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Supplemental information

A population-based study of precision health assessments using multi-omics network-derived biological functional modules

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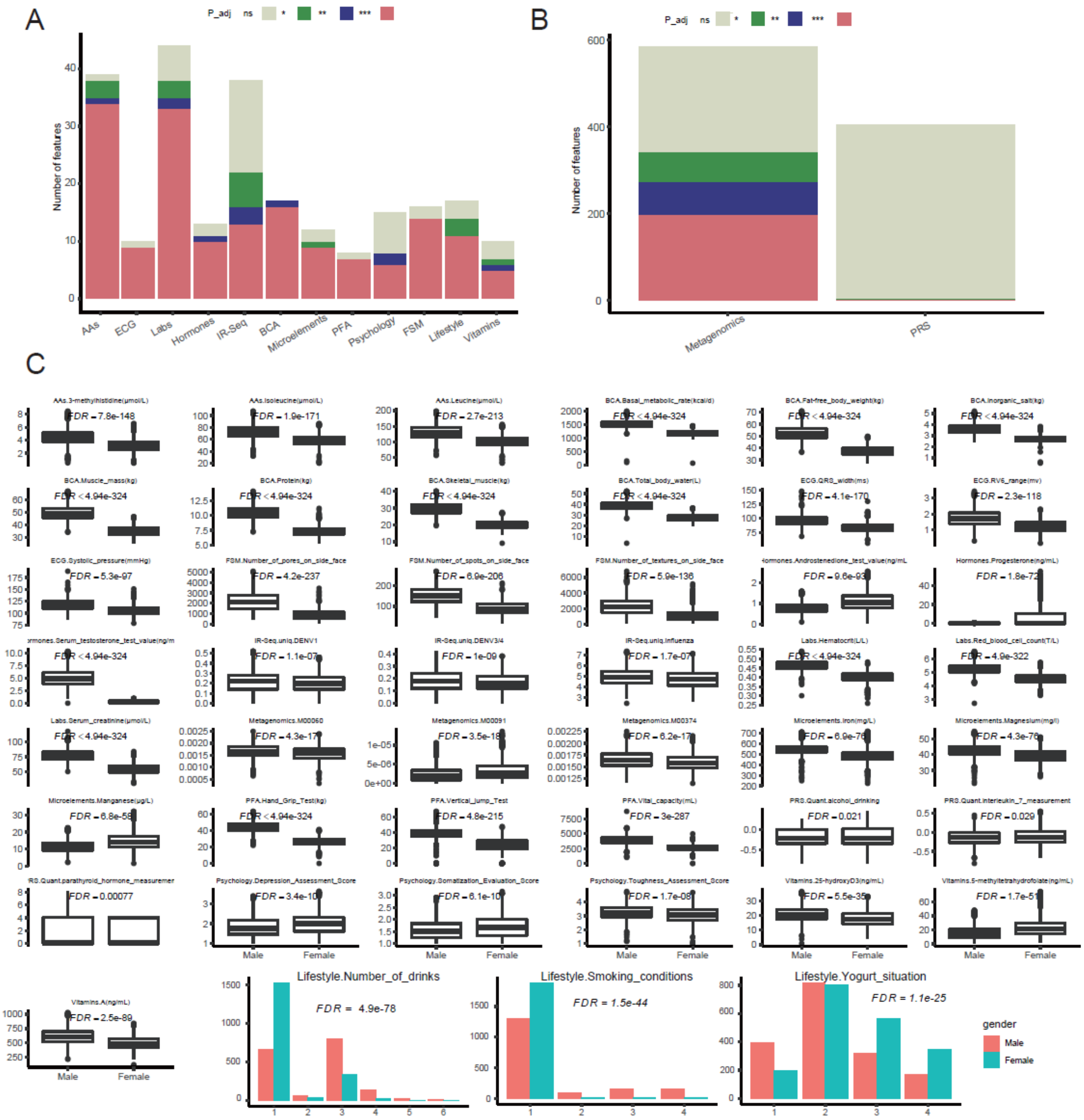
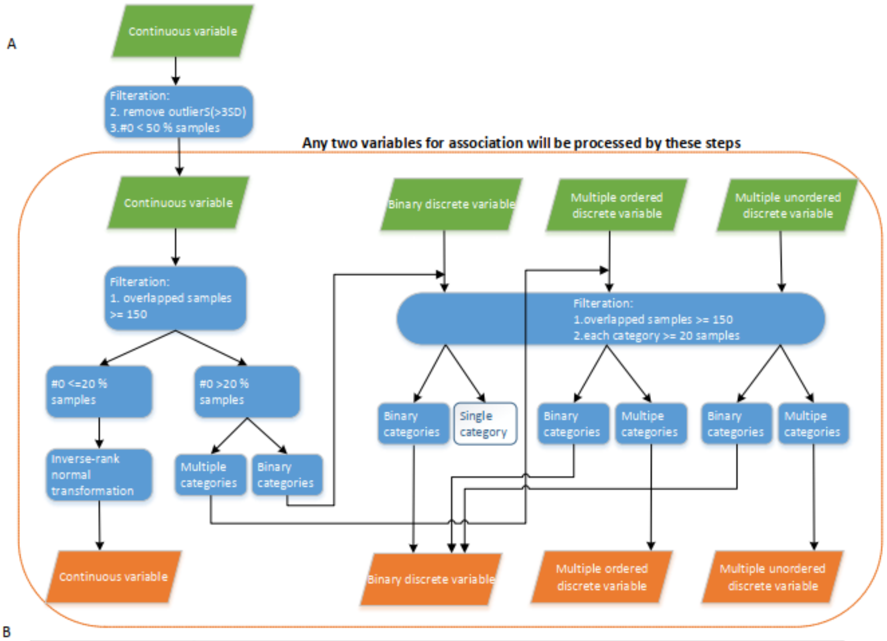


Figure S1. Gender difference, Related to Figure 1. (A) (B) The number of features comparison between male and female for each section (p_{adj}, adjusted p-values. ns, non-significant; *, p_{adj} <0.05; **, p_{adj} <0.01; ***, p_{adj}<0.001). (C) Top 3 significantly different features between males and females for each section. FDR, adjusted p-values.



B

	Continuous variable	Binary discrete variable	Multiple ordered discrete variable	Multiple unordered discrete variable
Continuous variable	Linear regression(Age)	Linear regression(Age)	Linear regression(Age)	Linear regression(Age)
Binary discrete variable	-	Logistic regression(Age)	Logistic regression(Age)	Logistic regression(Age)
Multiple ordered discrete variable	-	-	Ordinal logistic regression(Age)	Ordinal logistic regression(Age)
Multiple unordered discrete variable	-	-	-	Multinomial logistic regression(Age)

Note: in order to eliminate the affection of different sample size between variables, all tests were done with the same sample size by bootstrap and repeated 500 times

Figure S2. Data processing and flowchart of inter-omic correlations of pairwise features from two sections, Related to Figure 1. (A) The data processing and redefine the types of variables(features). (B) Conditional regression with age adjusted to detect inter-omics associations.

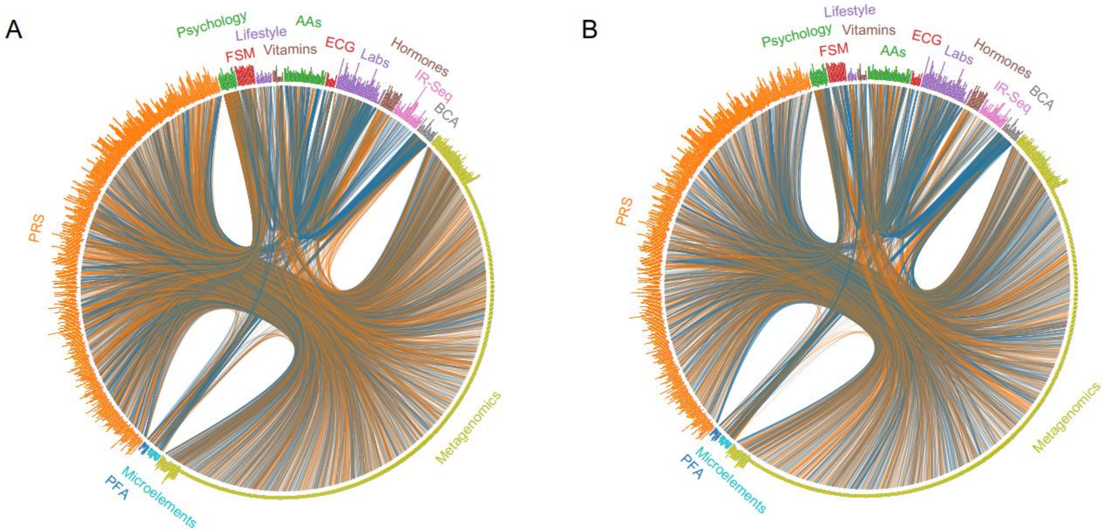


Figure S3. All significant correlations (padj <0.001) of pairwise features from two sections for male (A) and female (B), Related to Figure 1. Orange line represents one positive correlation and blue line represents negative correlation.

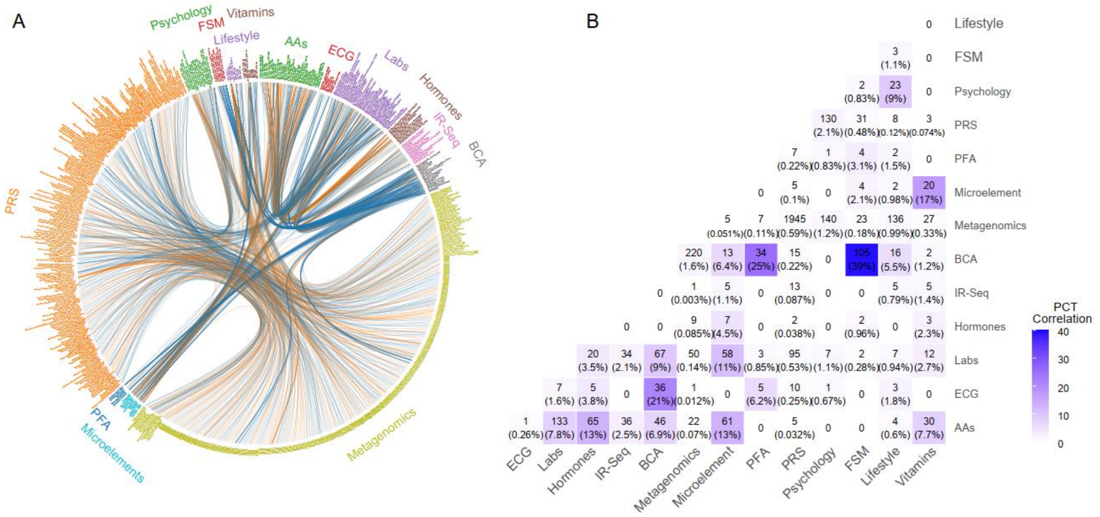


Figure S4. Inter-omic correlations of pairwise features from two sections for female, Related to Figure 1. (A) Top 1000 correlations of pairwise features from two sections. Orange line represents positive correlation and blue line represents negative correlation. (B) The number and proportion of significant correlations (p_{adj} <0.001) for per pair of sections. The percentages are the proportion of significant correlations out of all possible pairwise correlations between per pair sections.

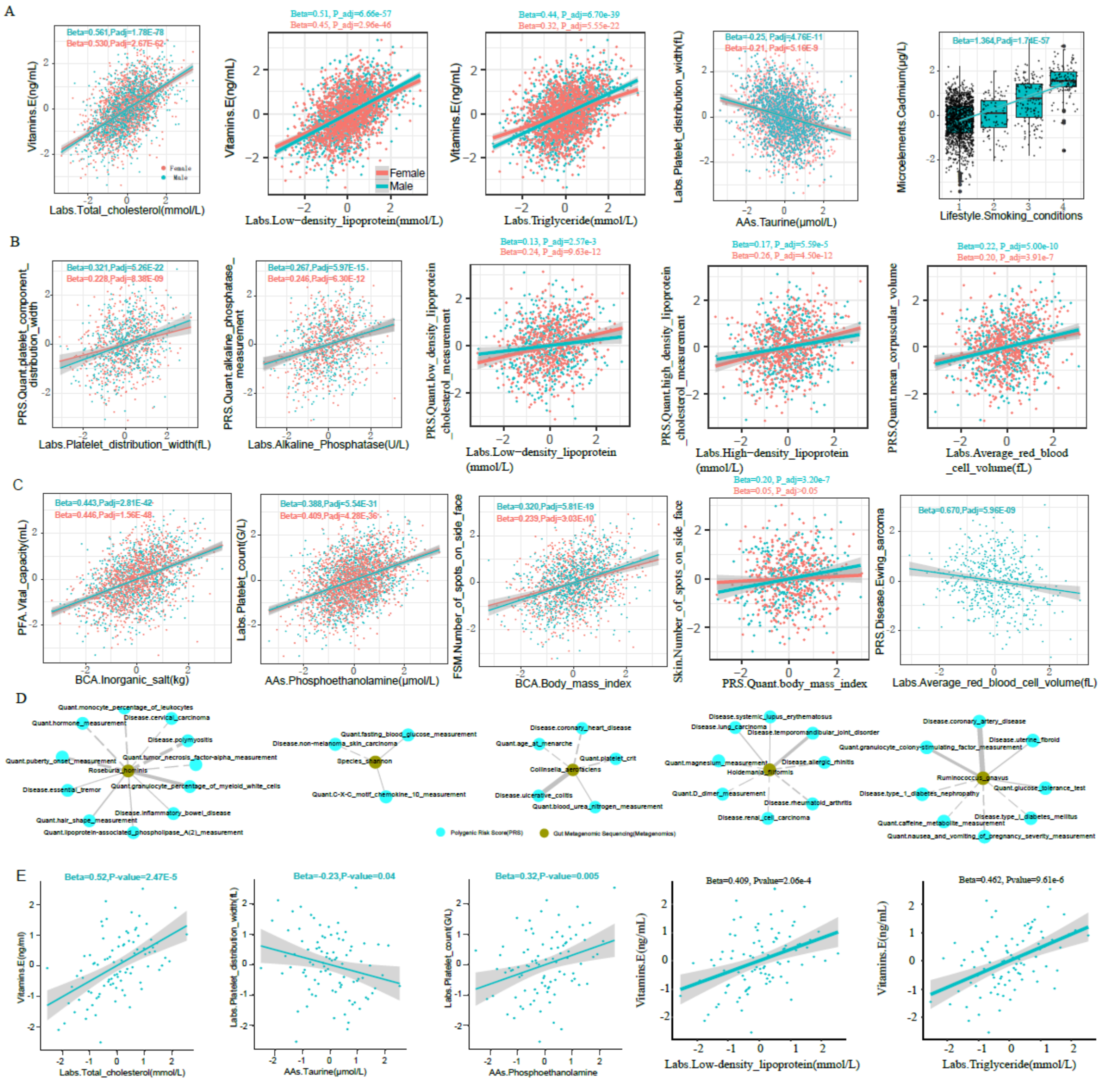


Figure S5. Representative significant inter-omic correlations of pairwise features, Related to Figure 1. (A) The representative known correlations that have been previously reported. (B) The representative correlations between PRS and Labs. (C) Selected correlations (with very small *p* values) that have not been reported. (D) A star network with a central node based on metagenomics, surrounded by the features of PRS. (E) Representative correlations validated by the independent HE dataset.

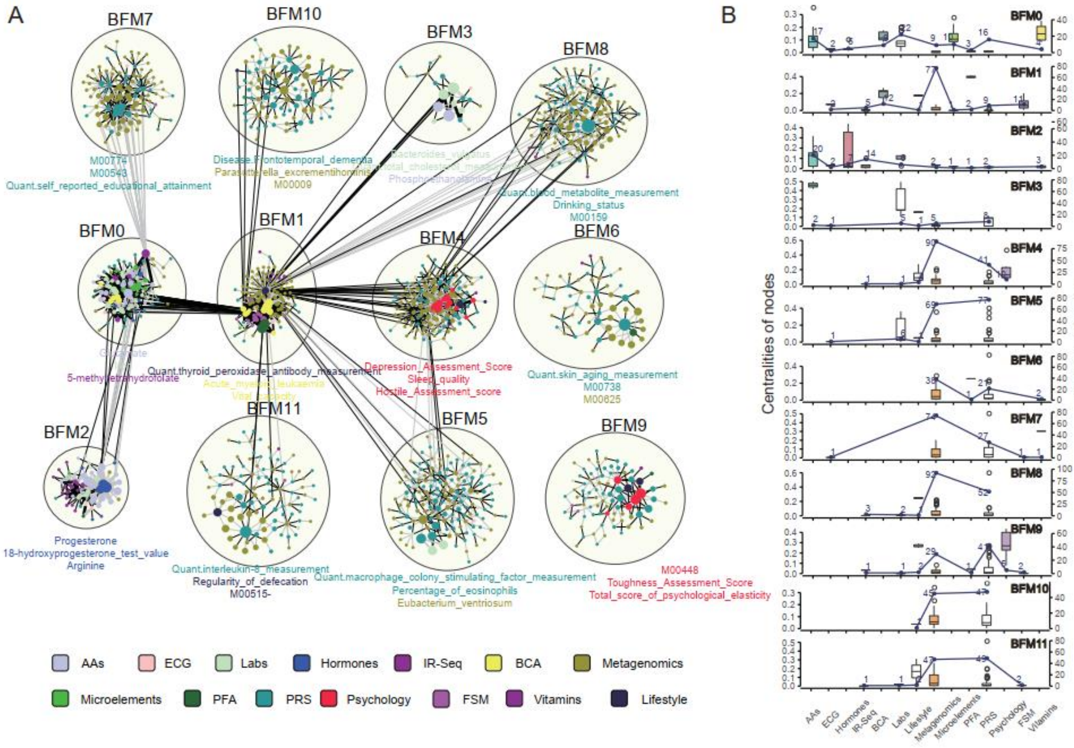


Figure S6. Networks of all BFMs in females, Related to Figure 2. (A) All nodes and edges of BFMs in females. BFMs were constructed by the Louvain method, and overlapping nodes were added. The network in the circle is a BFM, and the top three features ranked by node centrality are listed below the network. The size of the node represents the centrality. The black line represents a positive correlation between paired features, while the grey line represents a negative correlation. (B) Statistics in each section for each BFM. The boxplot shows the centralities of nodes (left y axis), and the red line shows the number of nodes (right y axis) in each section.

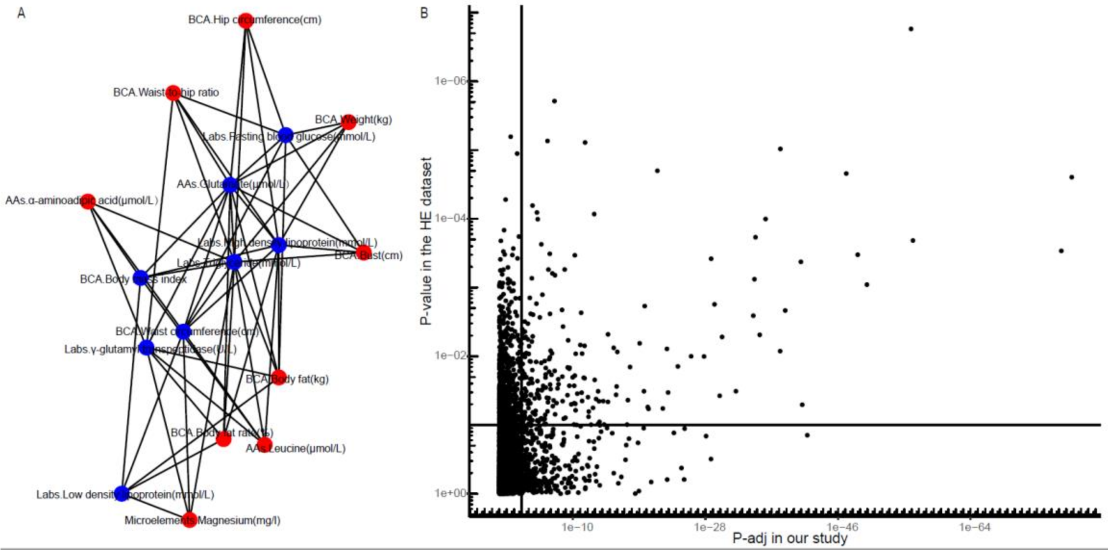


Figure S7. Network of features with cardiometabolic disease in females and the correlations comparison between our cohort and HE dataset, Related to Figures 1 and 3. (A) Sub-network in BFM 0 in females. The markers are associated with cardiometabolic disease from two published studies with multi-omic data (blue nodes) and are closely connected nodes with them (red nodes). The red node connected at least six blue nodes. (B) The correlations comparison between our cohort and HE dataset. Each dot represents a pairwise features.

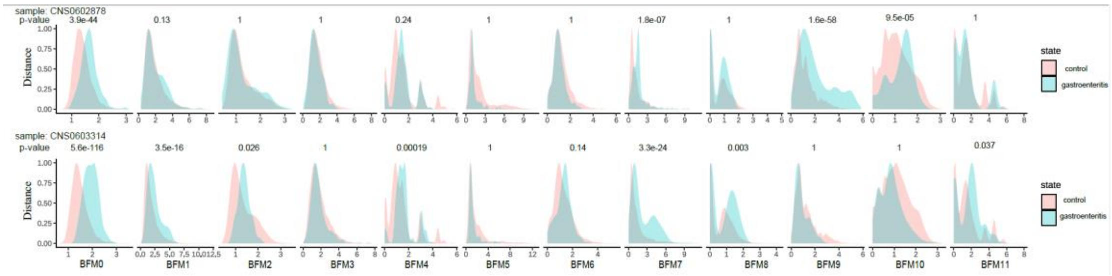


Figure S8. Comparison of the similarity distance in each BFM for the two individuals, Related to Figure 4. (one-tailed Mann-Whitney test). We randomly selected individuals from the cohort as the benchmark group in BFM-ash.

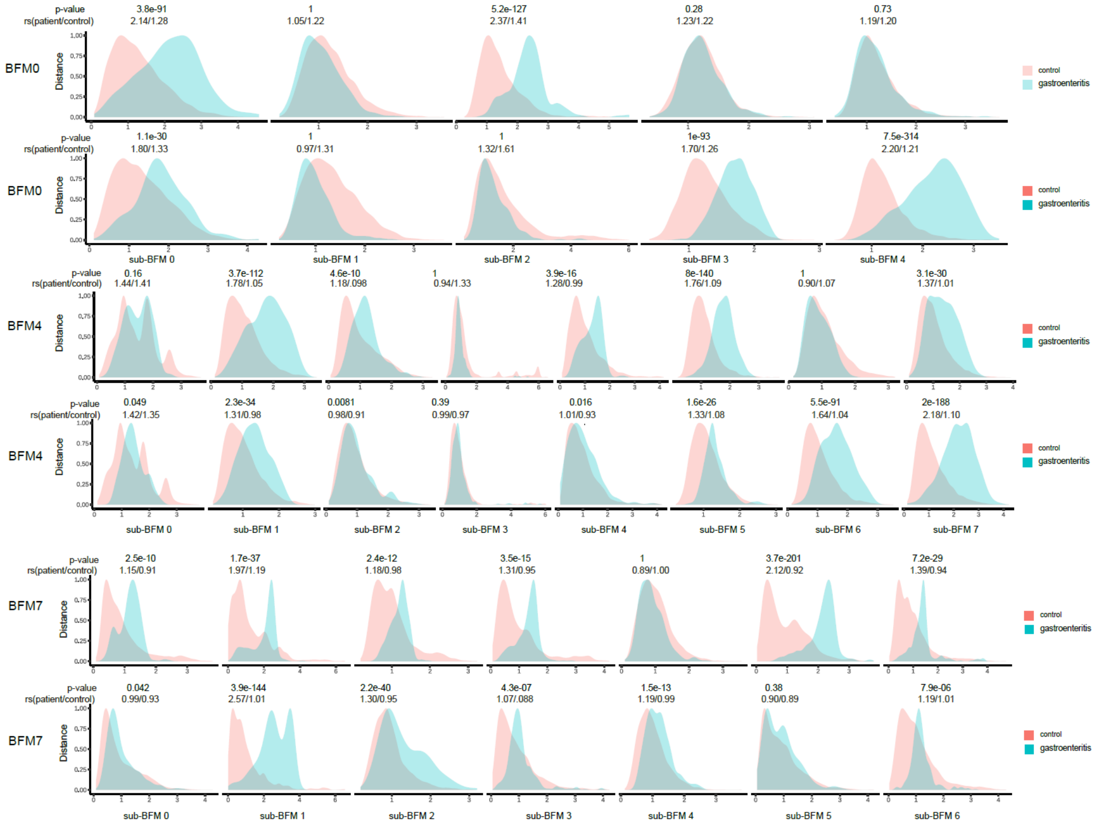


Figure S9. Comparison of the similarity distance in each sub-BFM of BFM 0, 4, 7 for the two patients with gastroenteritis, Related to Figure 4. Each line represents one patient (one-tailed Mann-Whitney test). rs, risk score.

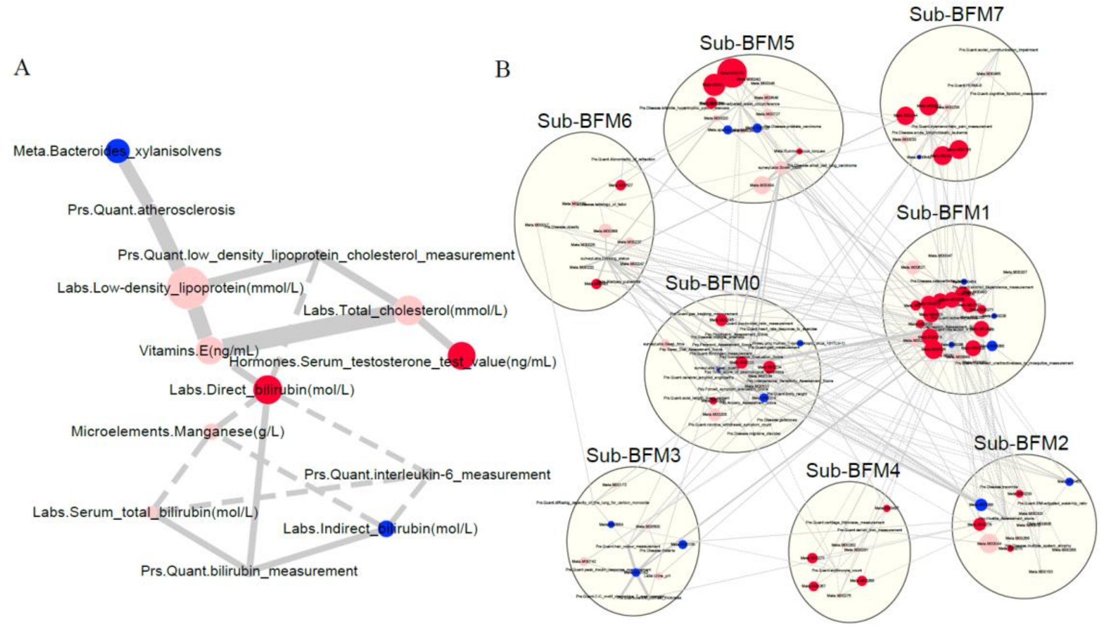
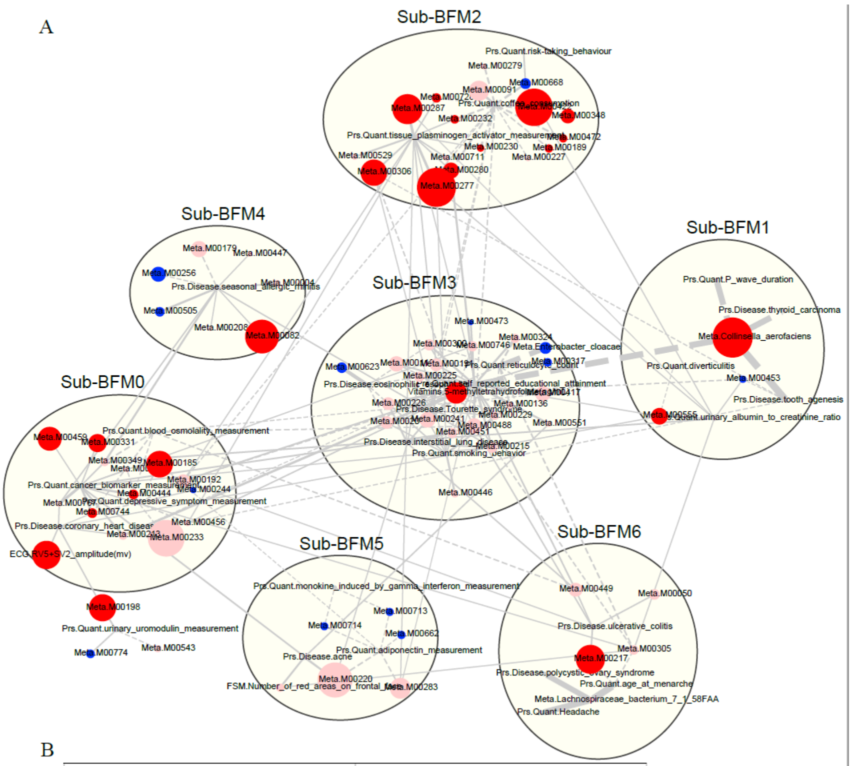


Figure S10. Networks of BFM 0 and BFM4 for two female patients with gastroenteritis, Related to Figure 4. (A) Sub-BFM 0 in BFM 0. (B) BFM4. The nodes were classified into four groups: feature score > 0 in both patients (red), feature score > 0 in one patient (pink), feature score <= 0 in both patients (blue) and no data (grey); node size represents the average feature scores in the two patients; the line width represents the regression coefficient; the solid line represents the positive correlation; and the dashed line represents the negative correlation.



B

levelB	levelC
Environmental information processing	Peptide and nickel transport system
Environmental information processing	Mineral and organic ion transport system
Environmental information processing	Bacterial secretion system
Environmental information processing	Phosphate and amino acid transport system
Environmental information processing	Saccharide, polyol, and lipid transport syste
Environmental information processing	Drug efflux transporter/pump
Environmental information processing	Drug resistance
Environmental information processing	Two-component regulatory system

Figure S11. Network of BFM 7 for two female patients with gastroenteritis, Related to Figure 4. (A) The network of BFM 7. The nodes were classified into four groups: feature score > 0 in both patients (red), feature score > 0 in one patient (pink), feature score <= 0 in both patients (blue) and no data (grey); node size represents the average feature scores in the two patients; the line width represents the regression coefficient; the solid line represents the positive correlation; and the dashed line represents the negative correlation. (B) GMMs' annotation by KEGG database for 13 GMMs in sub-BFM 0 in BFM 7.

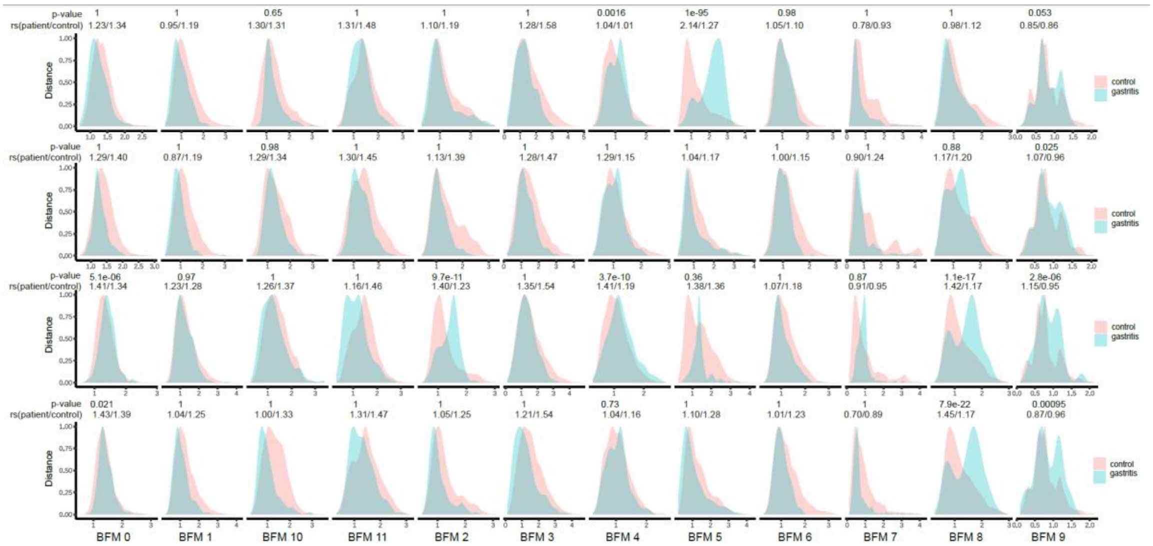


Figure S12. Comparison of the similarity distance in each BFM for the four patients with gastritis, Related to Figure 4. Each line represents one patient (one-tailed Mann-Whitney test). rs, risk score.

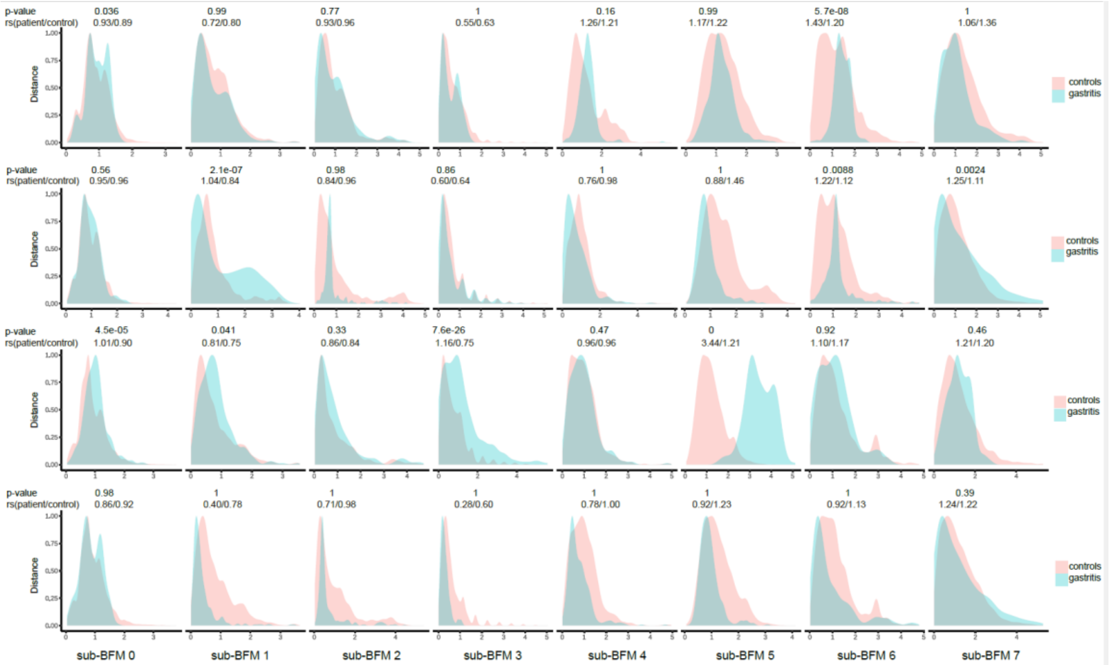


Figure S13. Comparison of the similarity distance in each sub-BFM of BFM9 for the four patients with gastritis, Related to Figure 4. Each line represents one patient (one-tailed Mann-Whitney test). rs, risk score.

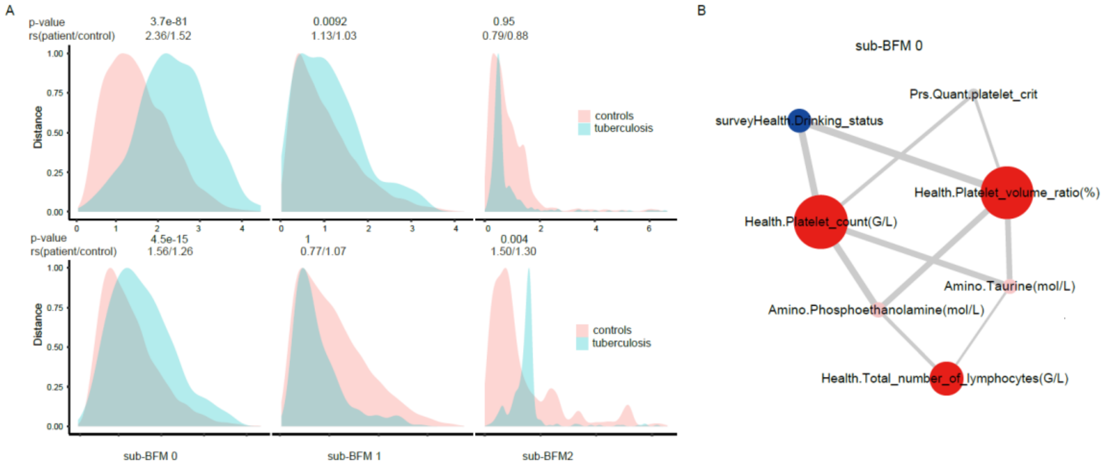


Figure S14. Comparison of sub-BFMs of BFM3 for the two patients with tuberculosis, Related to Figure 4. (A) Comparison of the similarity distance in each sub-BFM of BFM3. Each line represents one patient (one-tailed Mann-Whitney test). rs, risk score. (B) The network of sub-BFM 0 in BFM 3. The nodes were classified into four groups: feature score > 0 in both patients (red), feature score > 0 in one patient (pink), feature score <= 0 in both patients (blue) and no data (grey); node size represents the average feature scores in the two patients; the line width represents the regression coefficient; the solid line represents the positive correlation; and the dashed line represents the negative correlation.

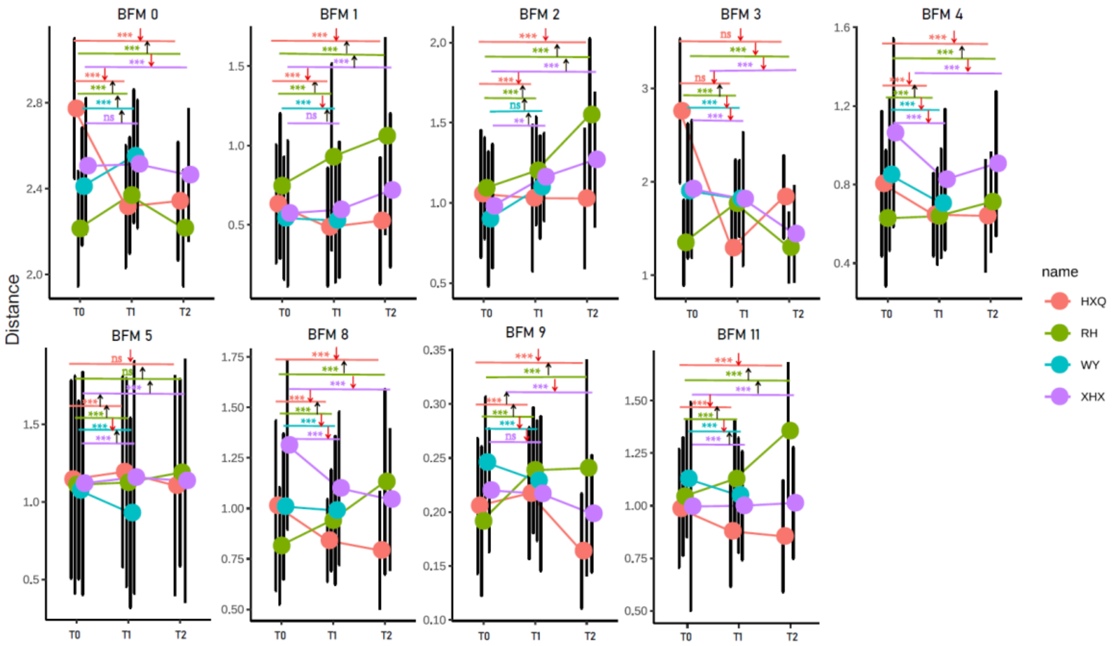


Figure S15. Change in similarity distance at three timepoints in partial BFMs for the case group, Related to Figure 5. ↑ and ↓ indicate the direction of distance change.

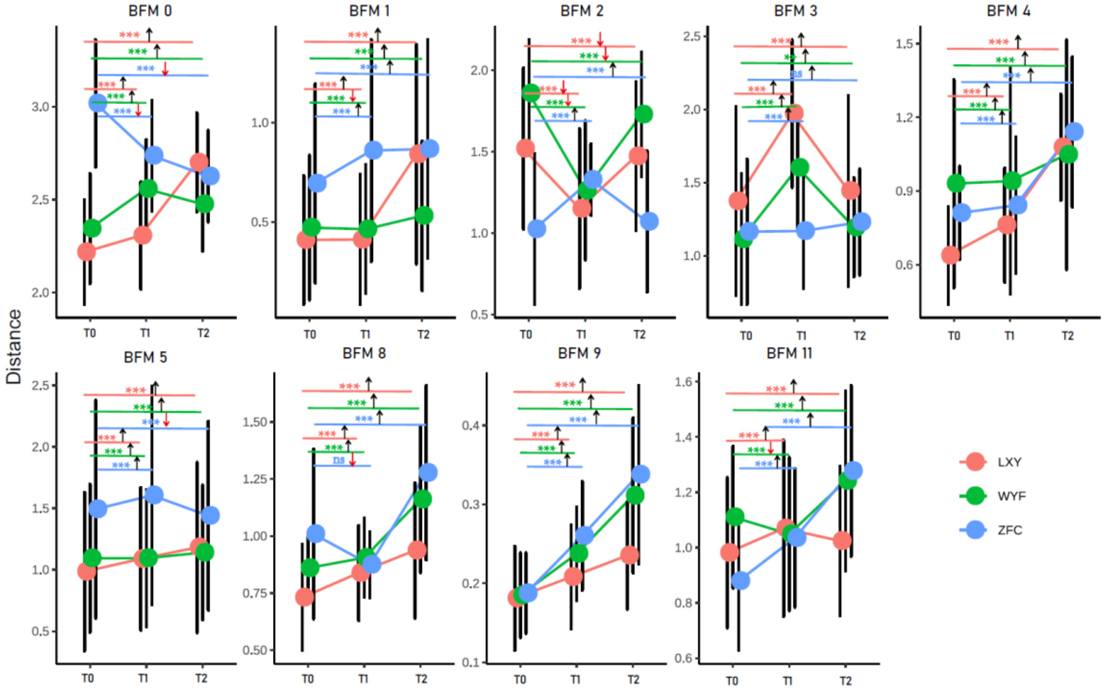


Figure S16. Change in similarity distance at three timepoints in all BFMs for the control group, Related to Figure 5. ↑ and ↓ indicate the direction of distance change.

Figure S17. Change of features between T1 and T2 in control group, Related to Figure 5. Change of feature: T2-T1, the value in T2 minus the value in T1 for each feature. (A) the features in BFM 6. (B) the features in BFM 7. (C) intestinal bacteria in BFM4, 6, 7, 8 and 9. The color in the bar represents the study (PMID) reported that the bacterium was correlated with seasonal change in human beings.

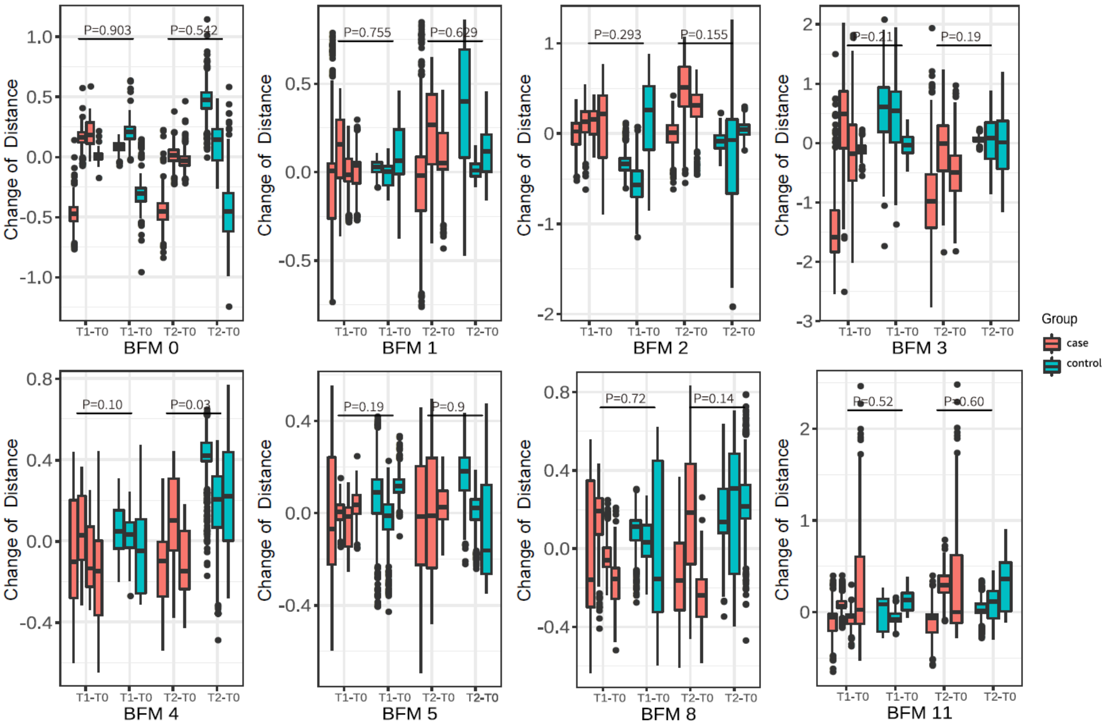


Figure S18. Comparison between the case and control groups in partial BFMs, Related to Figure 5. The case includes four samples and control includes three samples.

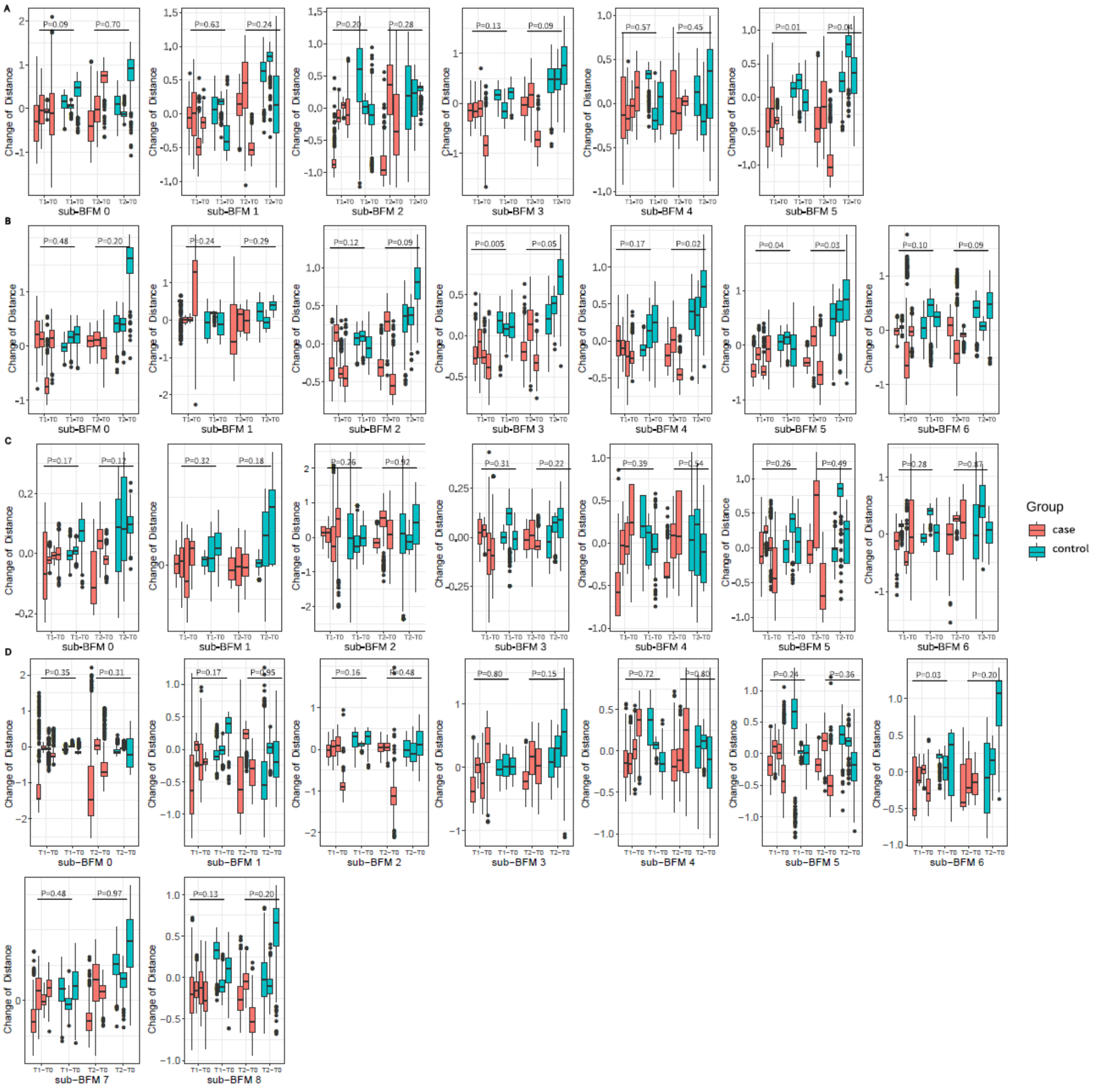


Figure S19. Comparison between the case and control group in sub-BFMs of BFM 6(A), 7(B), 9(C) and 10(D), Related to Figure 5. The case includes four samples and control includes three samples.

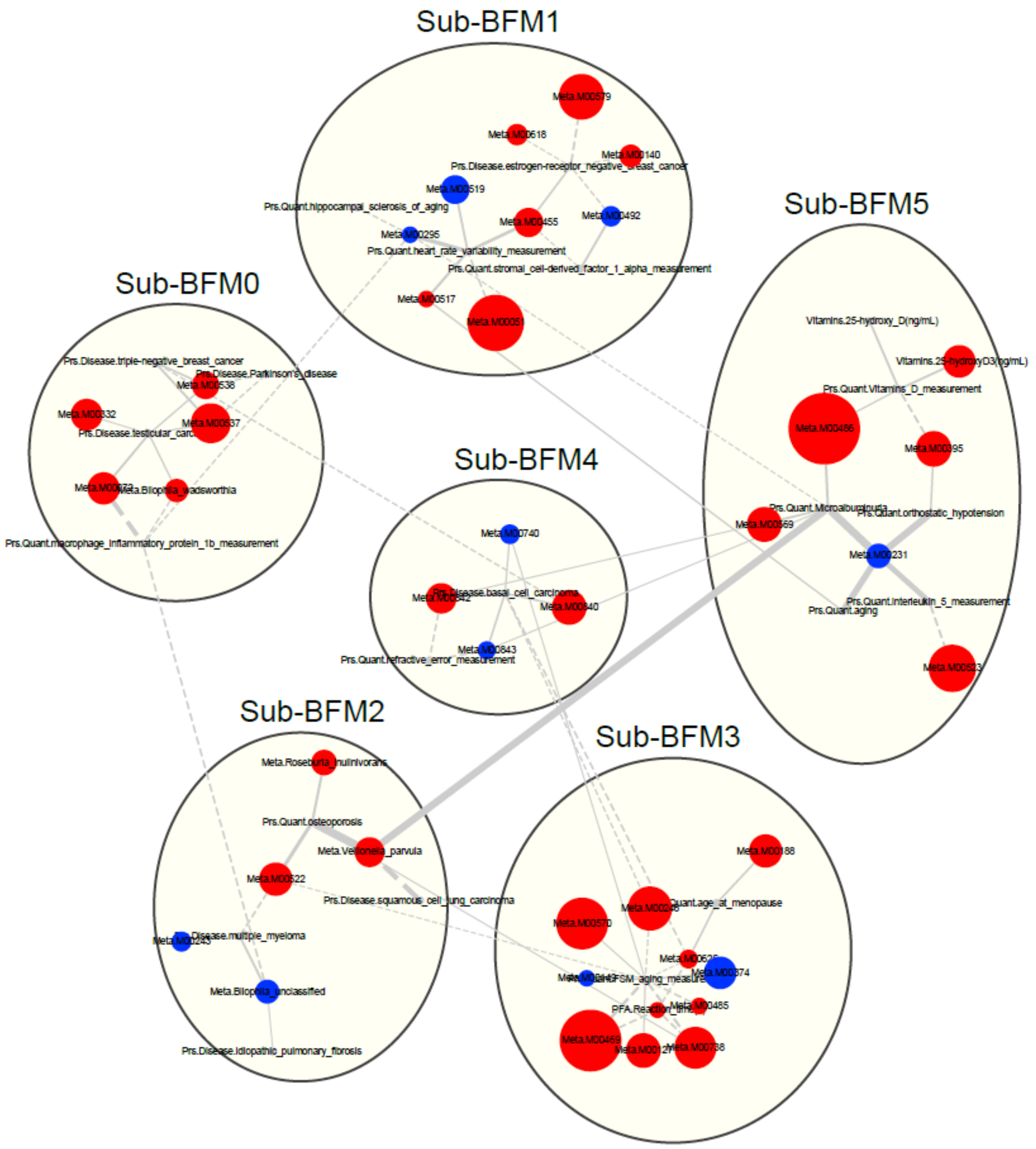


Figure S20. Network of BFM6 at T1 for GSE intervention, Related to Figure 5. Node size represents the absolute value of the intervention score; the nodes were classified into three groups: intervention score < 0 (red), intervention score > 0 (blue) and no data (grey); the line width represents regression coefficient; the solid line represents the positive correlation; and the dashed line represents the negative correlation.

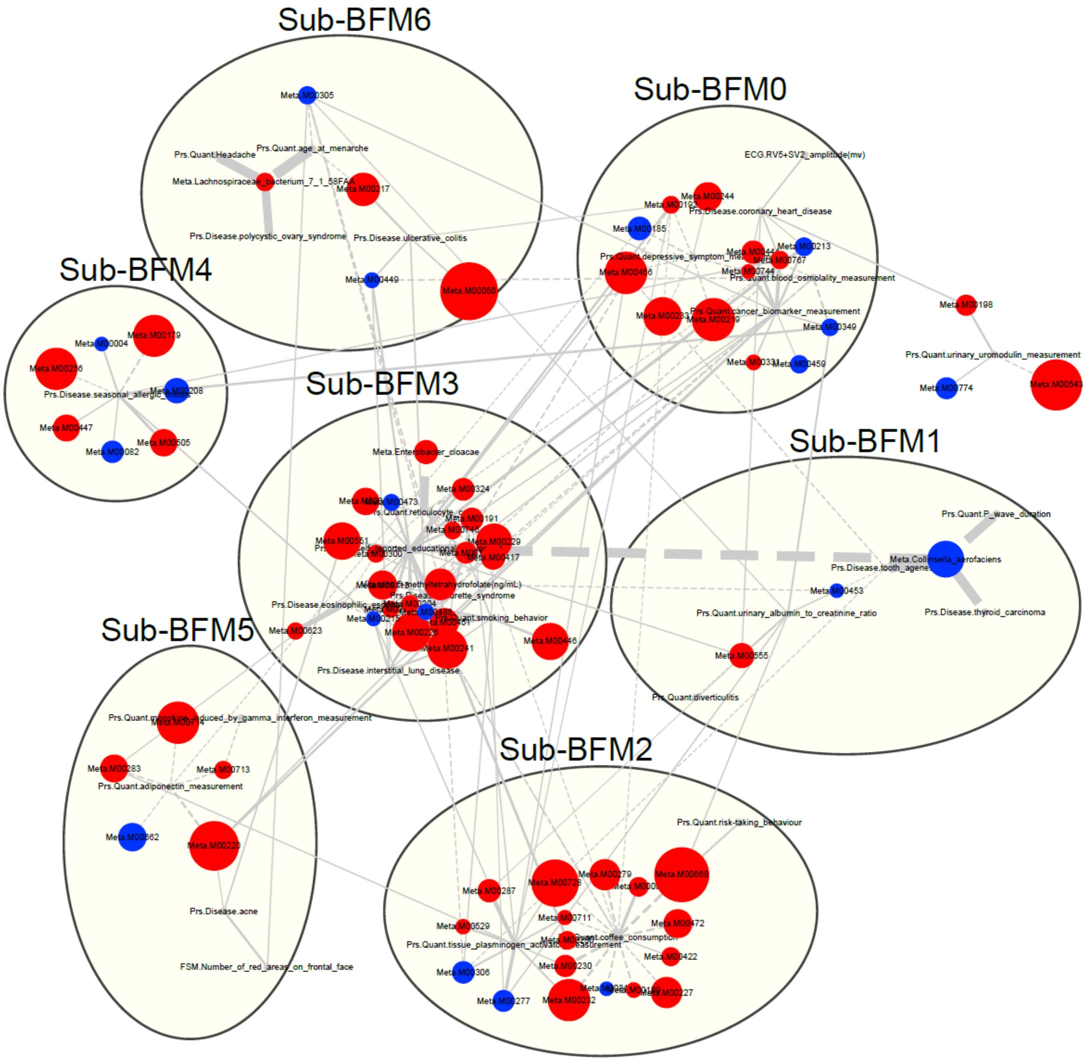


Figure S21. Network of BFM7 at T1 for GSE intervention, Related to Figure 5. Node size represents the absolute value of the intervention score; the nodes were classified into three groups: intervention score < 0 (red), intervention score > 0 (blue) and no data (grey); the line width represents regression coefficient; the solid line represents the positive correlation; and the dashed line represents the negative correlation.

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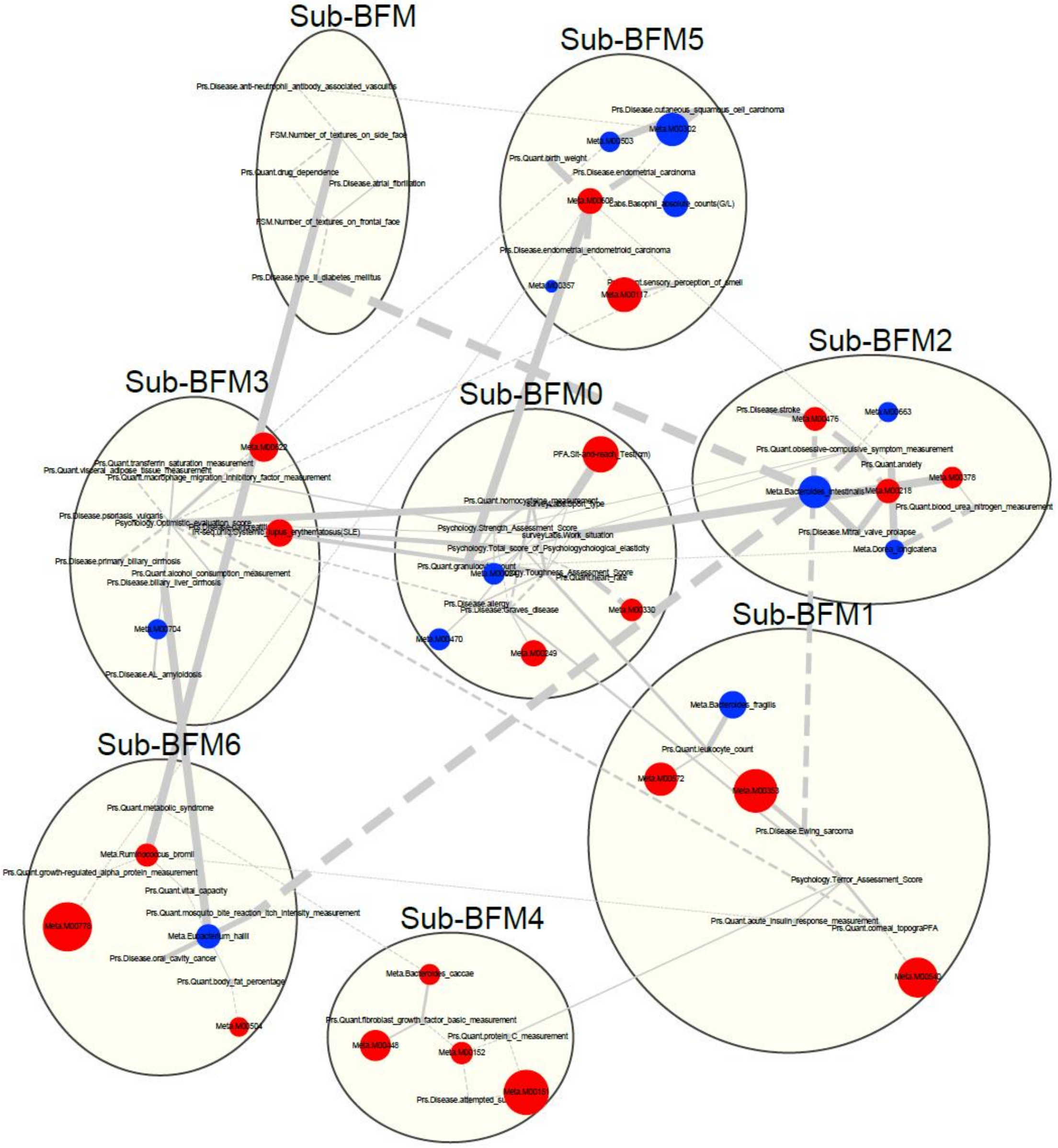

Figure S22. Network of BFM9 at T1 for GSE intervention, Related to Figure 5. Node size represents the absolute value of the intervention score; the nodes were classified into three groups: intervention score < 0 (red), intervention score > 0 (blue) and no data (grey); the line width represents regression coefficient; the solid line represents the positive correlation; and the dashed line represents the negative correlation.

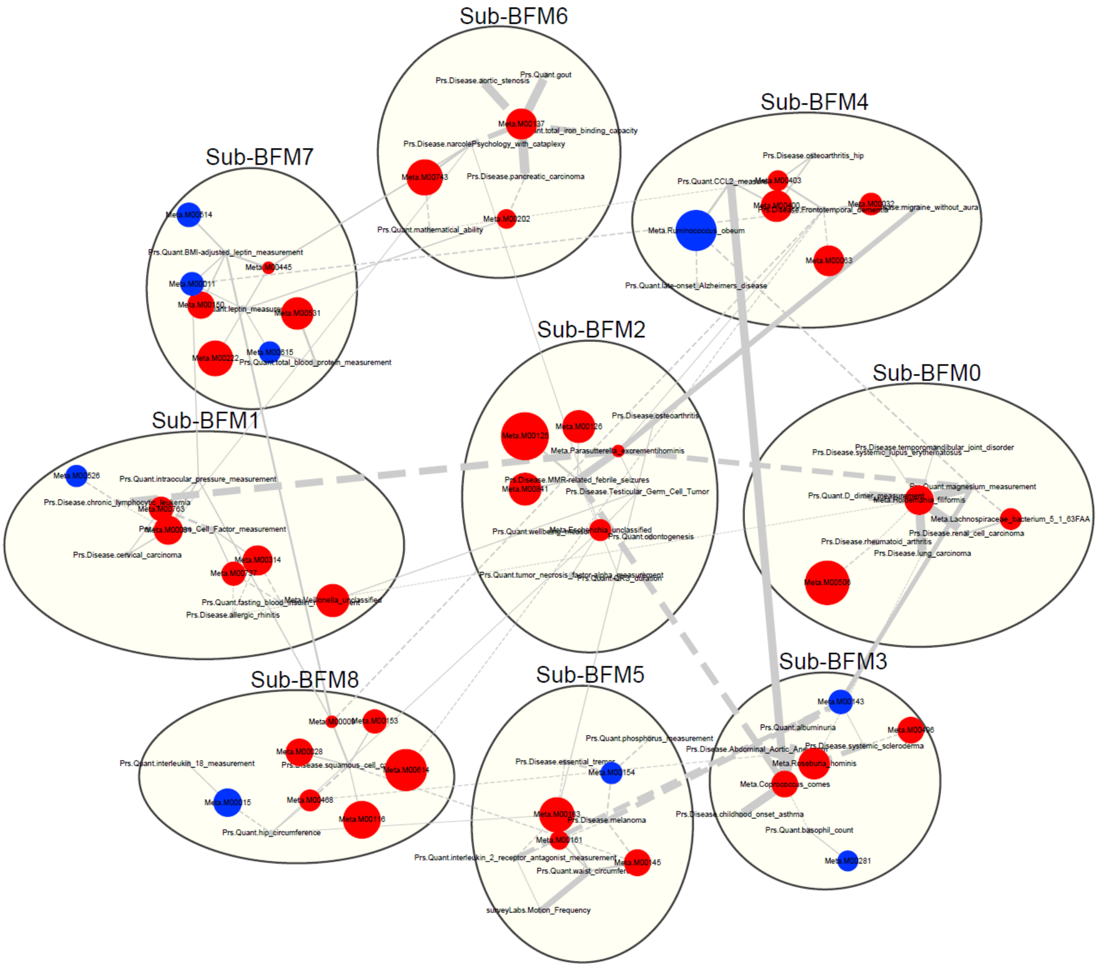

Figure S23. Network of BFM10 at T1 for GSE intervention, Related to Figure 5. Node size represents the absolute value of the intervention score; the nodes were classified into three groups: intervention score < 0 (red), intervention score > 0 (blue) and no data (grey); the line width represents regression coefficient; the solid line represents the positive correlation; and the dashed line represents the negative correlation.

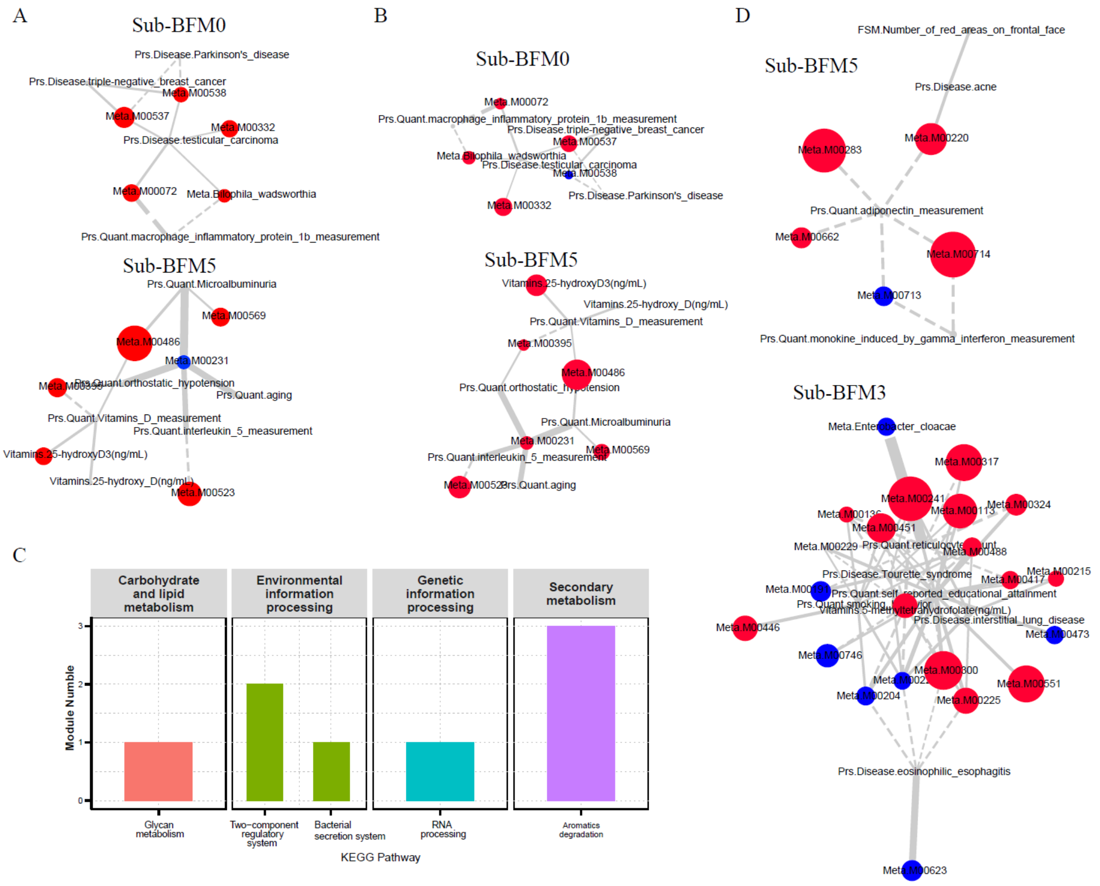

Figure S24. Networks of anomalous sub-BFMs at both T1 and T2, Related to Figure 5. The networks of sub-BFM0 and sub-BFM5 in BFM6 from T1(A) to T2(B). Node size represents the absolute value of the intervention score; the nodes were classified into three groups: intervention score < 0 (red), intervention score > 0 (blue) and no data (grey); the line width represents regression coefficient; the solid line represents the positive correlation; and the dashed line represents the negative correlation. (C) GMMs' annotation by KEGG database for the eight features with intervention scores less than zero. (D) The networks of sub-BFM 3 and 5 in BFM 7 at T2.

Table S4. The information of top 20 correlations that ranked by P-adj in our study was showed in both our study and HE dataset, Related to Figure 1.

Feature 1	**Feature 2**	**Type**	**P-value**	**beta**	**P-adj**	**P-value (HE dataset)**	**beta (HE dataset)**
Health.Total_cholesterol(mmol/L)	Vitamin.E(ng/mL)	Continuous_variable:Continuous_variable	3.56E-84	0.56	1.78E-78	2.5E-05	0.52
Microelement.Iron(mg/L)	Health.Hematocrit(L/L)	Continuous_variable:Continuous_variable	1.87E-82	0.54	4.66E-77	2.9E-04	0.37
Health.Low-density_lipoprotein(mmol/L)	Vitamin.E(ng/mL)	Continuous_variable:Continuous_variable	6.66E-62	0.51	6.66E-57	2.1E-04	0.41
Amino.3-methylhistidine(μmol/L)	Health.Serum_creatinine(μmol/L)	Continuous_variable:Continuous_variable	1.44E-61	0.47	1.20E-56	1.7E-07	0.54
Hormone.Serum_testosterone_test_value(ng/mL)	Inbody.Body_fat_rate(%)	Continuous_variable:Continuous_variable	1.66E-55	-0.48	1.18E-50	9.1E-04	-0.38
Hormone.Serum_testosterone_test_value(ng/mL)	Inbody.Body_fat(kg)	Continuous_variable:Continuous_variable	3.35E-54	-0.47	2.09E-49	3.3E-04	-0.43
Amino.Glutamate(μmol/L)	Inbody.Body_fat(kg)	Continuous_variable:Continuous_variable	1.67E-52	0.44	7.56E-48	2.2E-05	0.41
Inbody.Body_fat_rate(%)	Health.Triglyceride(mmol/L)	Continuous_variable:Continuous_variable	4.73E-47	0.44	1.48E-42	1.4E-01	0.16
Inbody.Body_fat(kg)	Health.Triglyceride(mmol/L)	Continuous_variable:Continuous_variable	2.89E-46	0.43	7.22E-42	5.1E-02	0.24
Amino.Glutamate(μmol/L)	Inbody.Body_fat_rate(%)	Continuous_variable:Continuous_variable	4.64E-46	0.43	1.10E-41	4.2E-04	0.35
Hormone.Serum_testosterone_test_value(ng/mL)	Inbody.Body_mass_index	Continuous_variable:Continuous_variable	8.00E-44	-0.45	1.48E-39	2.2E-03	-0.37
Health.Triglyceride(mmol/L)	Vitamin.E(ng/mL)	Continuous_variable:Continuous_variable	4.03E-43	0.44	6.70E-39	9.6E-06	0.46
Health.Serum_alanine_aminotransferase(U/L)	Inbody.Body_mass_index	Continuous_variable:Continuous_variable	4.49E-43	0.41	7.23E-39	8.4E-03	0.34
Health.Serum_alanine_aminotransferase(U/L)	Inbody.Body_fat(kg)	Continuous_variable:Continuous_variable	5.20E-41	0.41	6.84E-37	1.0E-04	0.41
Amino.Glutamate(μmol/L)	Inbody.Body_mass_index	Continuous_variable:Continuous_variable	3.51E-40	0.42	4.28E-36	4.9E-03	0.32
Health.Serum_alanine_aminotransferase(U/L)	Inbody.Body_fat_rate(%)	Continuous_variable:Continuous_variable	1.35E-39	0.41	1.61E-35	1.9E-04	0.36
Inbody.Body_mass_index	Health.High-density_lipoprotein(mmol/L)	Continuous_variable:Continuous_variable	1.93E-39	-0.41	2.24E-35	7.6E-04	-0.37
Inbody.Body_fat(kg)	Health.High-density_lipoprotein(mmol/L)	Continuous_variable:Continuous_variable	2.83E-39	-0.42	3.21E-35	2.6E-03	-0.33
Inbody.Body_fat_rate(%)	Health.High-density_lipoprotein(mmol/L)	Continuous_variable:Continuous_variable	7.09E-37	-0.39	7.38E-33	3.2E-02	-0.28
Amino.Phosphoethanolamine(μmol/L)	Health.Platelet_count(G/L)	Continuous_variable:Continuous_variable	5.88E-35	0.39	5.54E-31	5.2E-03	0.32

Table S5. The information of top 20 correlations that ranked by the P-value in HE dataset was showed in both our study and HE dataset, Related to Figure 1.

Feature 1	**Feature 2**	**Type**	**P-value**	**beta**	**P-adj**	**P-value (HE dataset)**	**beta (HE dataset)**
Hormone.12-Deoxycorticosterone_Test_Value(ng/mL)	Vitamin.A(ng/mL)	Continuous_variable:Continuous_variable	0.0244134	-0.0683111	0.1401143	5.25E-05	-0.3611511
Microelement.Cadmium(μg/L)	Vitamin.25-hydroxyD3(ng/mL)	Continuous_variable:Continuous_variable	0.0569676	0.0578163	0.2256551	0.0001463	0.3497171
Amino.Leucine(μmol/L)	Microelement.Iron(mg/L)	Continuous_variable:Continuous_variable	0.372466	0.0280031	0.62118	0.0002092	0.3903881
Inbody.Muscle_mass(kg)	Vitamin.B5(ng/mL)	Continuous_variable:Continuous_variable	0.0841793	0.0564238	0.2804877	0.000299	0.3992789
Health.Average_red_blood_cell_volume(fL)	Amino.valine(μmol/L)	Continuous_variable:Continuous_variable	0.0392926	-0.0667718	0.1836313	0.0003309	-0.3054032
Microelement.Zinc(mg/l)	Hormone.Progesterone(ng/mL)	Continuous_variable:Continuous_variable	0.5020348	0.0208288	0.7224824	0.0003892	-0.2967369
Inbody.Muscle_mass(kg)	Health.The_total_number_of_neutrophils(G/L)	Continuous_variable:Continuous_variable	0.0071048	0.0892956	0.0683834	0.0005099	-0.3505425
Amino.Tyrosine(μmol/L)	Health.Urine_pH	Continuous_variable:Continuous_variable	0.0822639	-0.0571195	0.2770798	0.0005491	0.3423448
Hormone.Serum_hydrocortisone_test_value(ng/mL)	Microelement.Lead(μg/L)	Continuous_variable:Continuous_variable	0.5040556	0.0214341	0.7239175	0.0005638	-0.3227413
Amino.Leucine(μmol/L)	Health.Percentage_of_lymphocytes(%)	Continuous_variable:Continuous_variable	0.1666598	0.0445341	0.4062526	0.0006438	0.3218343
Health.Direct_bilirubin(μmol/L)	Amino.α-aminoadipic_acid(μmol/L)	Continuous_variable:Continuous_variable	0.0068082	-0.0876878	0.0666578	0.0007537	-0.3463434
Health.Urine_pH	Vitamin.B5(ng/mL)	Continuous_variable:Continuous_variable	0.6696377	-0.0135993	0.8320545	0.0008486	0.3731539
Amino.Cystathionine(μmol/L)	Health.Urine_pH	Continuous_variable:Continuous_variable	0.1090671	-0.0521525	0.3227924	0.0008615	-0.3489506
Amino.Isoleucine(μmol/L)	Microelement.Iron(mg/L)	Continuous_variable:Continuous_variable	0.0063022	0.0870088	0.0636041	0.0008694	0.3432046
Hormone.Serum_testosterone_test_value(ng/mL)	Vitamin.25-hydroxy_D(ng/mL)	Continuous_variable:Continuous_variable	0.8034814	0.0074671	0.9066099	0.0009038	0.3569177
Health.USG	Amino.Argininosuccinic_acid(μmol/L)	Continuous_variable:Continuous_variable	0.3222776	-0.0300221	0.5756737	0.0009164	-0.3940329
Inbody.Height(cm)	Hormone.Serum_dehydroepiandrosterone(ng/mL)	Continuous_variable:Continuous_variable	0.937973	-0.0023383	0.9725164	0.0009233	0.3790254
Inbody.Body_fat_rate(%)	Amino.Ethanolamine(μmol/L)	Continuous_variable:Continuous_variable	0.9626038	0.0014997	0.9837137	0.0009568	-0.3160513
Microelement.Cadmium(μg/L)	Vitamin.Pyridoxine(ng/mL)	Continuous_variable:Continuous_variable	0.1899731	-0.0393591	0.4355928	0.0009831	-0.3635185

Table S8. BFMs comparison between males and females, Related to Figure 2. The similarities showed in the table were calculated using Sørensen–Dice coefficient.

A. Comparison by nodes in BFMs

	BFM11	BFM10	BFM9	BFM8	BFM7	BFM6	BFM5	BFM4	BFM3	BFM2	BFM1	BFM0
BFM5	0.099	0.048	0.113	0.085	0.367	0.106	0.113	0.098	0.027	0.077	0.037	0.141
BFM9	0.099	0.139	0.038	0.115	0.070	0.132	0.155	0.226	0.010	0.017	0.140	0.022
BFM6	0.119	0.180	0.120	0.106	0.024	0.066	0.190	0.107	0.023	0.029	0.037	0.081
BFM3	0.111	0.098	0.150	0.163	0.068	0.082	0.126	0.158	0.026	0.000	0.032	0.009
BFM2	0.121	0.126	0.085	0.157	0.043	0.052	0.155	0.123	0.026	0.000	0.048	0.053
BFM10	0.172	0.094	0.100	0.141	0.072	0.044	0.176	0.083	0.014	0.000	0.075	0.028
BFM0	0.010	0.030	0.032	0.031	0.000	0.000	0.023	0.024	0.016	0.270	0.204	0.436
BFM8	0.039	0.040	0.032	0.165	0.057	0.072	0.046	0.056	0.016	0.000	0.364	0.010
BFM7	0.000	0.030	0.081	0.073	0.000	0.019	0.010	0.053	0.000	0.384	0.000	0.014
BFM4	0.016	0.000	0.019	0.012	0.079	0.000	0.011	0.036	0.409	0.000	0.014	0.000
BFM1	0.000	0.000	0.041	0.000	0.000	0.000	0.000	0.025	0.000	0.000	0.000	0.179

B.Comparison by edges in BFMs

	BFM11	BFM10	BFM9	BFM8	BFM7	BFM6	BFM5	BFM4	BFM3	BFM2	BFM1	BFM0
BFM5	0.000	0.000	0.013	0.000	0.033	0.003	0.000	0.000	0.004	0.008	0.000	0.064
BFM9	0.000	0.000	0.000	0.000	0.000	0.005	0.004	0.000	0.000	0.000	0.000	0.000
BFM6	0.000	0.006	0.000	0.000	0.000	0.000	0.009	0.000	0.000	0.000	0.000	0.010
BFM3	0.000	0.000	0.009	0.000	0.000	0.000	0.000	0.031	0.000	0.000	0.000	0.000
BFM2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.003	0.000	0.000	0.000	0.000
BFM10	0.000	0.007	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BFM0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.024	0.109	0.248
BFM8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BFM7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.298	0.000	0.000
BFM4	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.423	0.000	0.000	0.000
BFM1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.050

Table S9. BFMs comparison between the Louvain and GN methods, Related to Figure 2. Edges in BFMs were used to calculate the similarity showed in the table. The similarities were calculated by using Sørensen–Dice coefficient.

A.Comparison in males

	GN1	GN3	GN4	GN22	GN13	GN28	GN34	GN30	GN2	GN12
BFM5	0.011	0.008	0.458	0.173	0.004	0.000	0.000	0.000	0.000	0.000
BFM9	0.002	0.003	0.000	0.000	0.042	0.000	0.000	0.011	0.000	0.000
BFM6	0.005	0.000	0.000	0.000	0.043	0.120	0.000	0.015	0.074	0.000
BFM3	0.000	0.651	0.000	0.005	0.000	0.015	0.000	0.021	0.000	0.000
BFM2	0.008	0.004	0.000	0.053	0.000	0.000	0.000	0.062	0.023	0.000
BFM10	0.000	0.005	0.012	0.000	0.054	0.018	0.008	0.028	0.056	0.000
BFM0	0.891	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.000
BFM8	0.000	0.000	0.000	0.000	0.000	0.049	0.434	0.000	0.022	0.351
BFM7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BFM4	0.010	0.028	0.000	0.000	0.024	0.000	0.000	0.000	0.000	0.000
BFM1	0.018	0.007	0.000	0.000	0.029	0.000	0.000	0.000	0.000	0.000

B . Comparison in females

	GN3	GN1	GN2	GN10	GN7	GN6	GN5	GN4	GN11	GN16
BFM5	0.033	0.000	0.000	0.025	0.289	0.067	0.006	0.088	0.034	0.032
BFM8	0.044	0.002	0.072	0.039	0.095	0.015	0.000	0.000	0.314	0.097
BFM4	0.787	0.000	0.002	0.008	0.000	0.000	0.000	0.000	0.000	0.000
BFM1	0.000	0.040	0.773	0.000	0.000	0.010	0.000	0.000	0.000	0.000
BFM7	0.019	0.002	0.000	0.044	0.006	0.000	0.716	0.000	0.000	0.000
BFM11	0.035	0.010	0.007	0.020	0.092	0.254	0.000	0.040	0.030	0.000
BFM0	0.002	0.607	0.000	0.000	0.000	0.000	0.000	0.018	0.000	0.005
BFM10	0.014	0.005	0.003	0.227	0.070	0.122	0.000	0.069	0.000	0.000
BFM9	0.018	0.002	0.007	0.021	0.007	0.121	0.000	0.254	0.011	0.000
BFM6	0.000	0.000	0.023	0.249	0.051	0.139	0.000	0.000	0.000	0.000
BFM2	0.000	0.415	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BFM3	0.004	0.046	0.000	0.029	0.000	0.000	0.000	0.000	0.000	0.000