

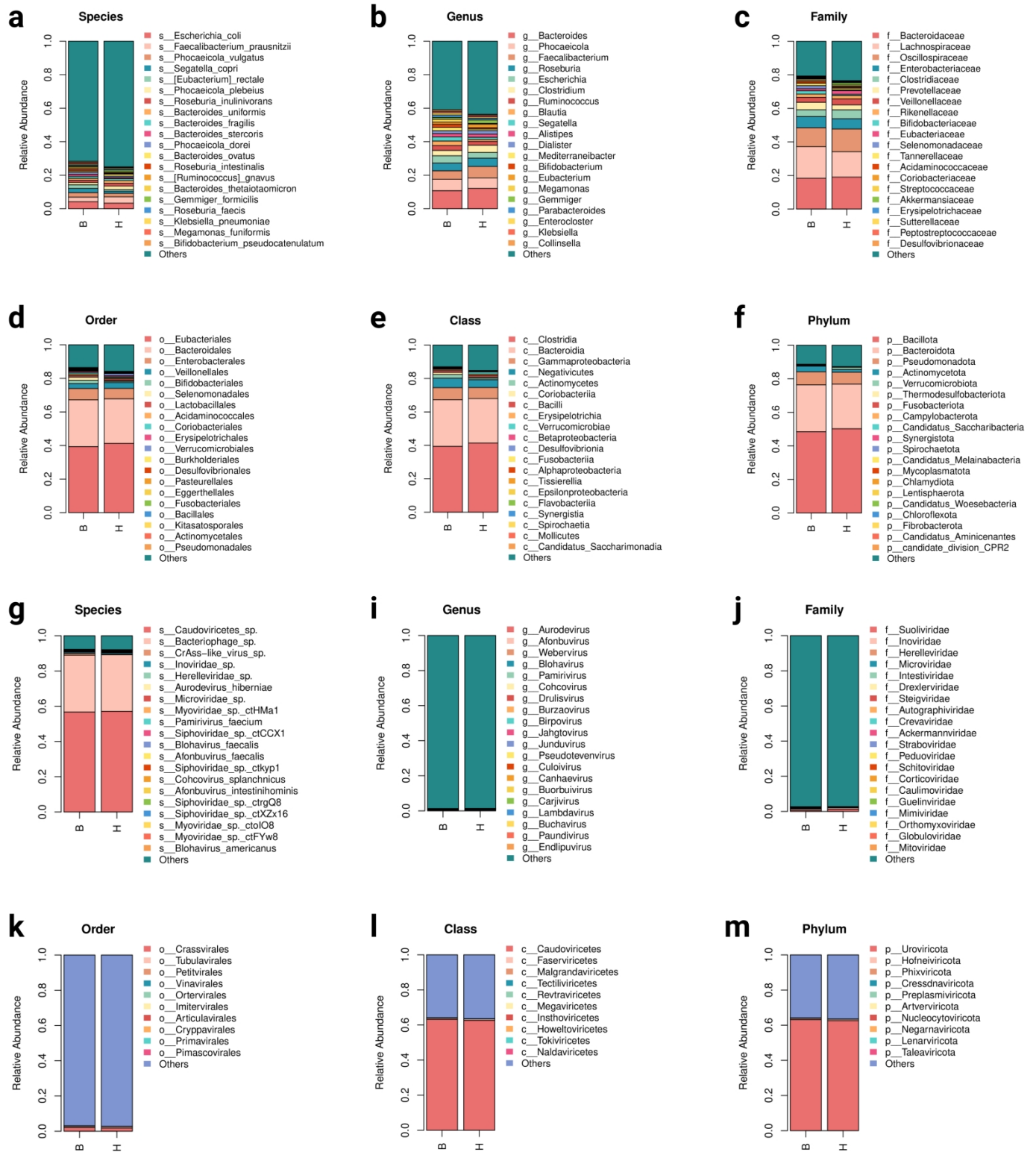


Figure S1. The identified members of gut bacteria and gut viruses.

Legend: This figure shows the members of gut bacteria (plot a-f) and gut viruses (plot g-m) identified by metagenomic sequencing. In each level, the identified members are ranked from bottom to top by decreasing relative abundance, and each color represents a specific member. Group B represents patients with bipolar depression, and Group H represents healthy controls. Only the 20 most-abundant taxa are shown (or the top 10 when the total number of identifiable taxa was > 10 but < 20). Remaining, low-abundance taxa are pooled into “others”.

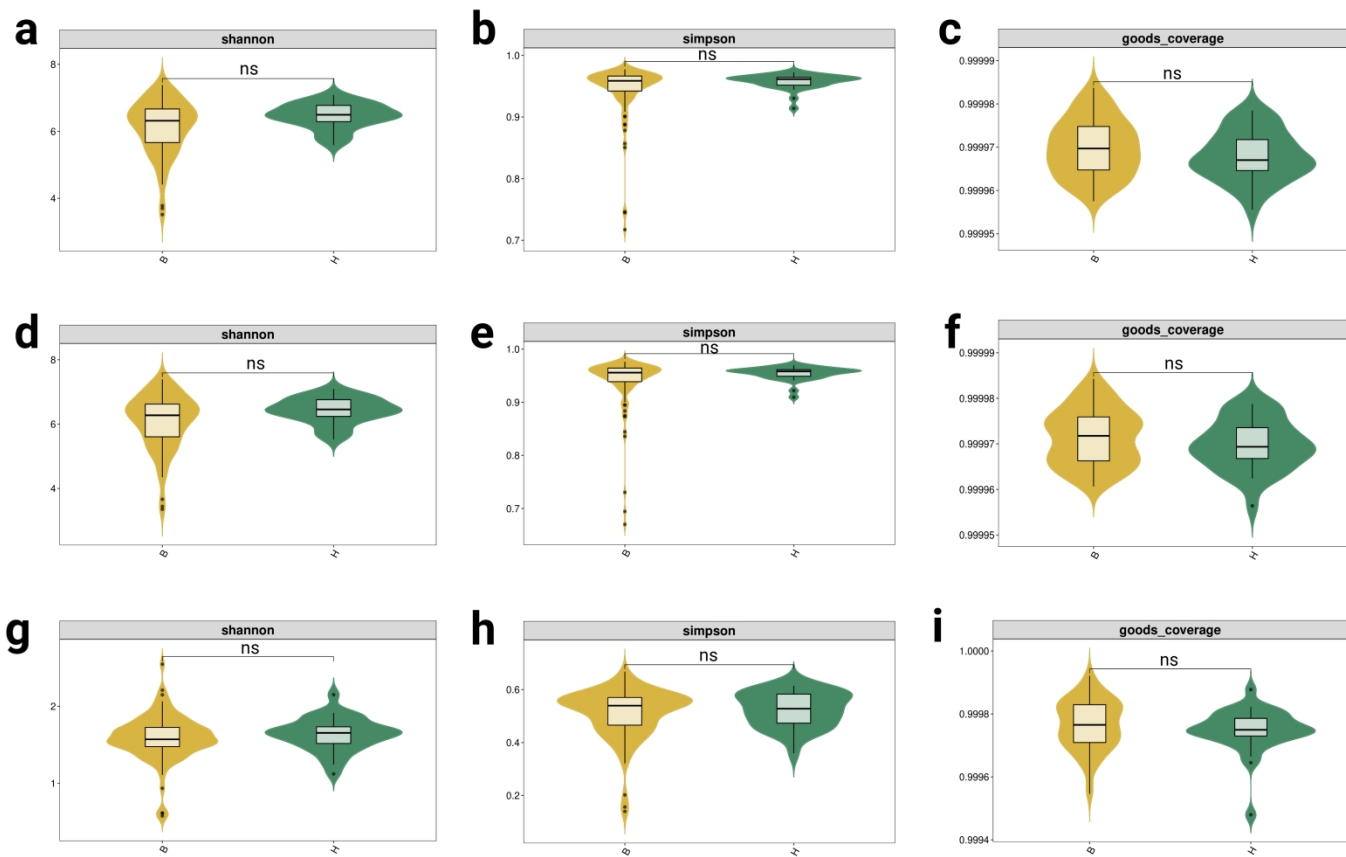


Figure S2. The rest indexes of α -diversity.

Legend: This figure shows the between-group comparisons of α -diversity indexes that failed to present significance. Plot a-c refer to total species, Plot d-f refer to bacteria, and Plot g-i refer to viruses. For each plot, the BD group is colored in yellow, and the HC group is colored in green.

Abbreviations: BD: bipolar disorder; HC: healthy control.

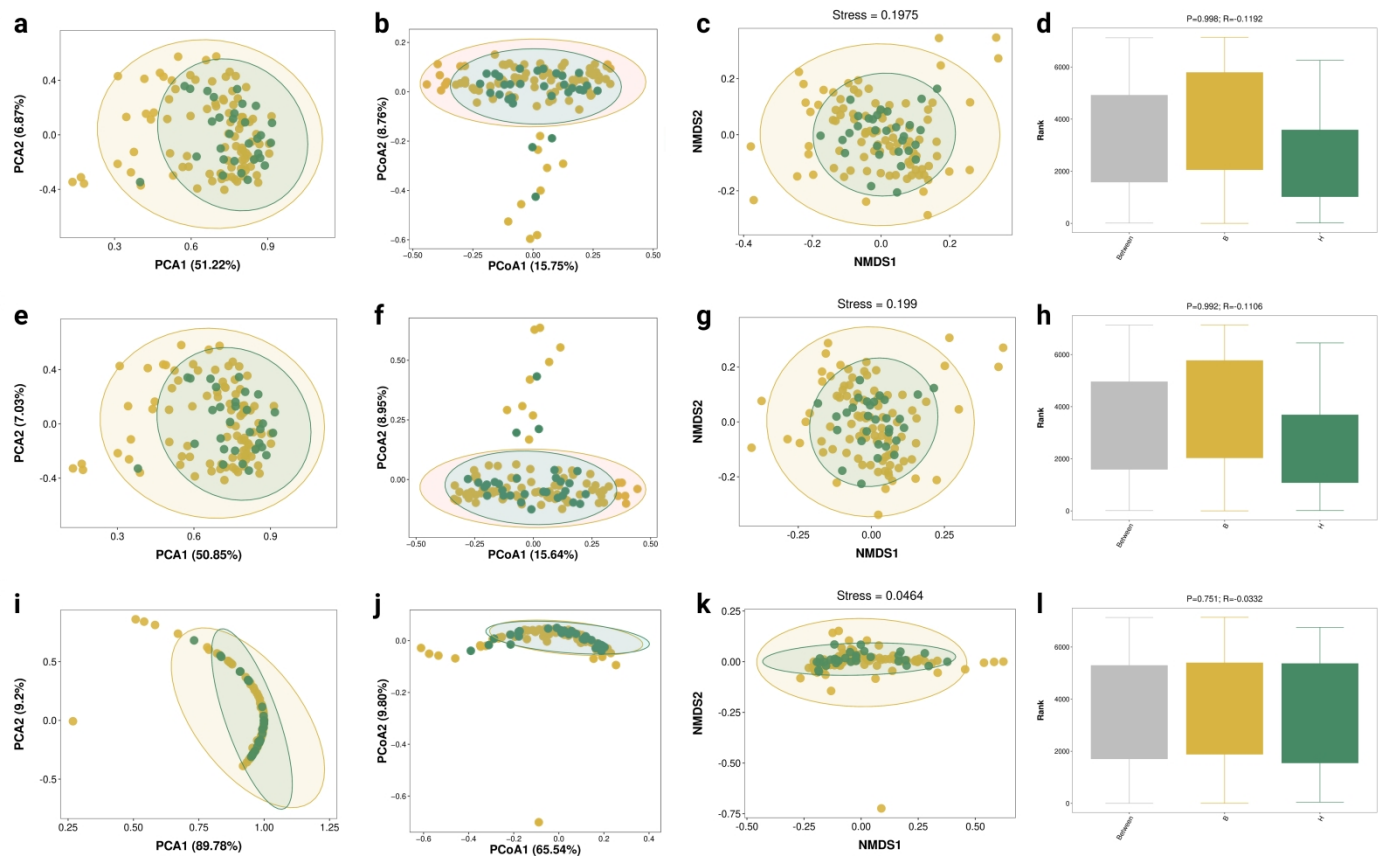


Figure S3. Analysis of β -diversity of the overall samples, gut bacteria, and gut viruses.

Legend: Plots in this figure illustrate significant differences in microbial community structure among different groups. Plot a-c: Multidimensional scaling and PCoA of microbial communities based on Bray-Curtis distance. Plot e-f: PCoA based on Jaccard distance. Plot g: NMDS with a stress value of 0.199. Plot i-k: PCoA based on Bray-Curtis distance with a high percentage of variance explained. Plot d, h, l: Boxplot showing the between-group abundance differences.

Abbreviation: PCoA: principal coordinate analysis; NMDS: non-metric multidimensional scaling.

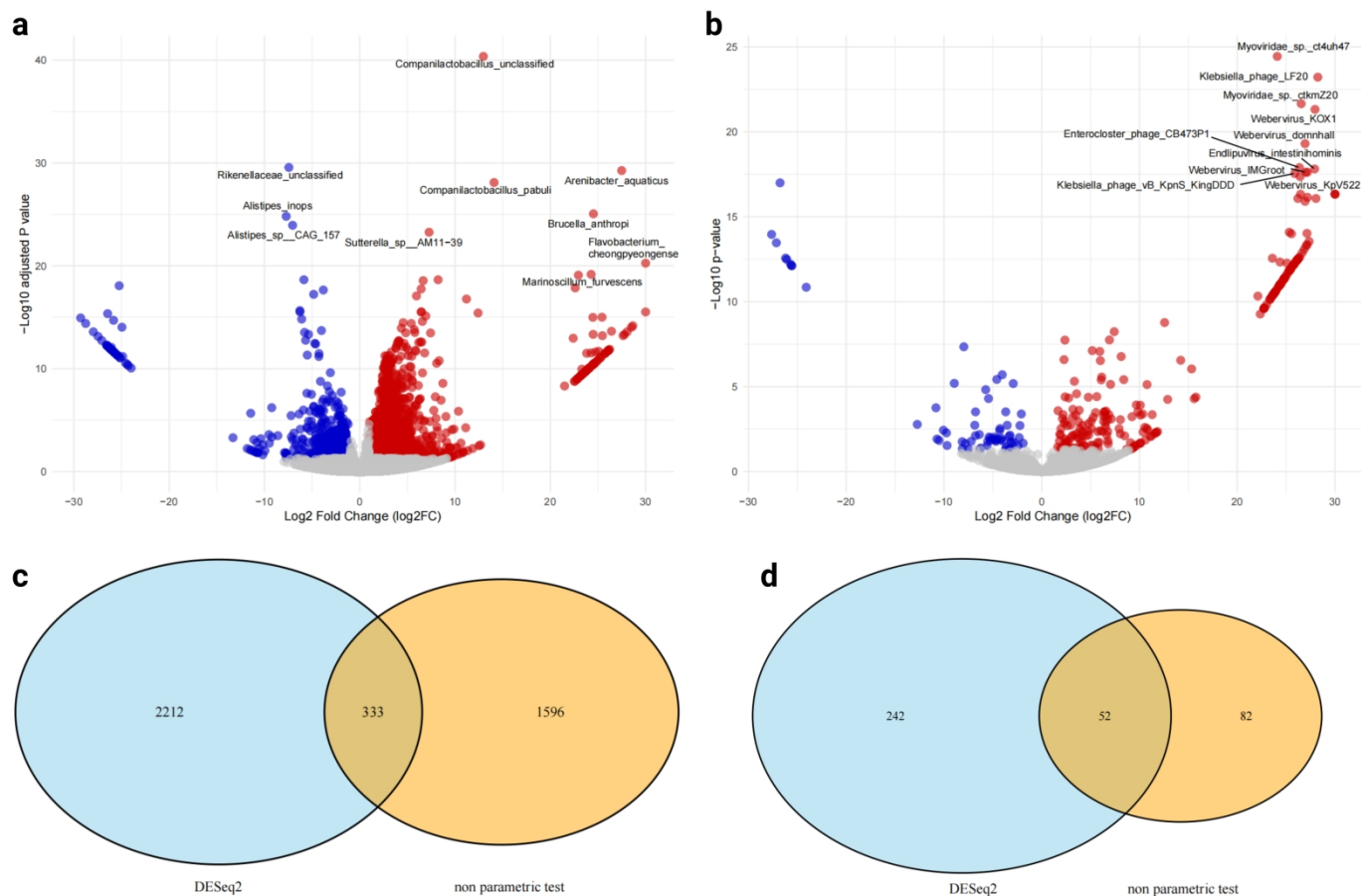


Figure S4. Results of DESeq2 analysis and the visualization of its results with non-parametric test results.

Legend: This figure showed the results of DESeq2 analysis for detecting significantly differential gut bacterial and viral members, as well as the Venn plots of results of DESeq2 and non-parametric test. Plot a-b: Volcano plot showing up-regulated microbial species (red spots), down-regulated species (blue spots), and insignificant species (gray spots) (patients v.s. healthy individuals). (a) Gut bacteria. (b) Gut viruses. Plot c-d: Venn plots. The blue circles show number of species detected by DESeq2, and the yellow circles represent species detected by non-parametric test.

Abbreviation: DESeq2: Differential Expression analysis for Sequence count data 2.

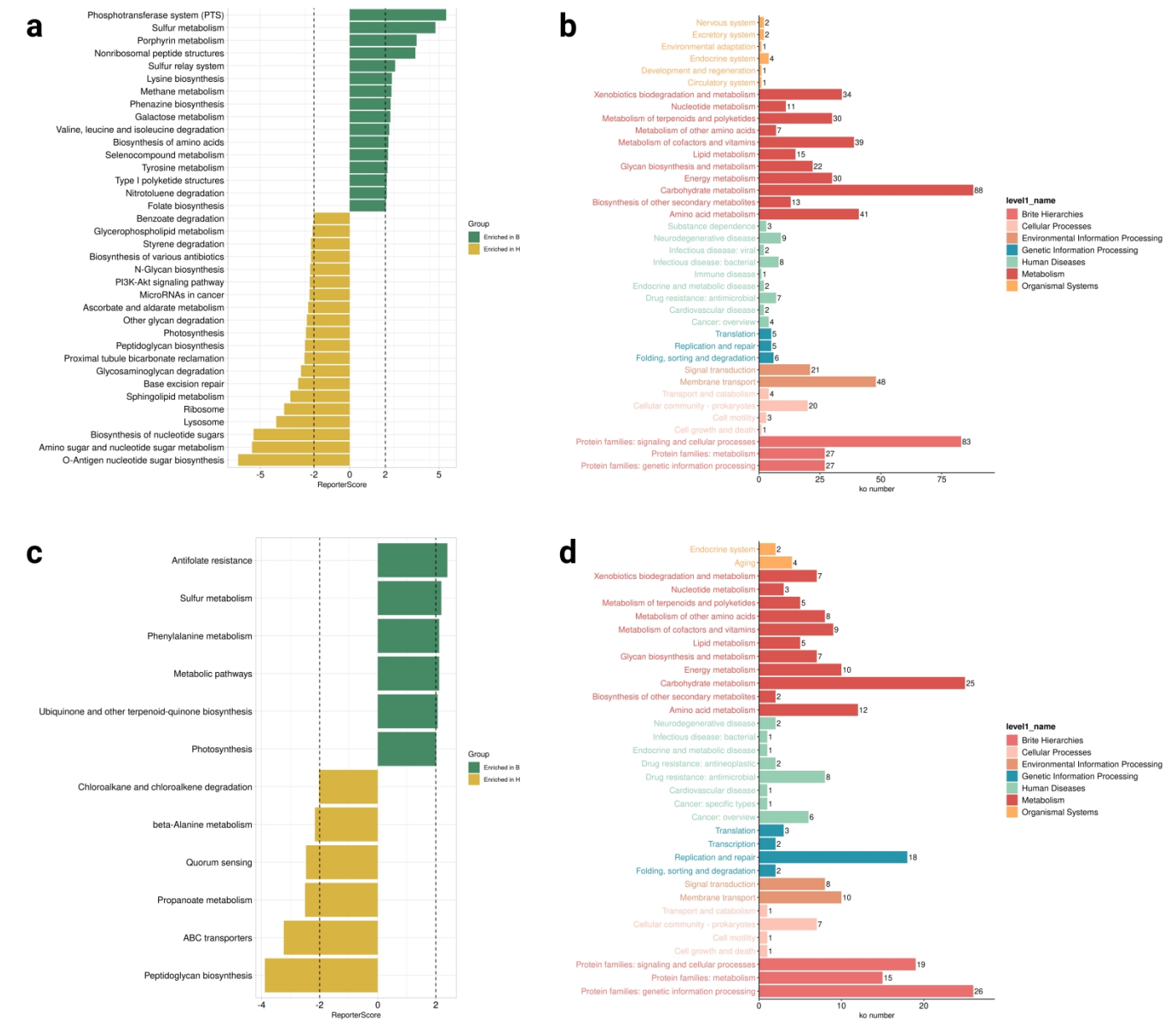


Figure S5. The functional profiling results of differential gut microbiota.

Legend: This figure presents the enrichment results of gut bacterial and viral species with significant between-group species (based on non-parametric test results). Plot a, c: Terms enriched in the two groups with ReporterScore no less than 2. Green bars represent enriching in patients, and yellow bars represent enriching in healthy individuals. (a) Gut bacteria. (c) Gut viruses. Plot b, d: Level 1 and 2 metabolic pathways significantly enriched. The horizontal axis shows KO number, and different colors represent different level 1 pathway sets.

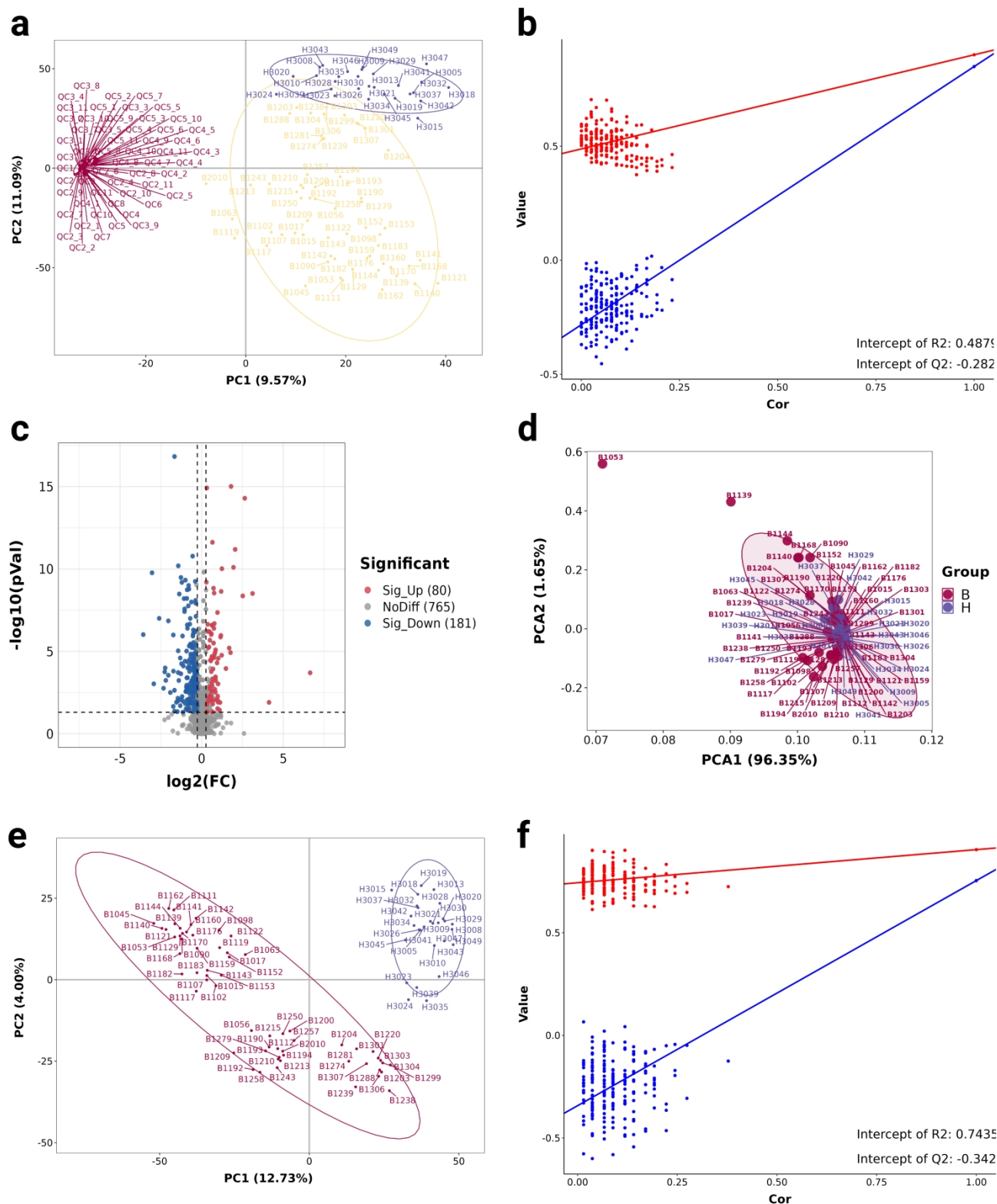


Figure S6. Supplemental plots for differential analyses of serum metabolites.

Legend: Plot a-b: Results of PLS-DA analysis of all the identified metabolites. Plot c: The volcano plot showing the up-regulated metabolites (red spots), down-regulated metabolites (blue spots), and metabolites with no between-group significance (gray spots) (patients v.s. healthy individuals). Plot d-f: Test results based on clustering showing the independence of each sample set. (d) PCA analyzing results of the significantly differential metabolites. (e, f) PLS-DA analyzing results of the significantly differential metabolites.

Abbreviation: FC: fold change.

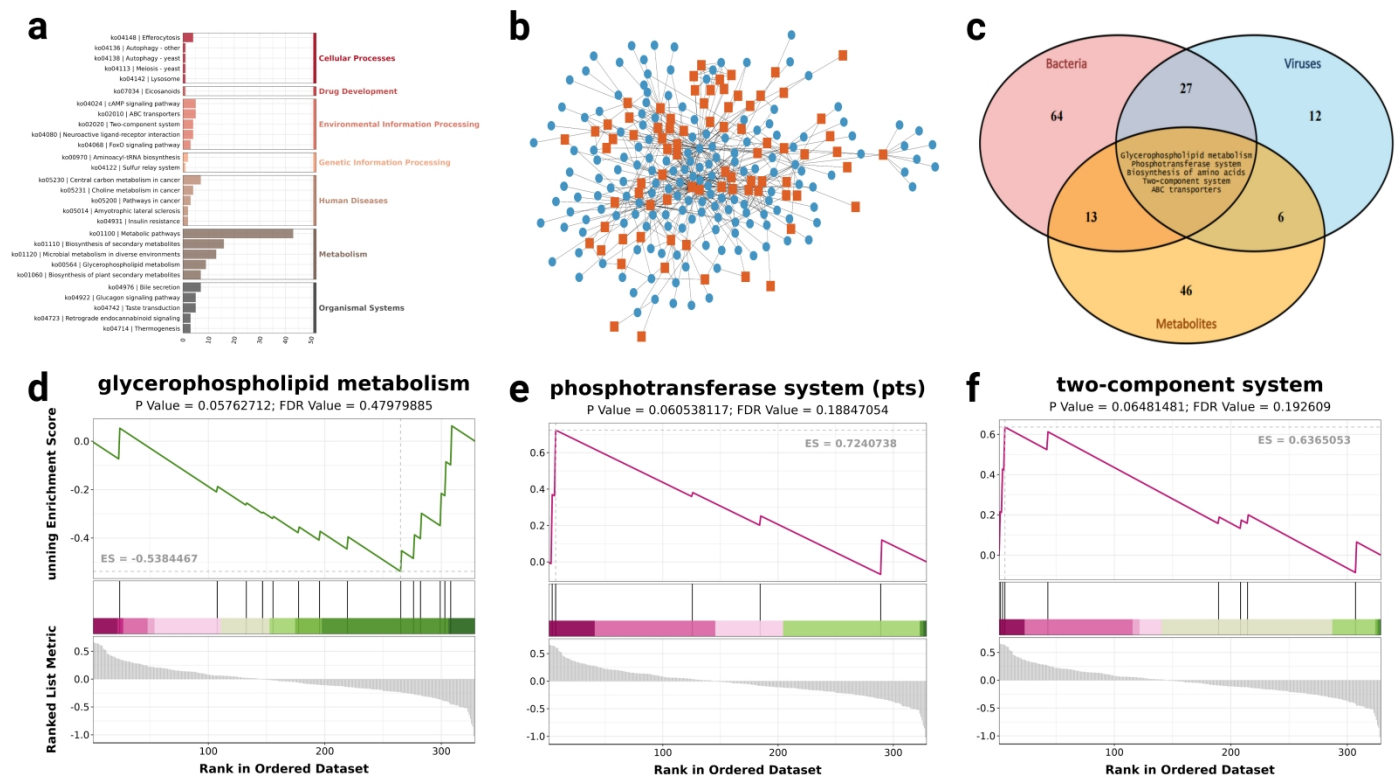


Figure S7. Enriching results of differential metabolites, network, Venn plot of the three enrichment sets of the three omics, and significant GSEA results.

Legend: Plot a: Enrichment of differential metabolites. Each color represents a set of pathways, and the horizontal axis shows the total enriched number of metabolites. Plot b: network of enriched metabolites and pathways. The orange squares represent pathways, with blue spots representing metabolites. Plot c: Venn plot showing the three enrichment sets of differential gut bacteria, gut viruses, and serum metabolites. Plot d-f: Significant results of GSEA analysis.

Abbreviations: GSEA: gene set enrichment analysis; FDR: false discovery rate.

