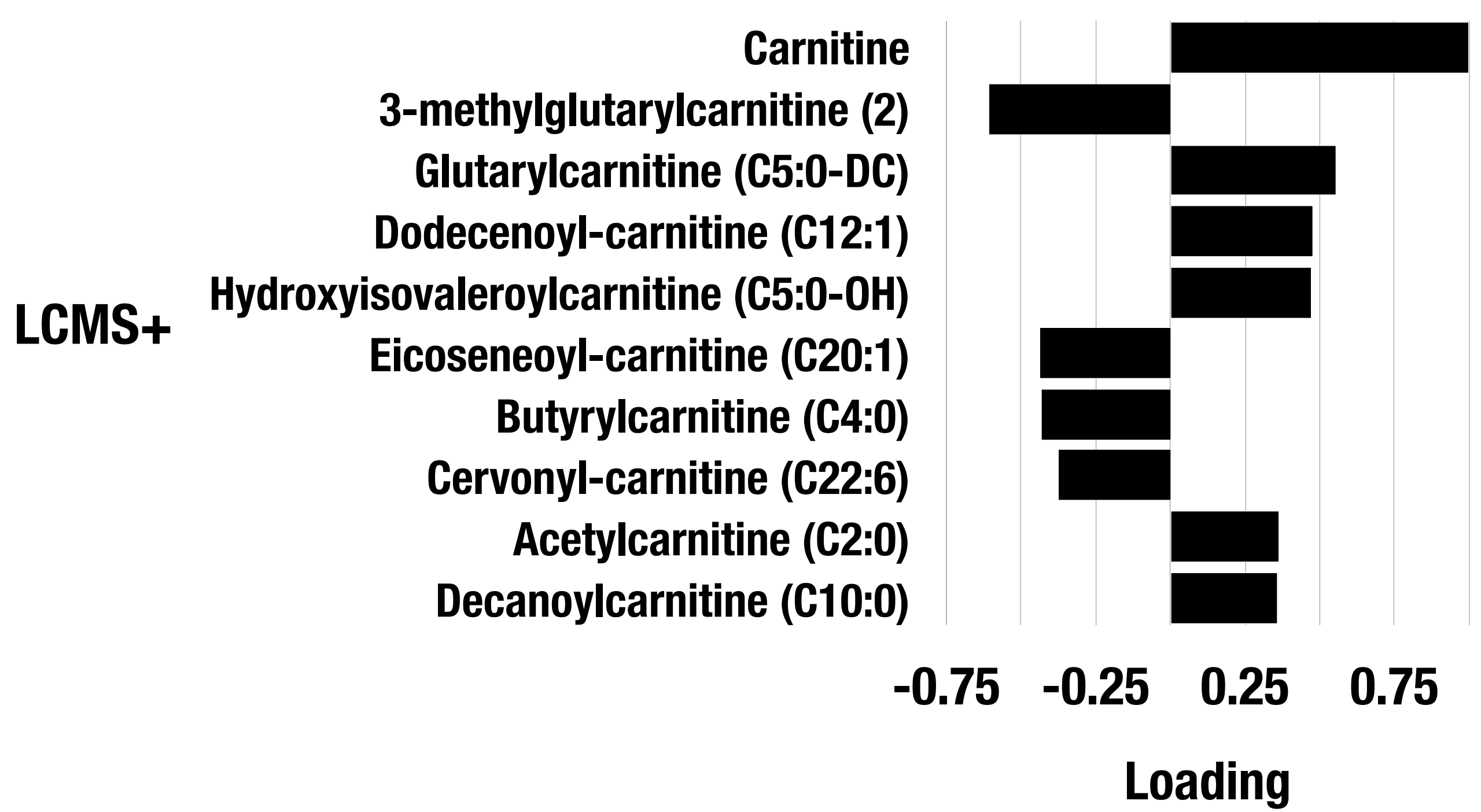


### Factor 5 values

Clinical variables

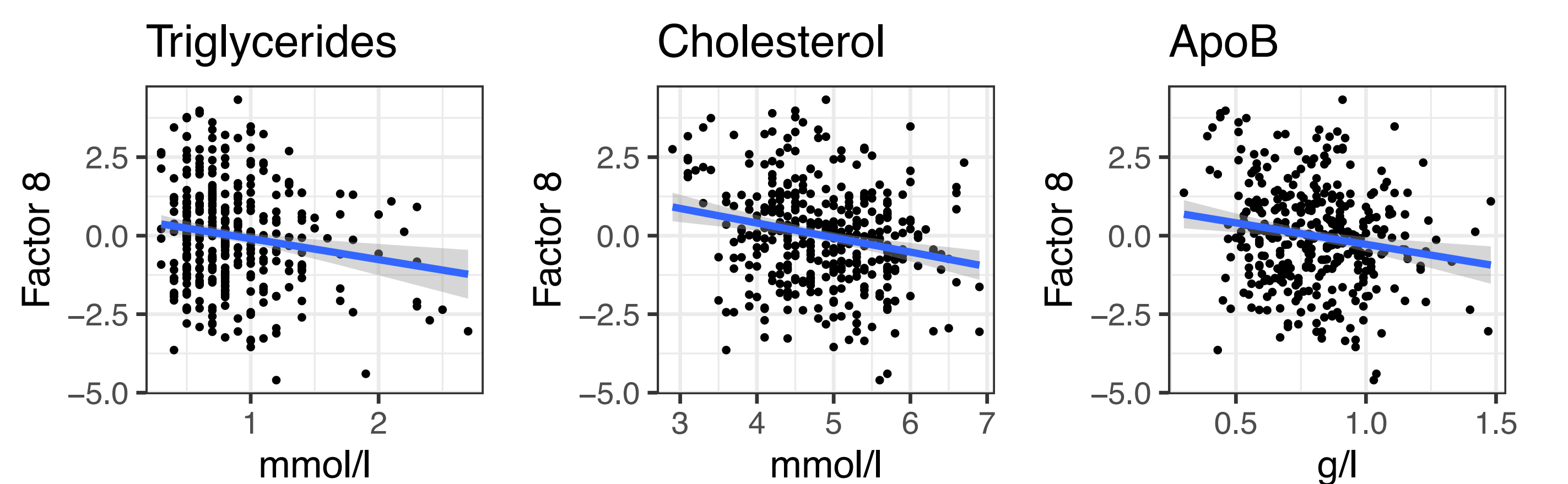


### Feature weights - Factor 8

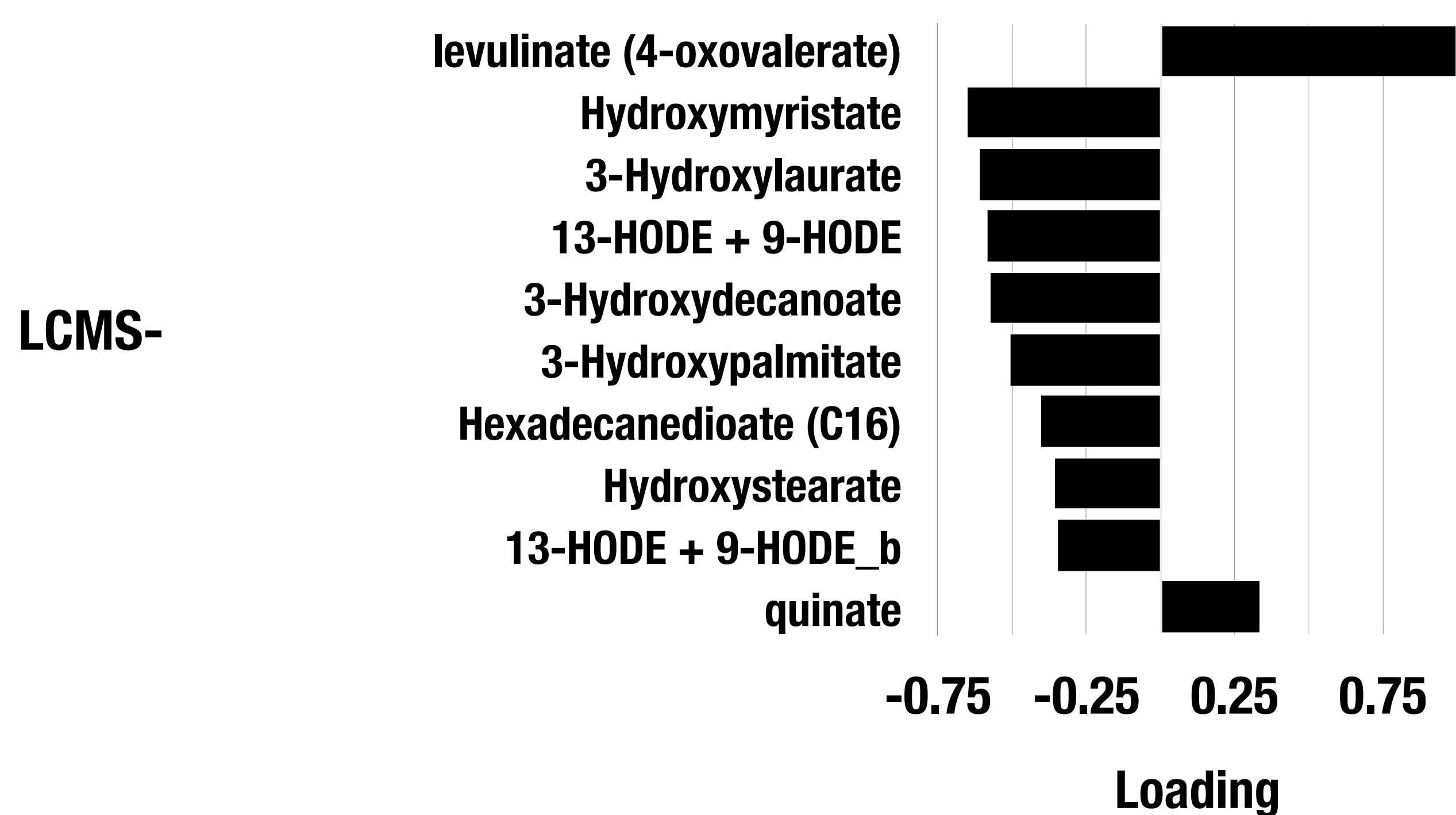


### Factor 8 values

Clinical variables

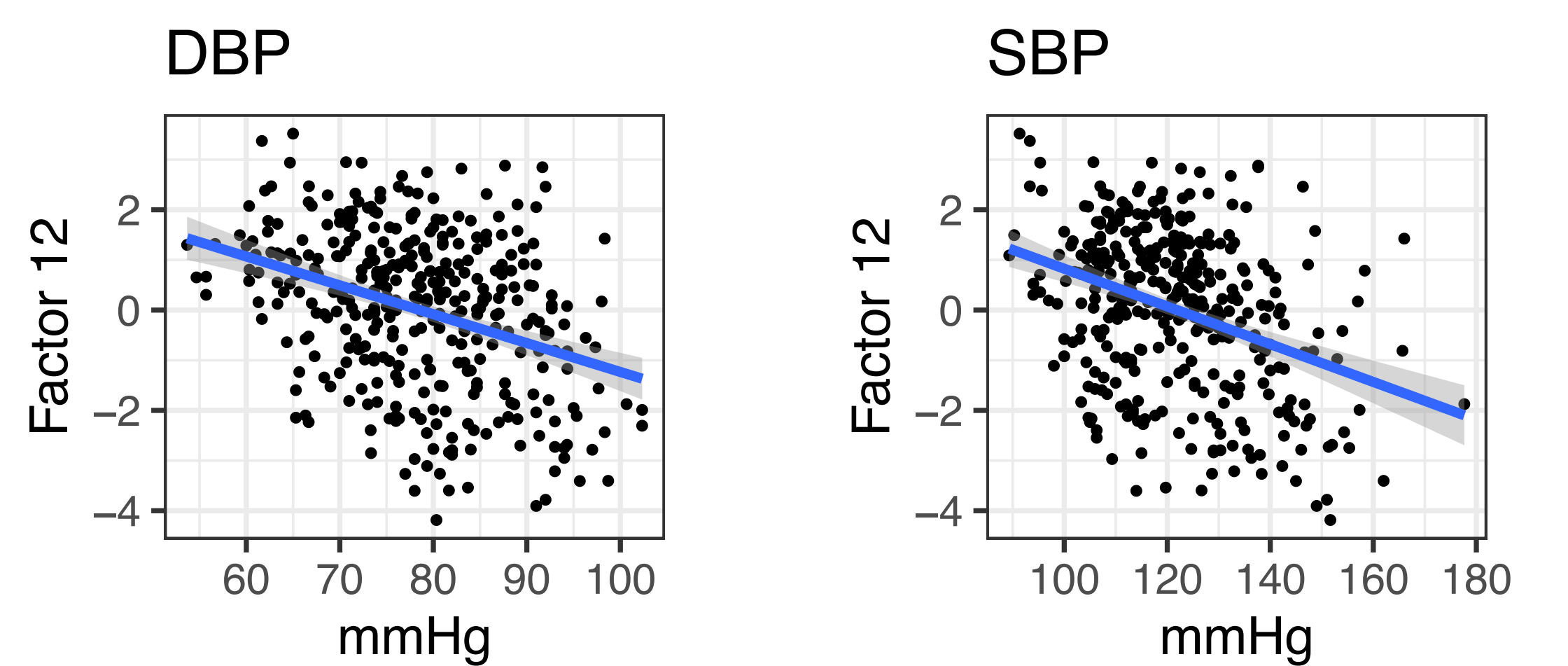


### Feature weights - Factor 12



### Factor 12 values

Clinical variables



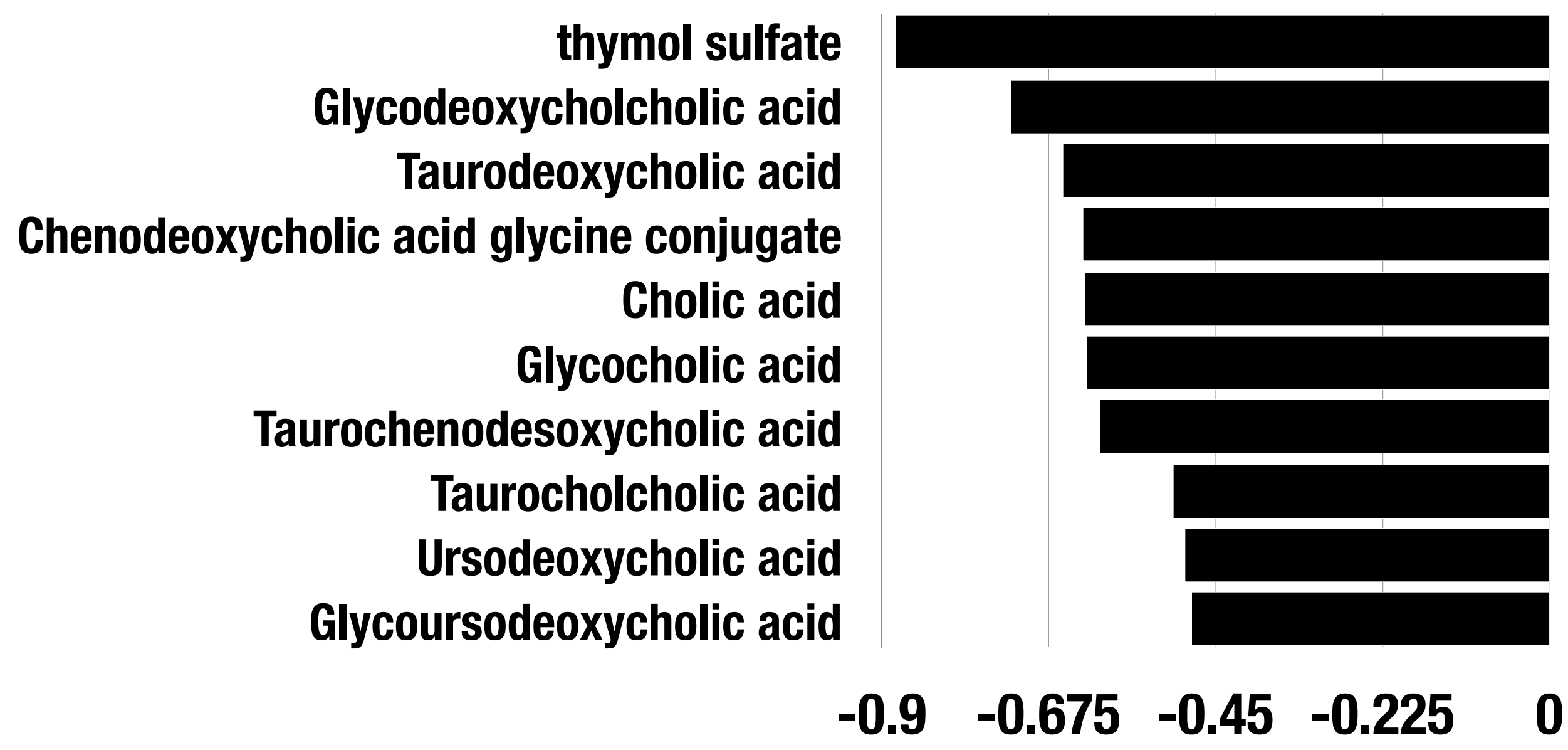
**Supplementary figure 11:** Factor 5, Factor 8 and Factor 12 are associated with fatty acids and acylcarnitines. The top scaled feature weights are shown. The association between the factor values for each sample and the phenotypic variables is shown. A regression line with 95% confidence interval is shown when appropriate.



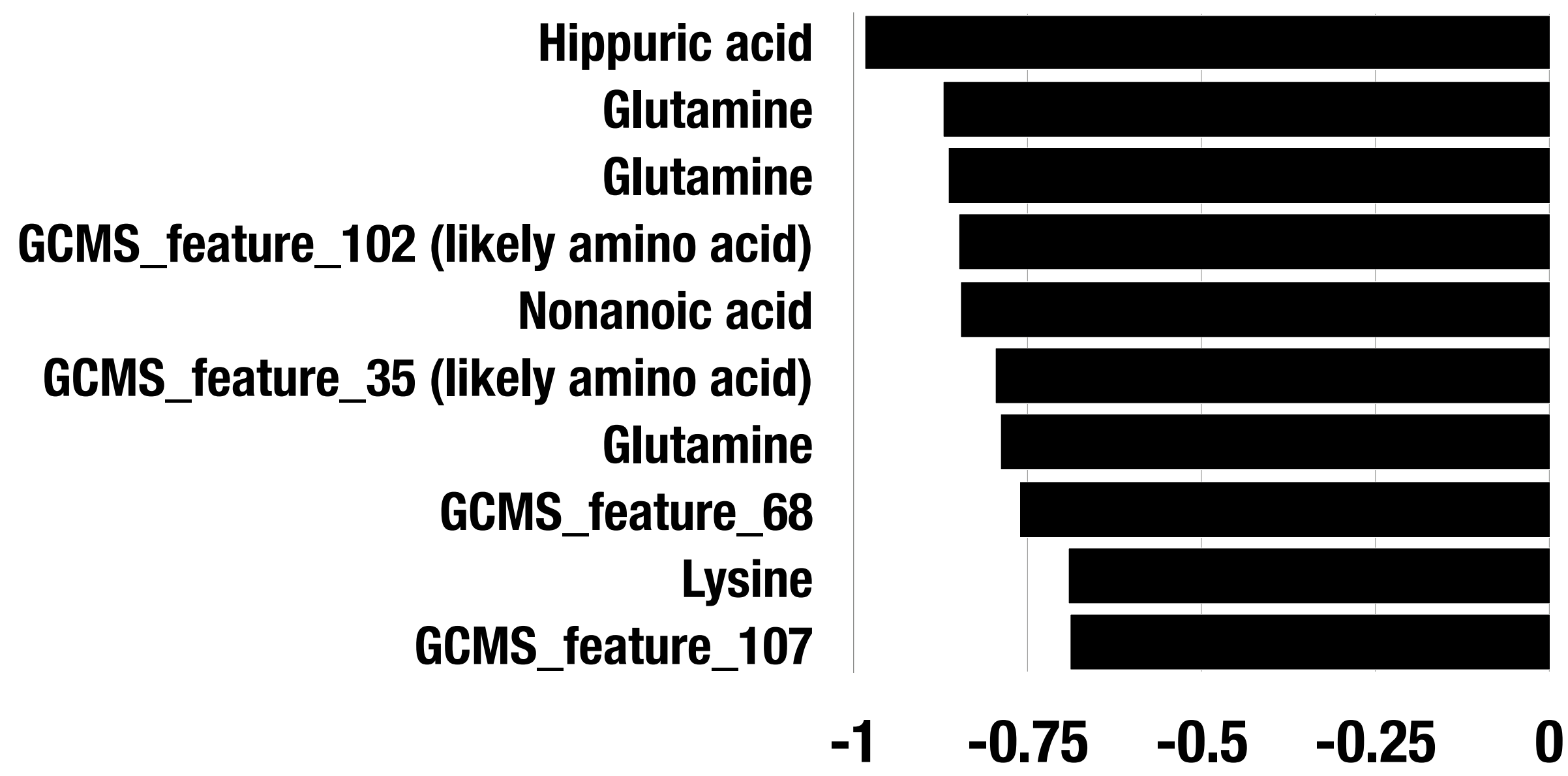
# A

## Feature weights - Factor 2

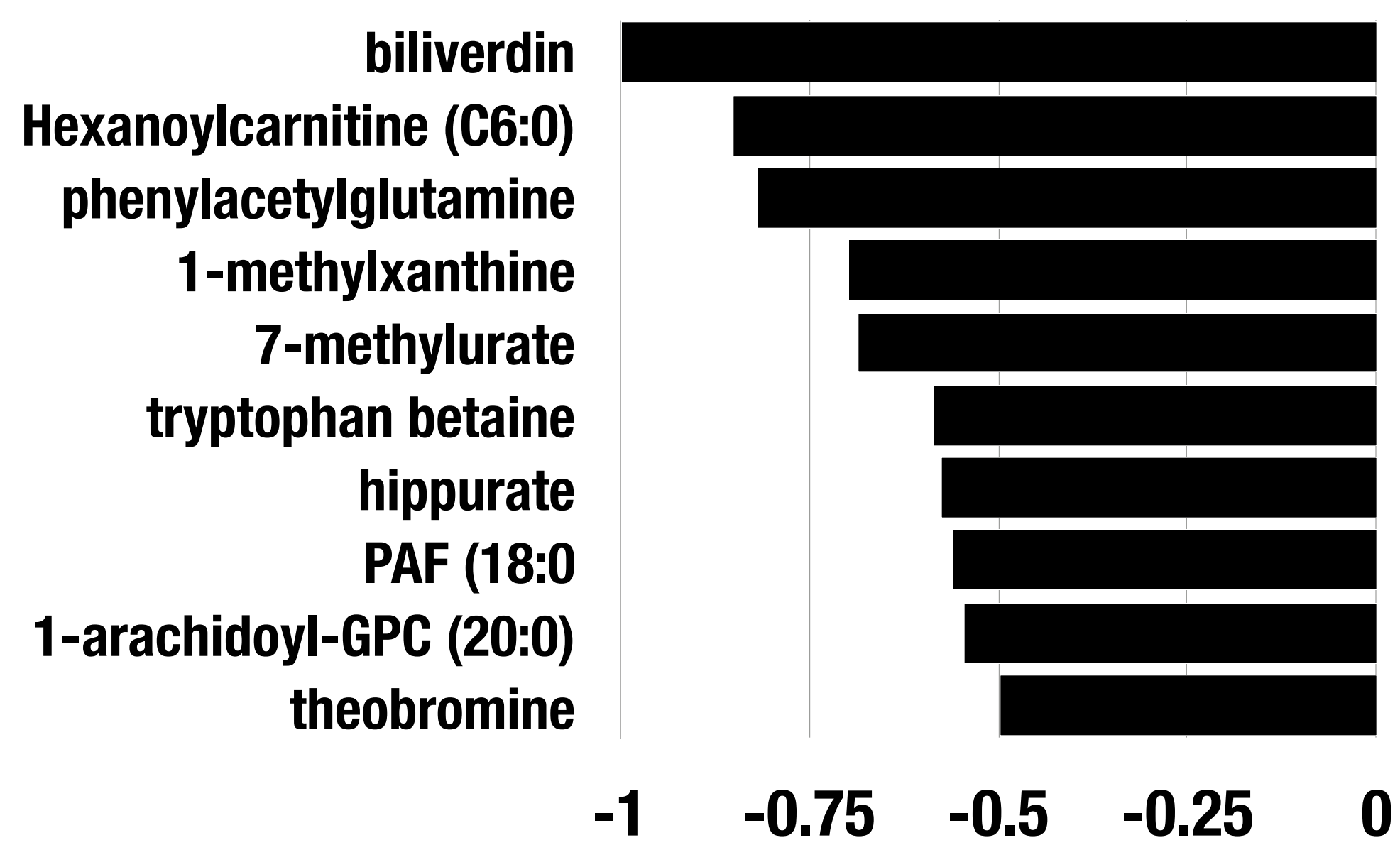
LCMS-



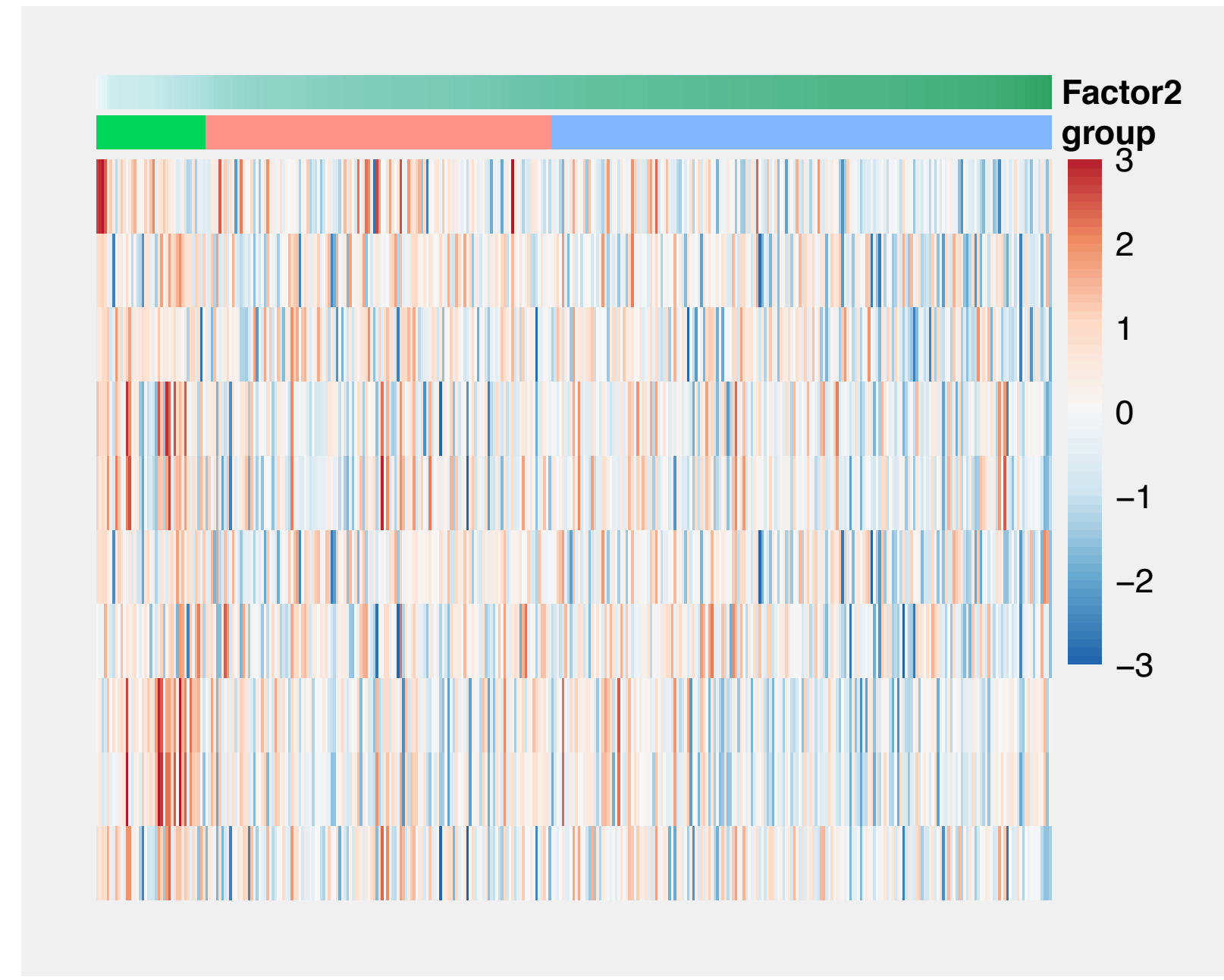
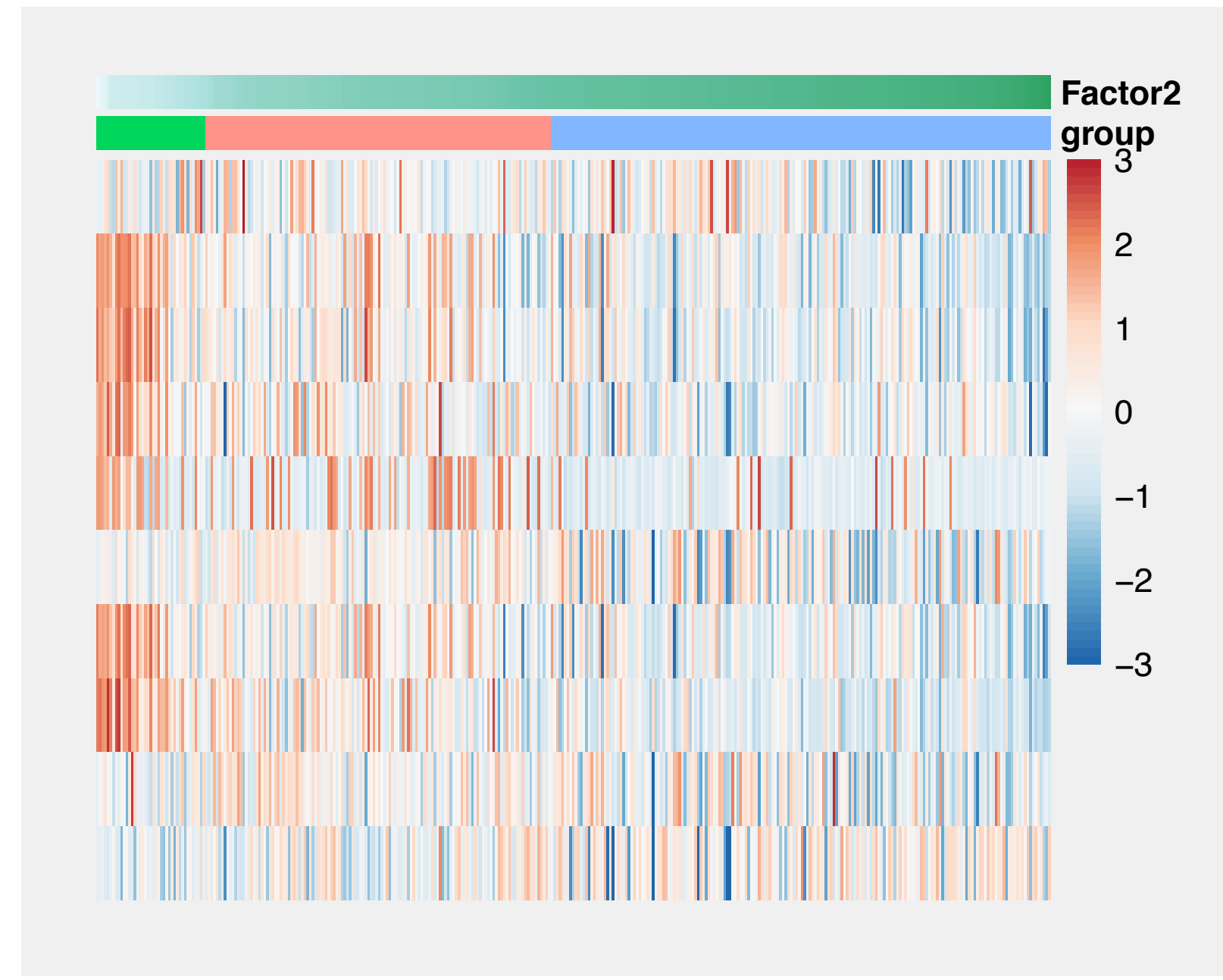
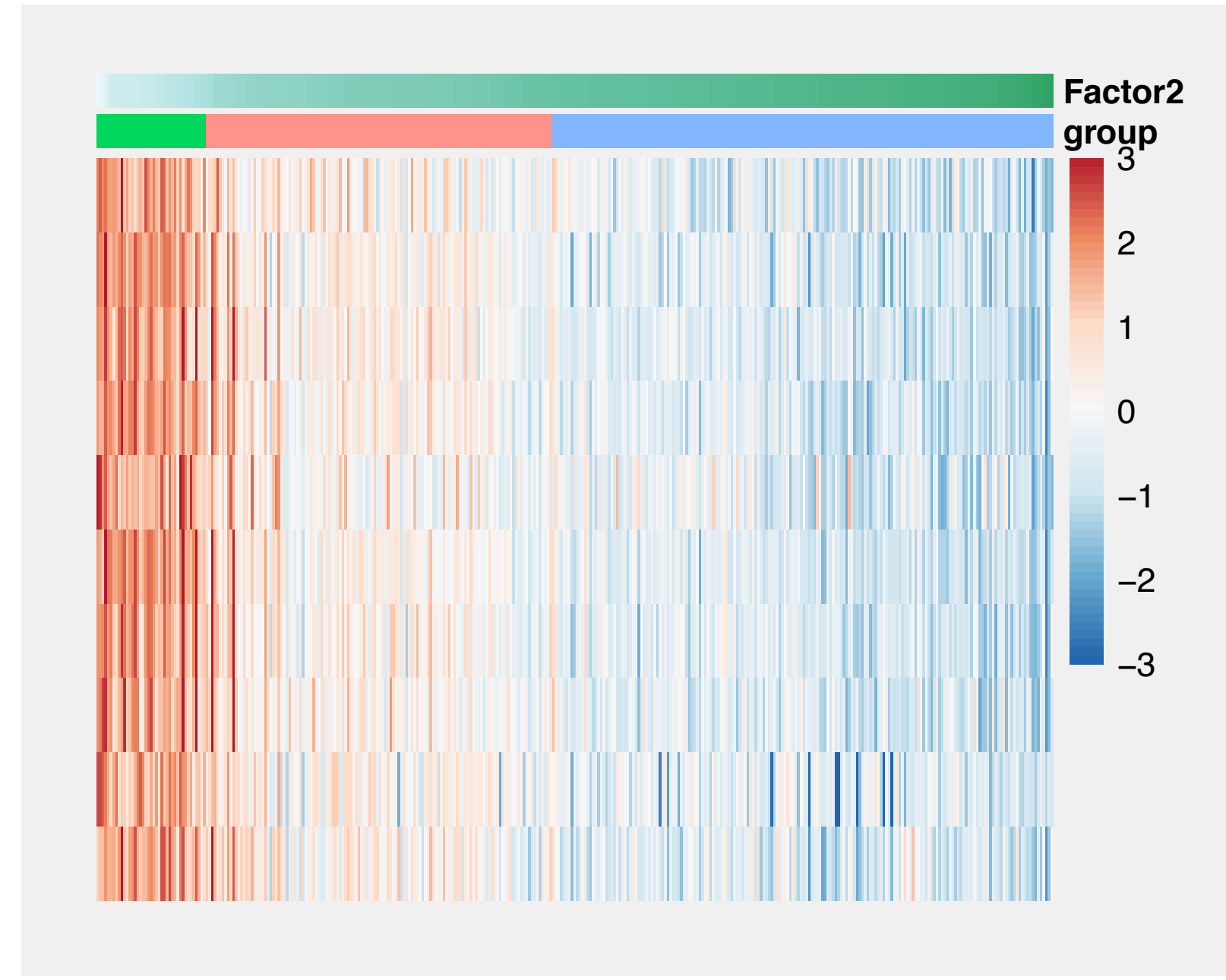
GCMS



LCMS+

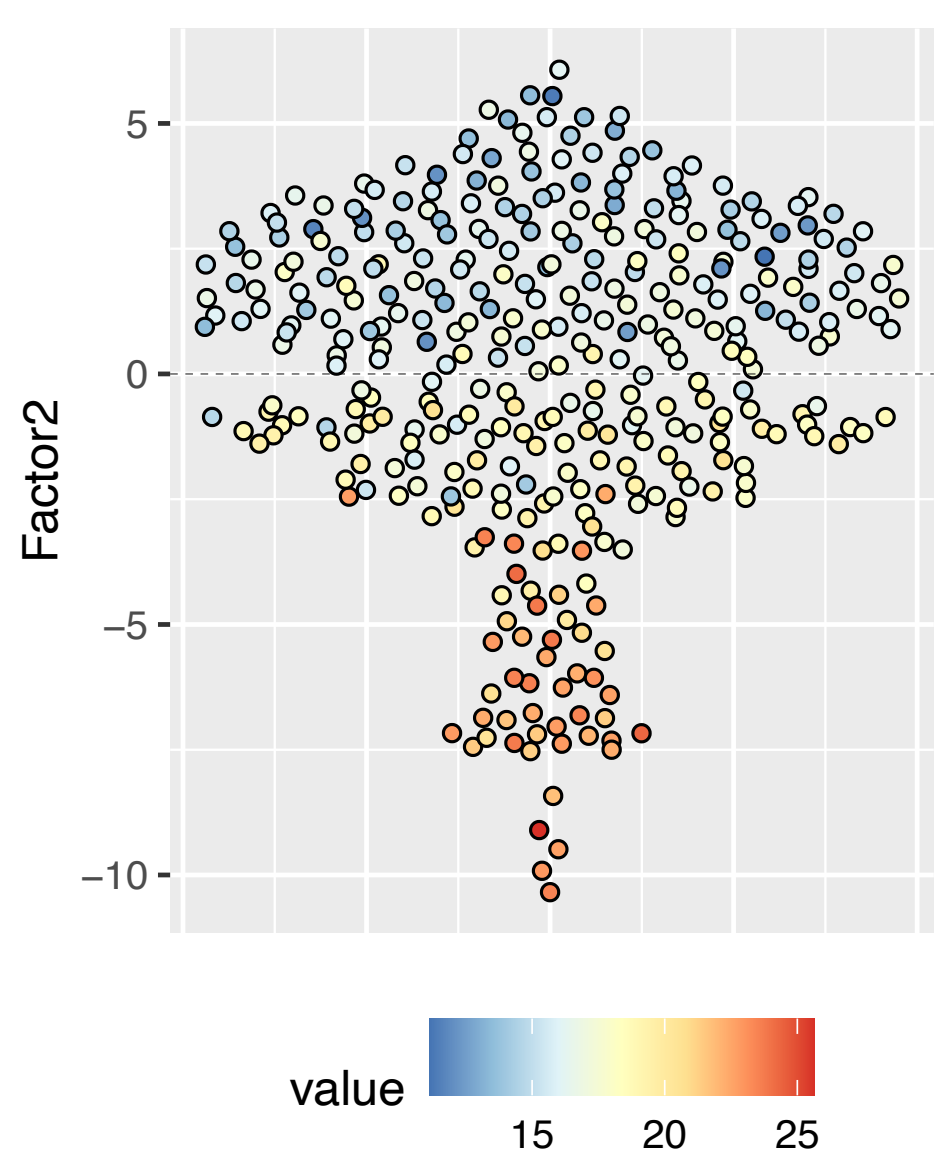


## Feature values

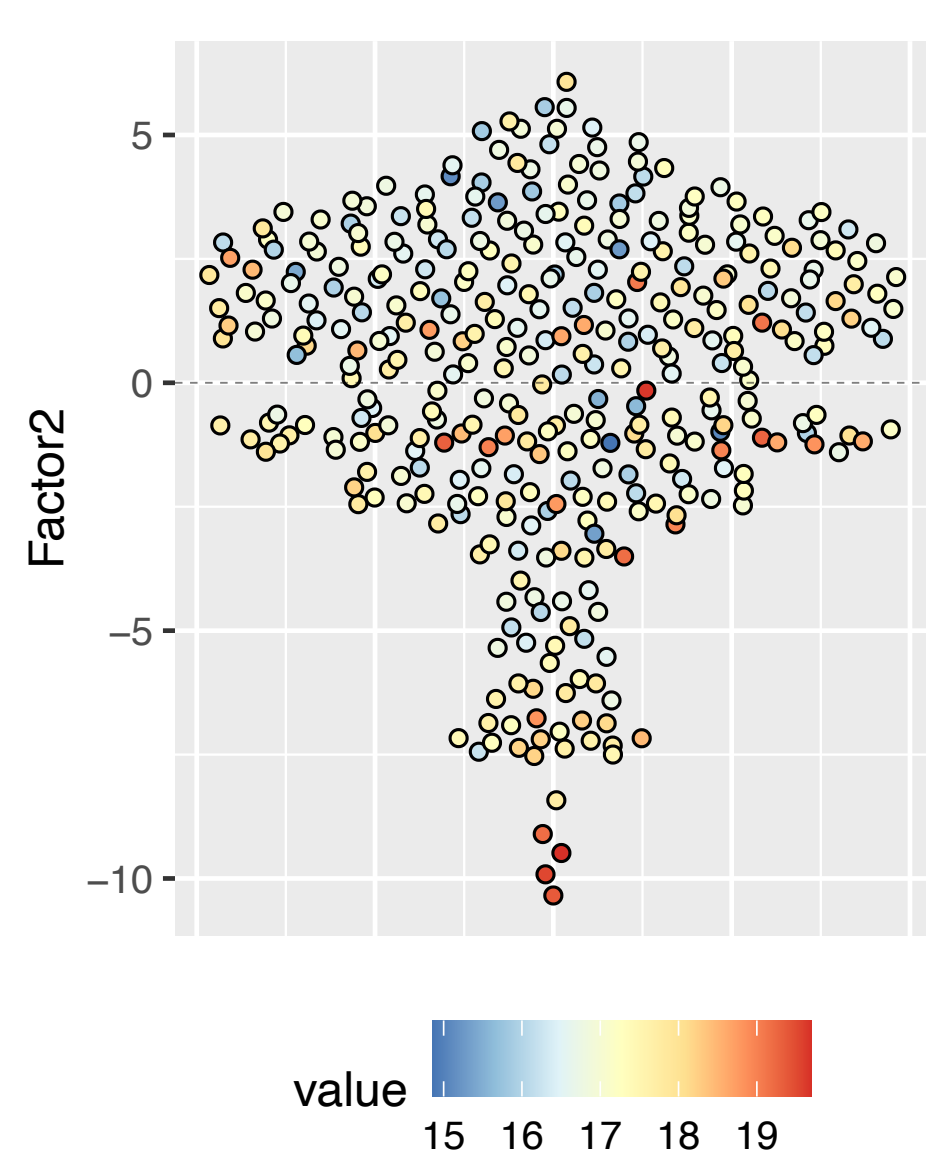


# B

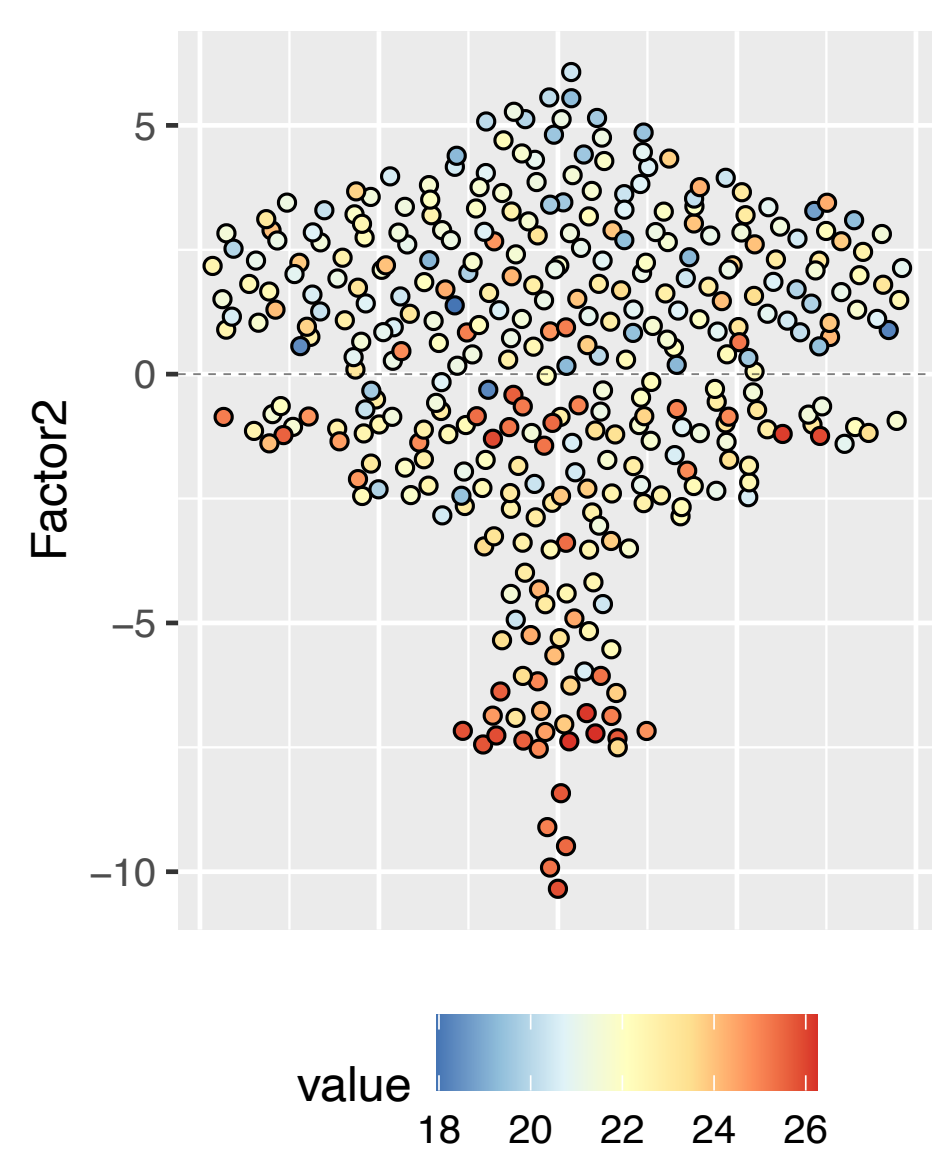
## Glycodeoxycholcholic acid



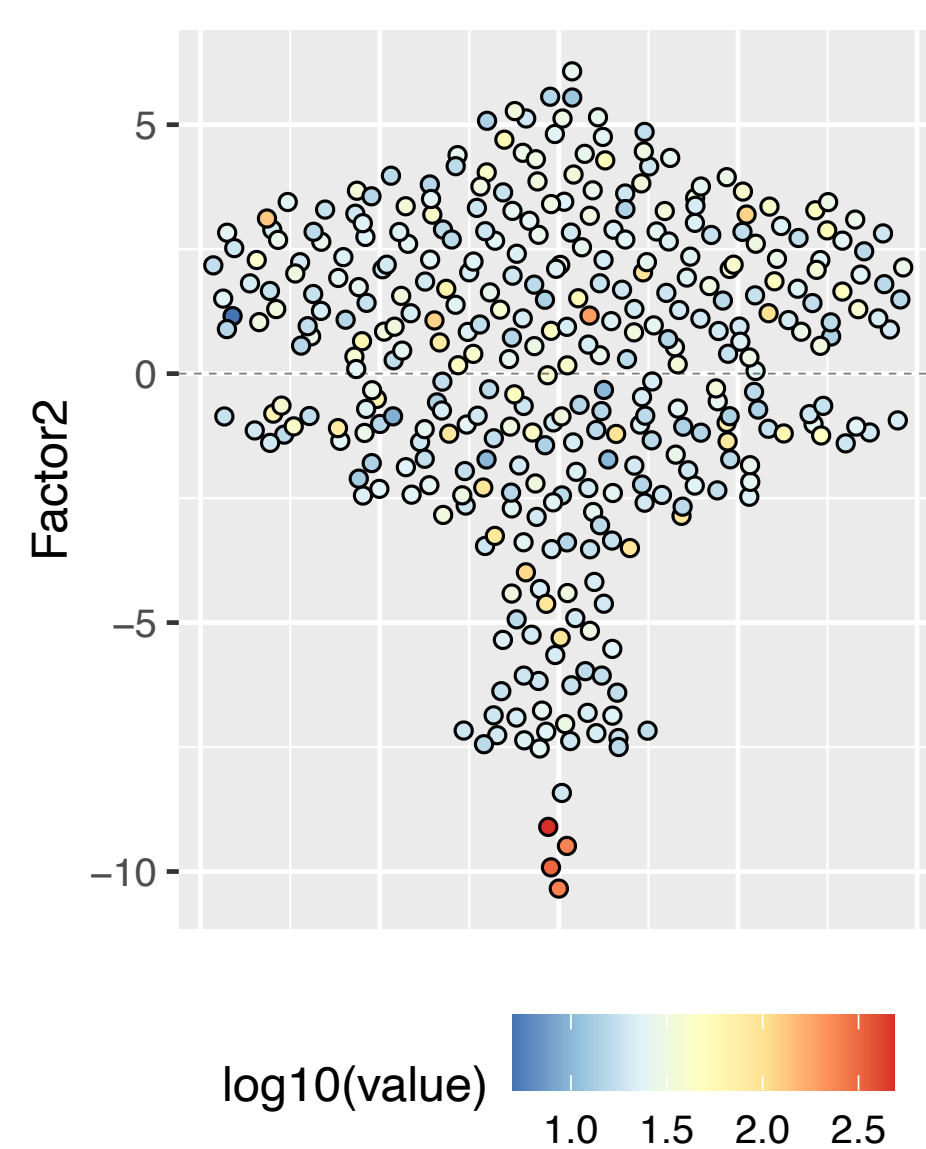
## Biliverdin



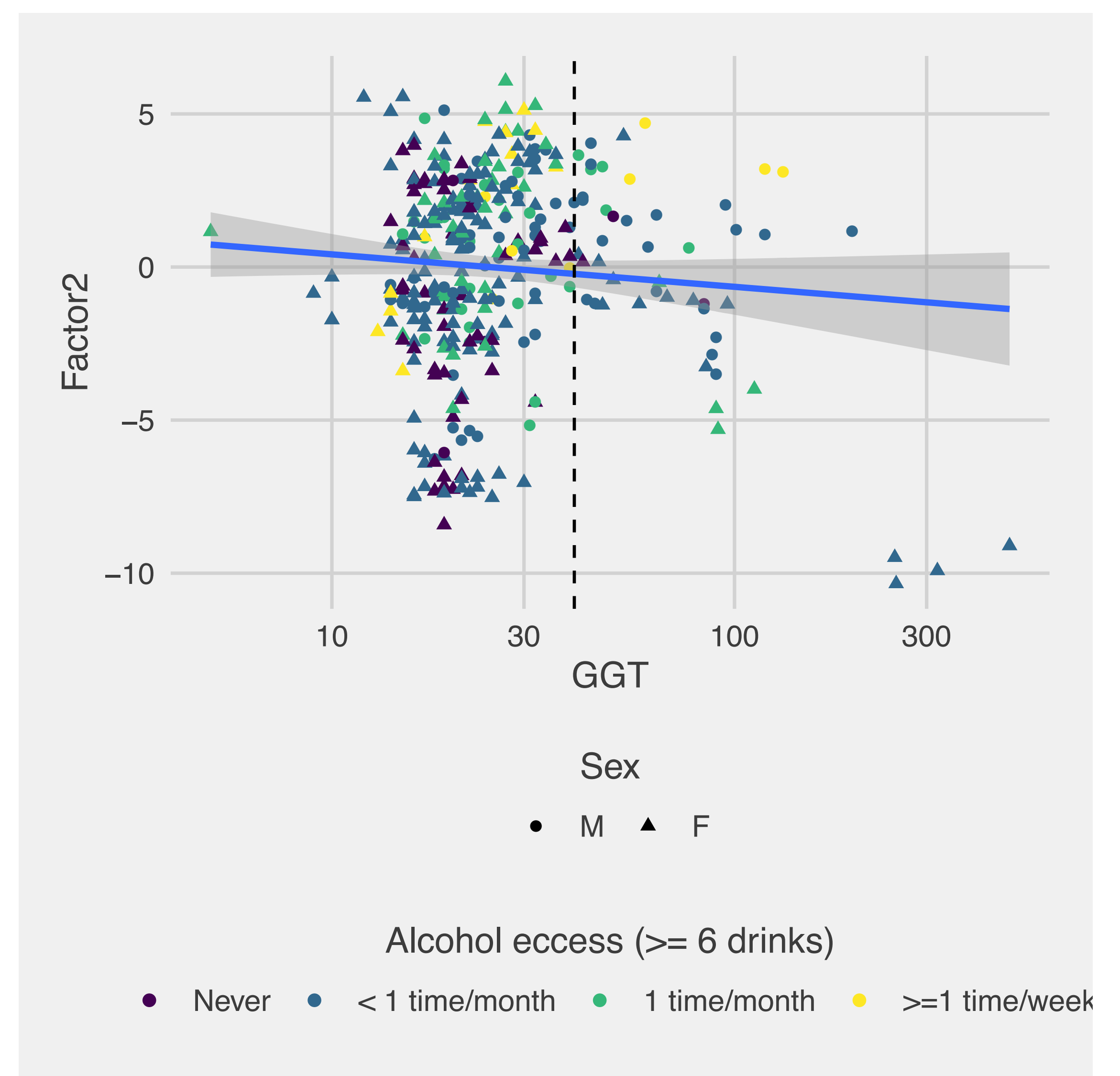
## Glutamine



## GGT



# C





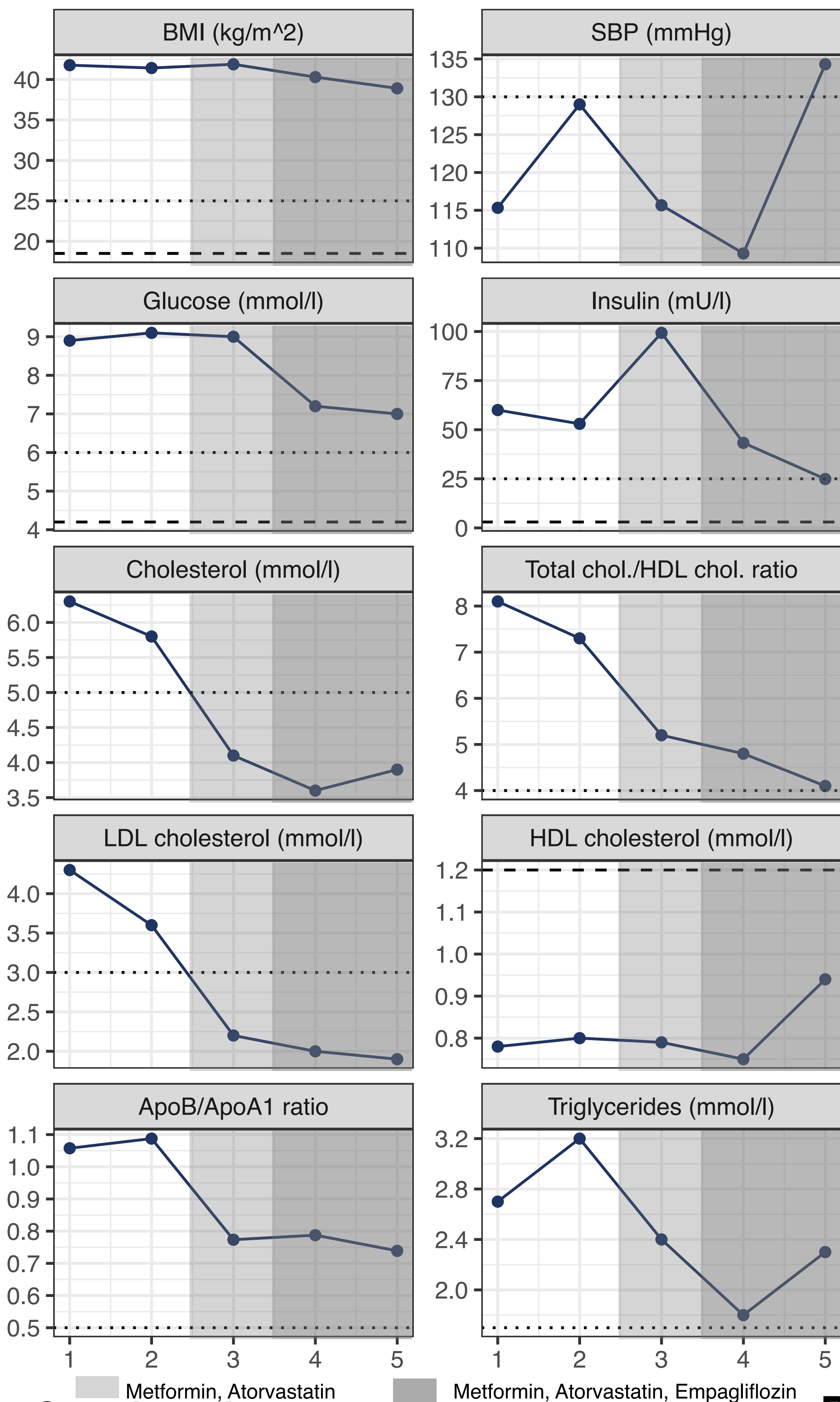
**Supplementary figure 12 (previous page):** **A.** Factor 2 is associated with hepatic function. The top negative scaled metabolite weights for Factor2 are shown, as well as their values (row z-score) as heatmaps. The association between the factor values for each sample and the phenotypic variables is shown. A regression line with 95% confidence interval is shown when appropriate. **B.** The Factor 2 values are shown for each sample and colored according to the value of the indicated feature. Although an influential individual with the lowest factor values had particularly elevated gamma-gultamyl transferase (GGT) levels, we did not observe a correlation between Factor 2 and GGT in the covariate-adjusted model. **C.** A scatterplot of the GGT values vs. the Factor 2 values for each sample. Dots are colored according to the frequency of excess alcohol use ( $\geq 6$  standard drinks).



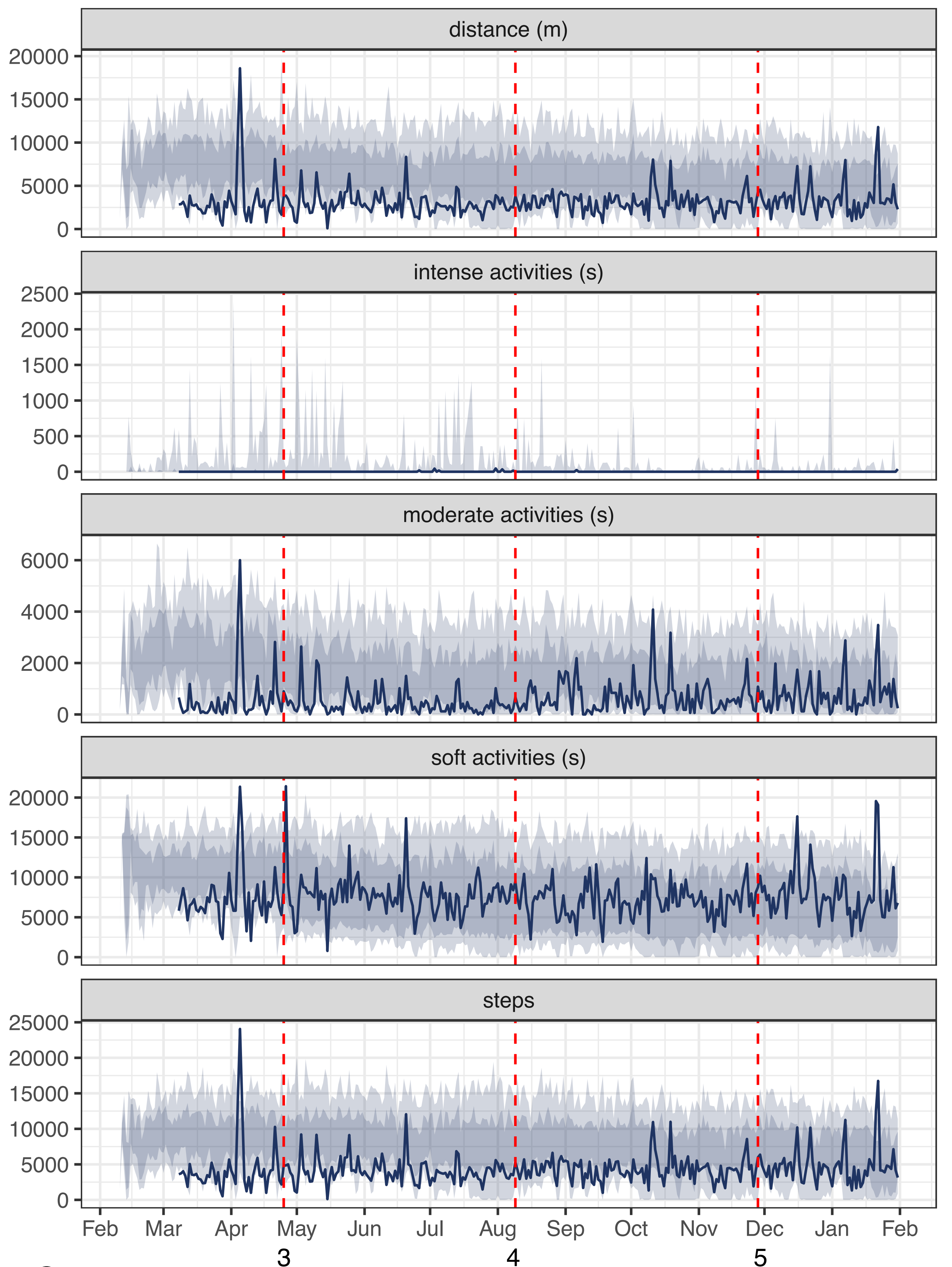
**Supplementary figure 13:** Association with genetic scores in the Between-Individual Network. All the edges between a GWAS summary score and another features were selected and shown here. Colors of the edges and nodes are the same as described in main Figure 5.



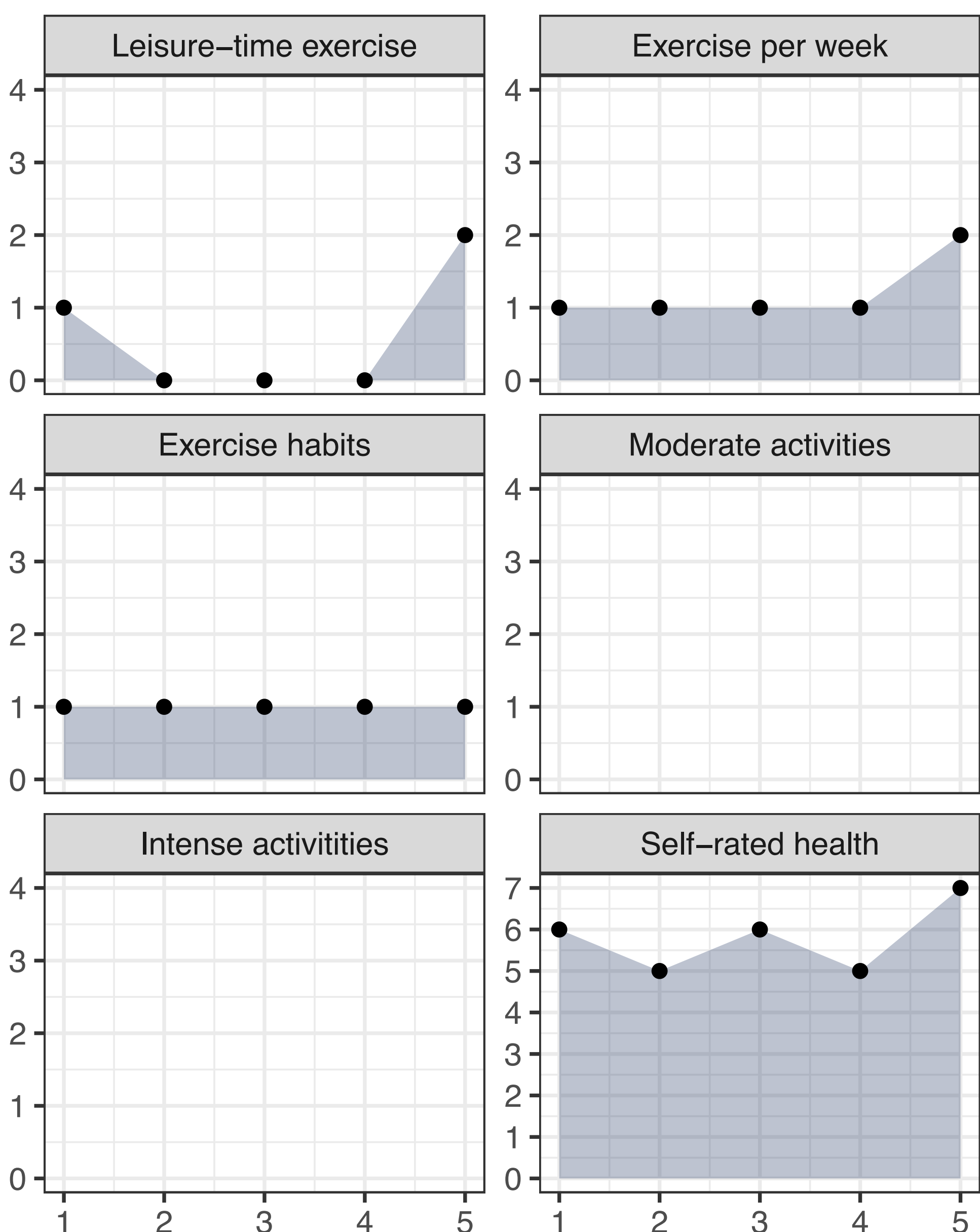
## A Clinical variables



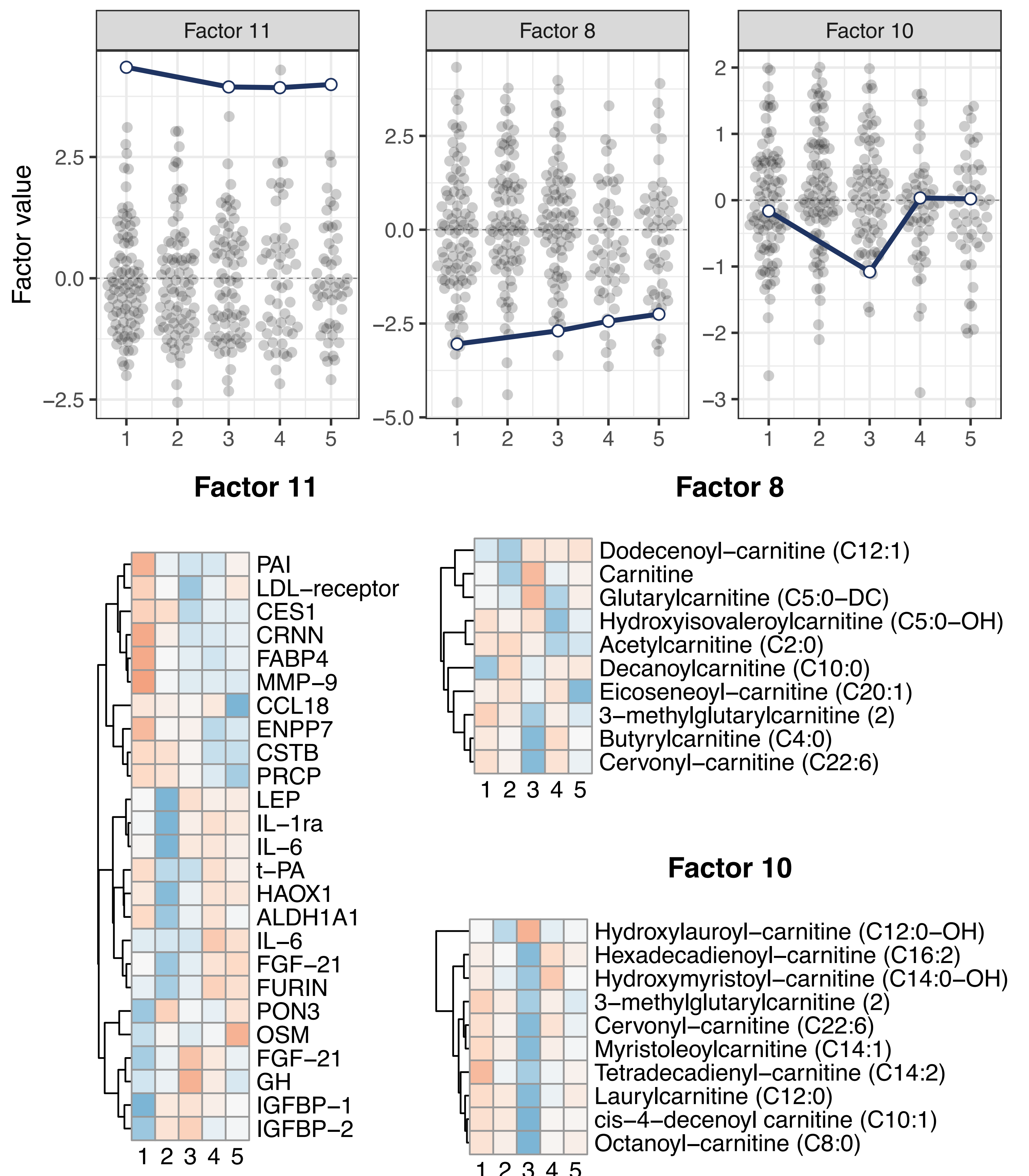
## B Activities



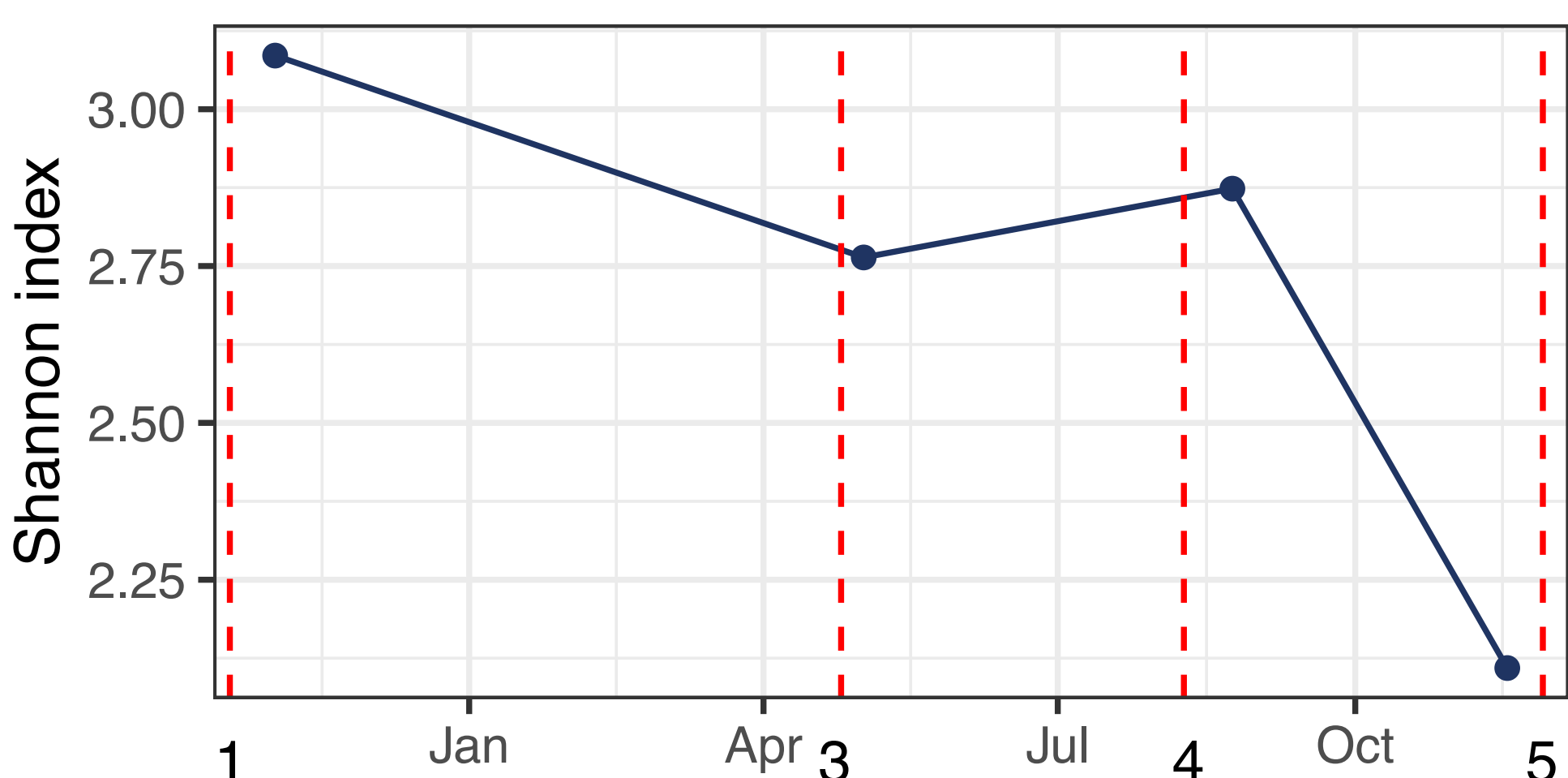
## C Questionnaire



## D MOFA



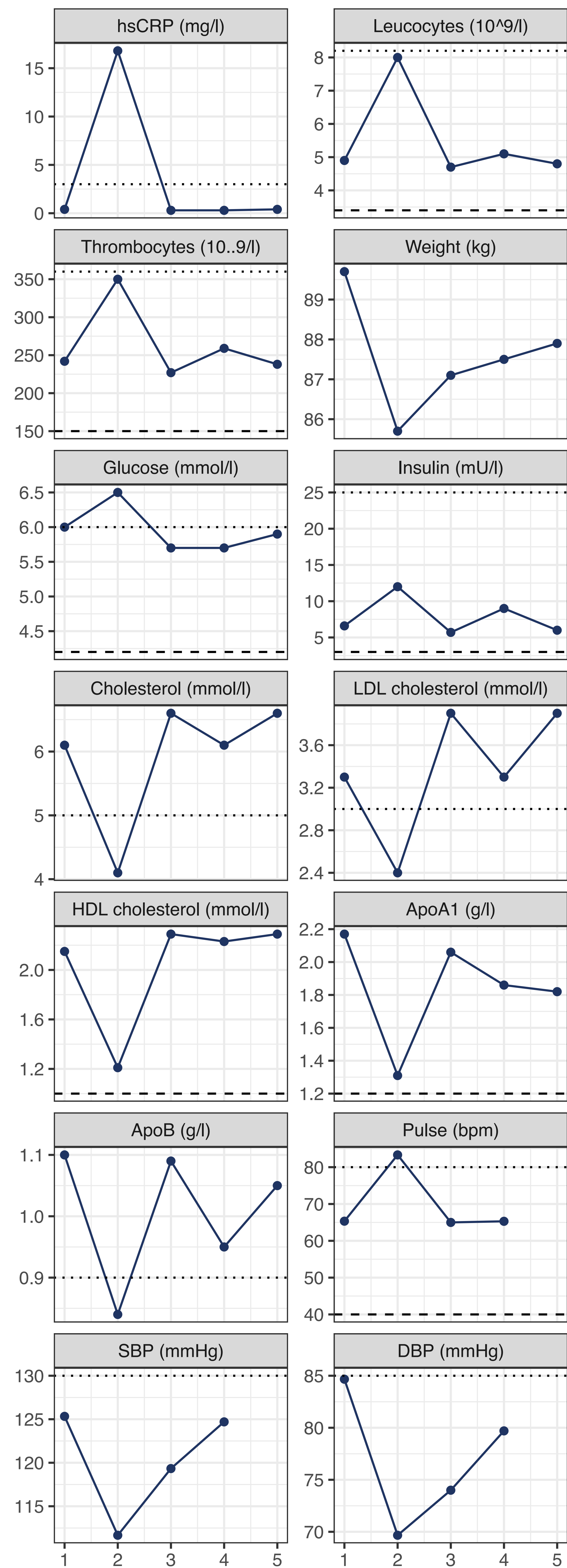
## E Gut microbiome diversity



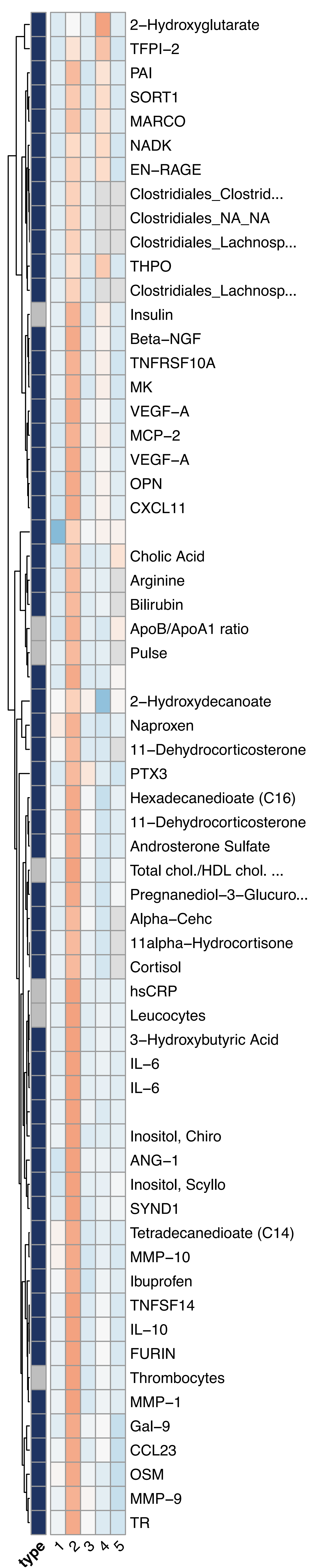
**Supplementary figure 14 (previous page):** A case study: one individual that was diagnosed with type 2 diabetes. **A.** Clinical parameters showing longitudinal changes. Reference values are shown (dashed line: lower normal value, dotted line: upper normal value). Grey-shaded areas mark periods of therapeutical intervention, consisting in Metformin and Atorvastatin before visit 2 and Metformin, Atorvastatin and Empagliflozin from visit 3 onward. **B.** Daily summary of the activities recorder by the smart watch included: distance, time spent in intense, moderate or soft activities and number of steps. The shaded area correspond to the 10, 25, 75 and 90 percentiles in the whole population. The study visits are marked with vertical dashed lines **C.** Selected lifestyle questions. The numbers correspond to orderer categories, where a higher number corresponds to higher frequency or more favorable outcome. **D.** Longitudinal values for selected MOFA+ factors (blue line) plotted together with the factor values for the remaining samples at each study visit (grey dots). **E.** Gut microbiome diversity (Shannon index). The vertical dashed line mark the date for the study visit, which could be different than the fecal sample collection date (dots).



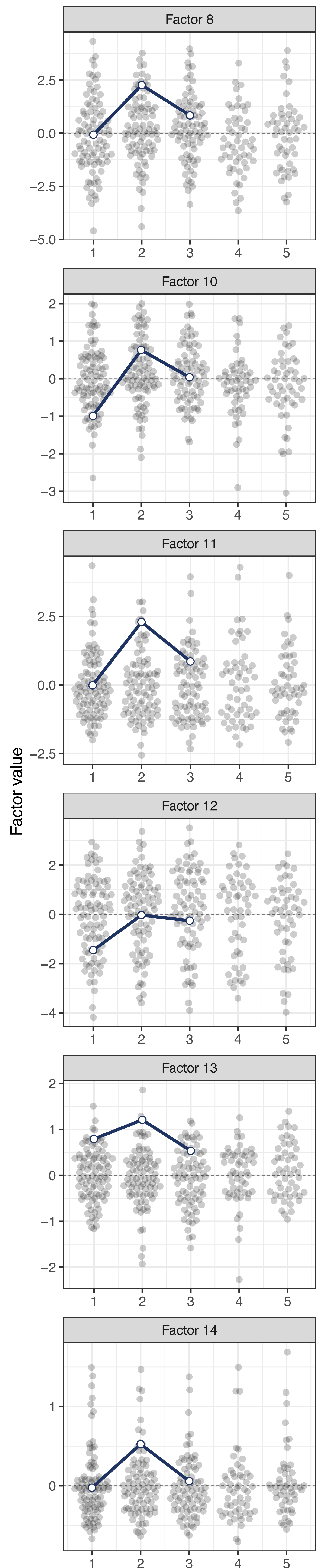
### A Clinical variables



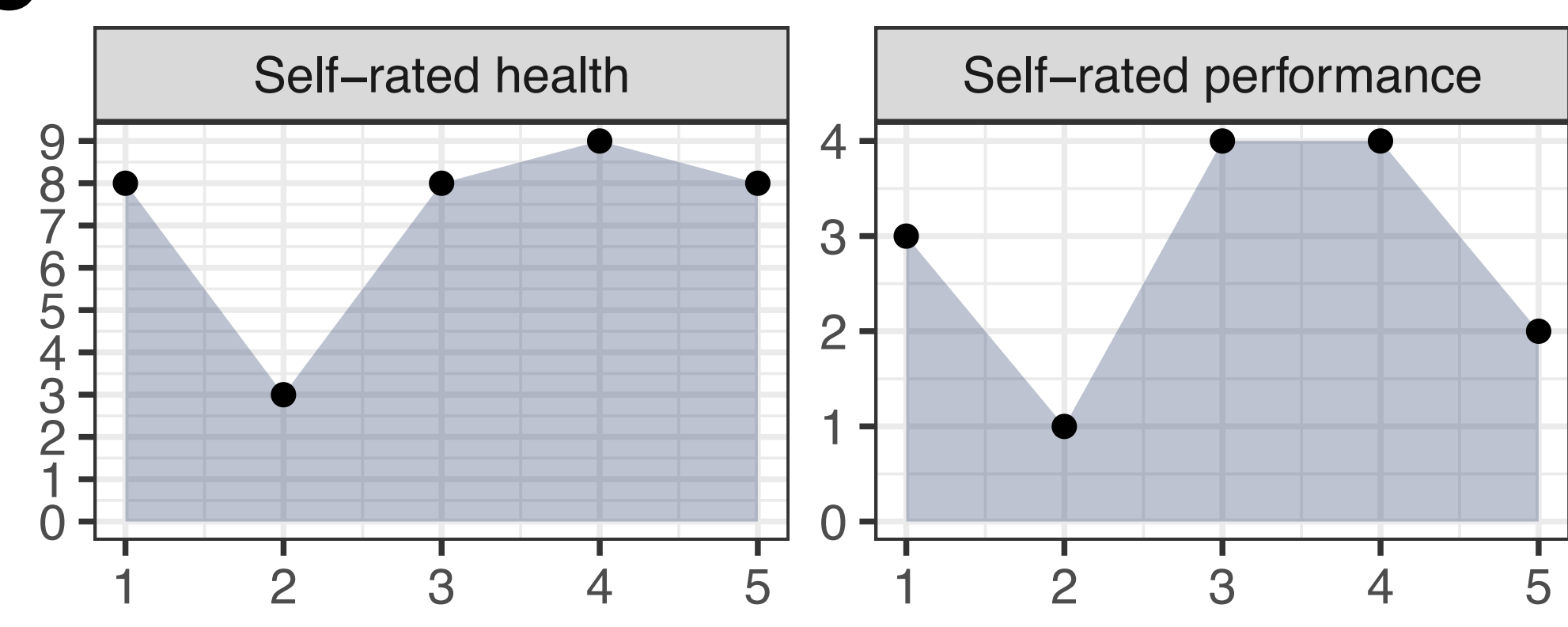
### B Spiking features



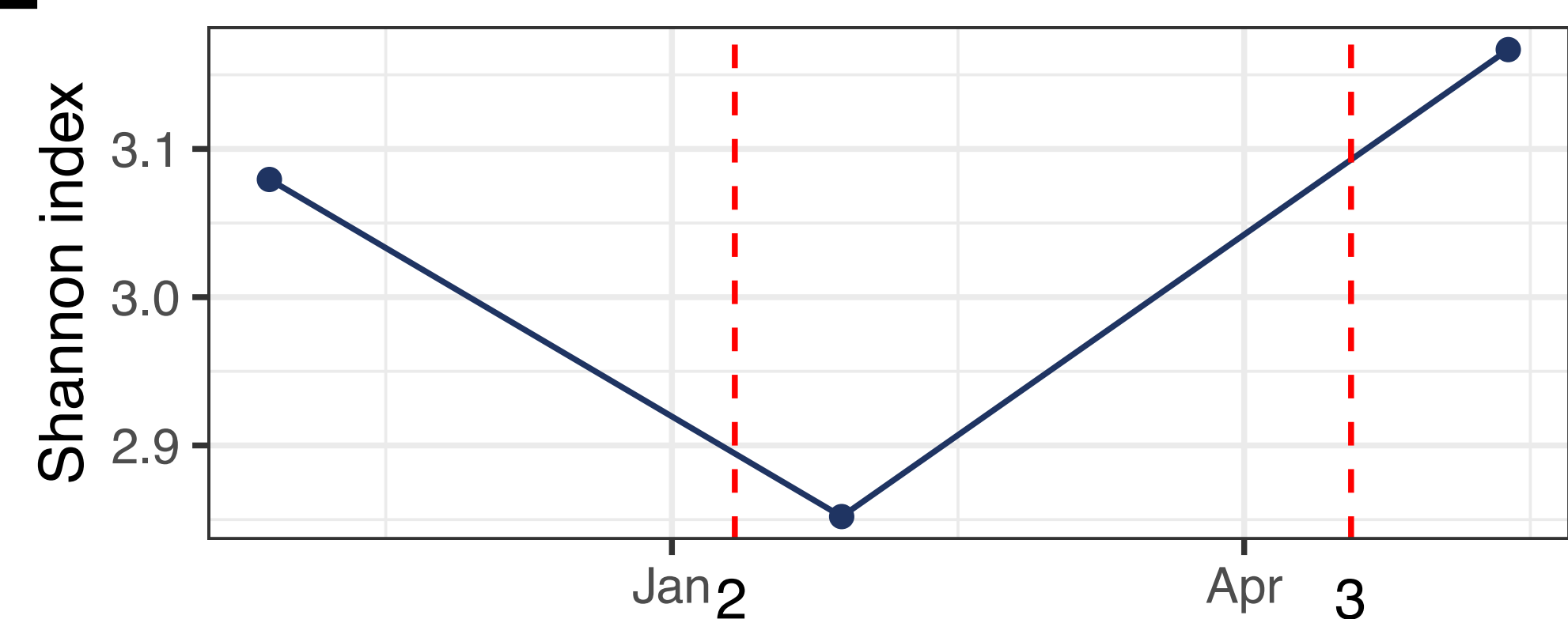
### D MOFA



### C Questionnaire



### E Gut microbiome diversity





**Supplementary figure 15 (previous page).** A participant reported an unspecified respiratory tract infection at the second visit and presented with a ill-health phenotype, corresponding to a broad alteration of the molecular space suggested by changes in several MOFA+ factors at the second visit, including a drop in the Factors linked to acylcarnitines and lipid metabolism (F8, F10), a change in the circulating lipid pool (F12) and possible hormonal changes (F14). **A.** Clinical parameters showing altered values at baseline and longitudinal changes. Reference values are shown (dashed line: lower normal value, dotted line: upper normal value). **B.** The features with positive local maxima values (i.e. a peak) at the second visit are shown as a heatmap (row z-score). An annotation column indicates the feature type (blue: omics, grey: clinical variables). Local peaks were considered only if the peak height was larger than the median value plus 2.5 times the median absolute deviation value. The features revealed a response to infection/inflammation signature (cytokines, chemokines, growth factors and proteases among others), increased circulation of certain FFAs, and steroid hormones changes. An elevation of blood glucose and a small change in insulin levels were also detected. The levels of anti-inflammatory drug naproxen, ibuprofen also reached a local maximum at visit two. **C.** Selected lifestyle questions. The numbers correspond to orderer categories, where a higher number corresponds to a more favorable outcome. **D.** Longitudinal values for selected MOFA+ factors (blue line) plotted together with the factor values for the remaining samples at each study visit (grey dots). The broad alteration of the molecular space at the second visit was suggested by changes in several MOFA+ factors (F8, F10, F12 and F14 acylcarnitines, lipid metabolism, fatty acids and hormonal changes). **E.** Gut microbiome diversity (Shannon index). The vertical dashed line mark the date for the study visit, which could be different than the fecal sample collection date (dots). A decrease in gut microbiome diversity was observed, accompanied by an increase in the abundance of taxa of the Clostridia class.