

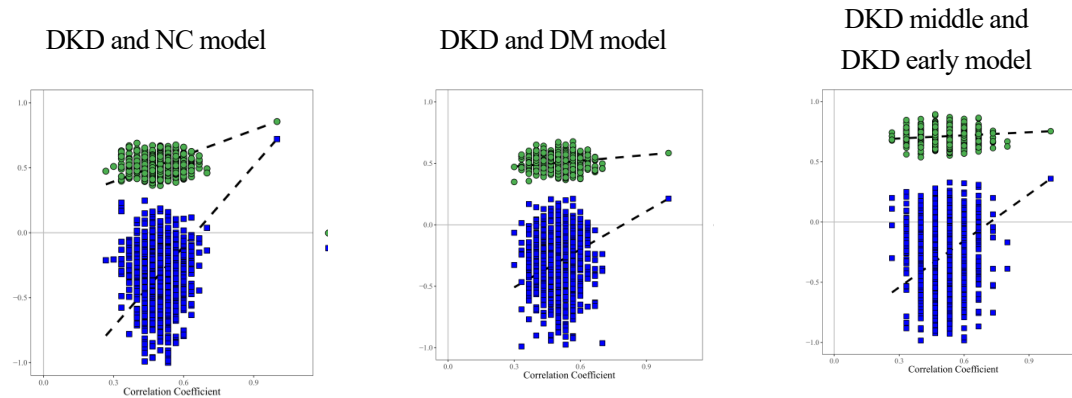


Figure S1. Permutation test of OPLS-DA for normal controls, patients with DM and DKD using the 180 serum metabolites. All three models underwent a 1000-time random permutation test, resulting in Q2Y values > 0.2. The Q2Y fitting curve in the permutation test had a Y-axis intercept < 0.

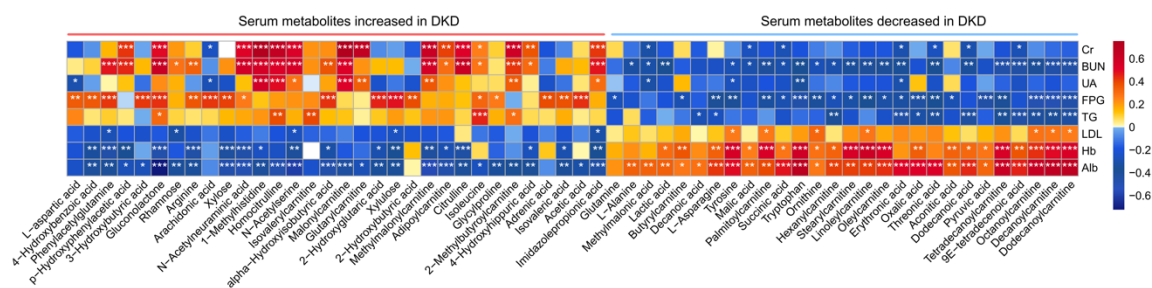


Figure S2. Interactions of disease-related metabolites and host clinical parameters in patients with DKD and NCs. Correlations were calculated with Spearman's correlation analysis. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. Abbreviations: DKD, diabetic kidney disease; NC, normal controls; Cr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; FPG, fasting plasma glucose; TG, triglyceride; LDL, low-density lipoprotein; Hb, hemoglobin; Alb, albumin.

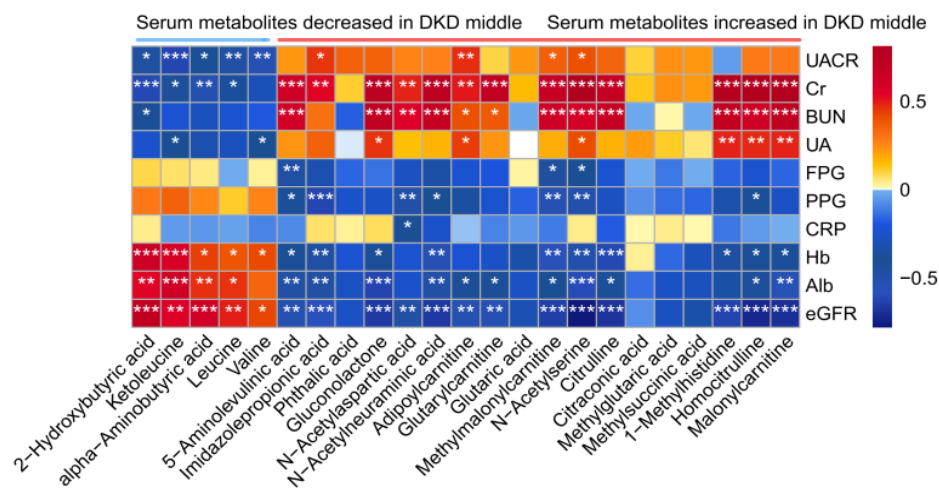


Figure S3. Interactions of disease-related metabolites and host clinical parameters in DKD middle group and DKD early group. Correlations were calculated with Spearman's correlation analysis. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. Abbreviations: DKD, diabetic kidney disease; UACR, urine albumin creatinine ratio; Cr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; CRP, C-reactive protein; Hb, hemoglobin; Alb, albumin; eGFR, estimated glomerular filtration rate.

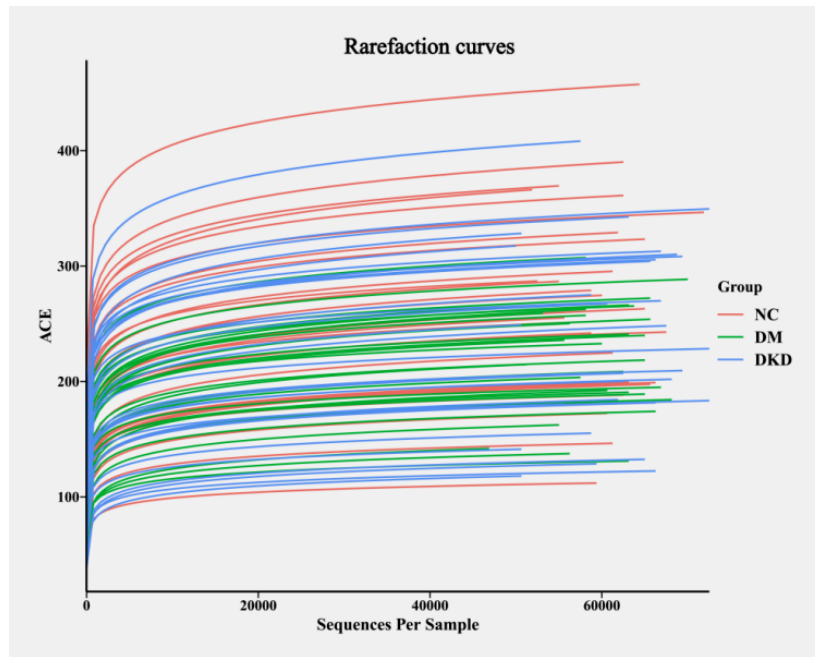
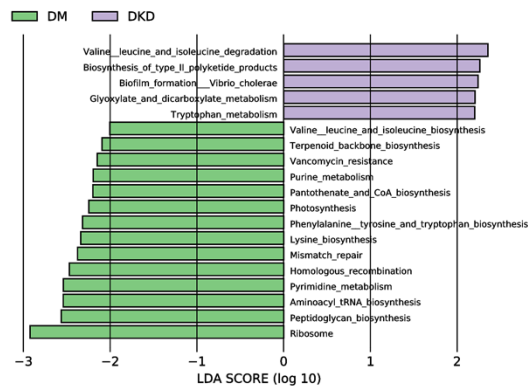
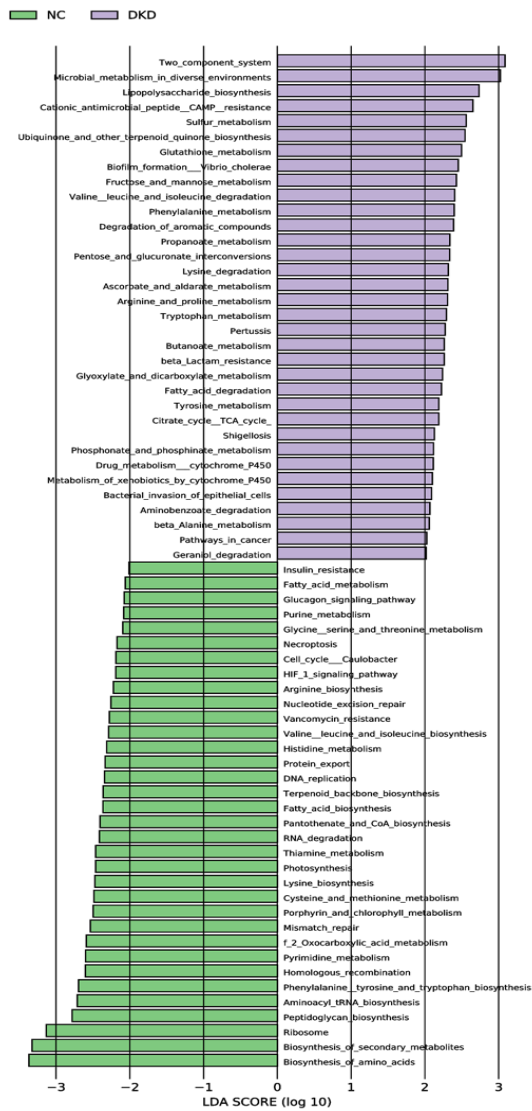


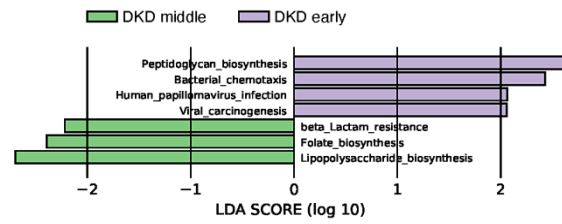
Figure S4. The rarefaction curve of gut microbiota between DKD, DM and NC groups. The horizontal coordinate represents the amount of randomly selected sequencing data and the vertical coordinate represents the Ace Indices. The red curve indicates NC group, the green curve indicates DM group, and the blue curve indicates DKD group.



A



B



C

Figure S6. Gut microbiota functional alterations in patients with DKD. KEGG pathway analysis of differentially abundant gut microbiota between (A)DKD and DM groups, (B) DKD and NC groups, and (C) DKD middle and DKD early groups. Pathways with LDA value > 2 and $P < 0.05$ were considered differentially abundant. Abbreviations: KEGG, Kyoto Encyclopedia of Genes and Genomes; NC, normal controls; DM, diabetic mellitus; DKD, diabetic kidney disease; LDA, linear discriminant analysis.

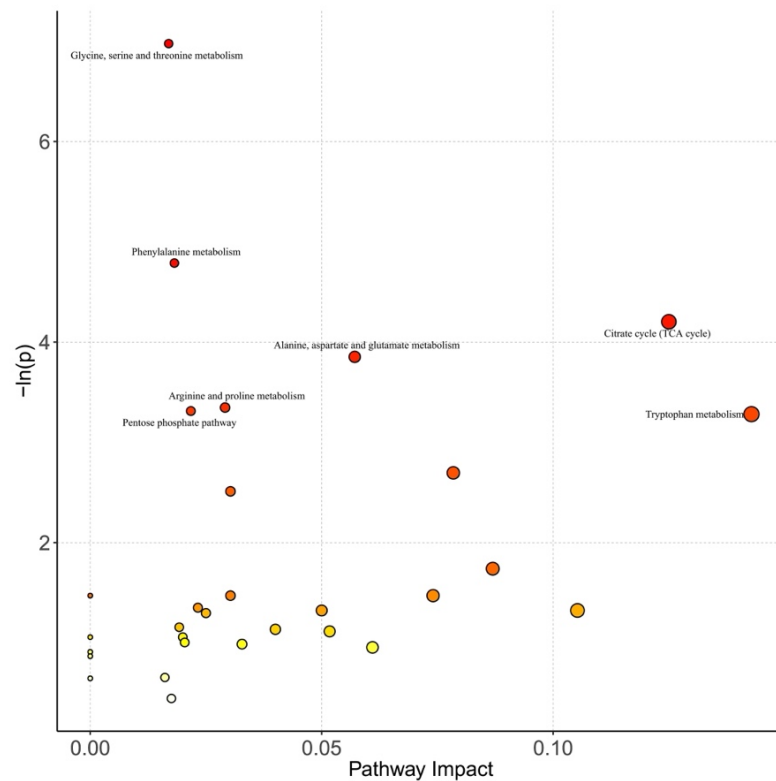


Figure S7. The bubble plot of KEGG analysis. Each bubble in the figure represents a KEGG pathway. The horizontal axis indicates the relative importance of metabolites in the pathway, and the vertical axis indicates the statistical significance of metabolites in the pathway. Pathways with $P < 0.05$ or impact value > 2 were considered differentially abundant.

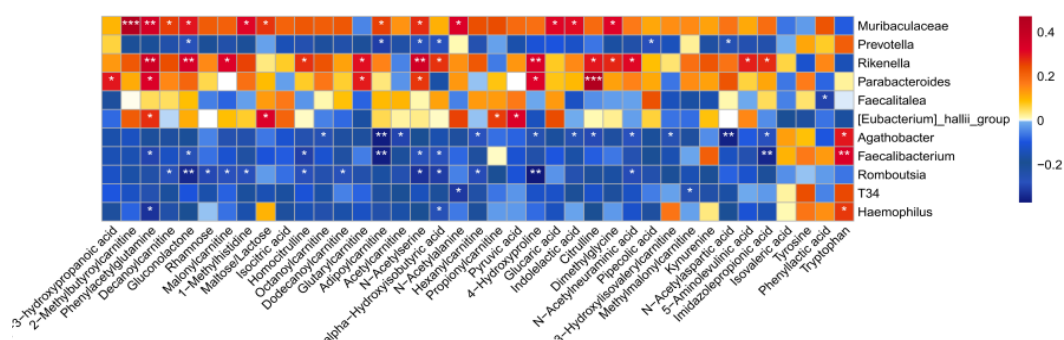


Figure S8. Differentially abundant serum metabolites between DKD and DM groups and their associations with gut microbiota. Correlations were calculated with Spearman's correlation analysis. *** $P<0.001$, ** $P<0.01$, * $P<0.05$. Abbreviations: DM, diabetic mellitus; DKD, diabetic kidney disease.

Table S1. The serum metabolites differentially abundance between patients with DKD and NCs.

Class	Metabolite	VIP	P value	FDR	FC(DKD/NC)
Carnitines	Dodecanoylcarnitine	2.2356	0.0000	0.0000	0.2827
Carnitines	Decanoylcarnitine	2.1792	0.0000	0.0000	0.3164
Carbohydrates	Erythronic acid	2.1306	0.0000	0.0000	0.6303
Carnitines	Octanoylcarnitine	2.1166	0.0000	0.0000	0.3820
Carbohydrates	Threonic acid	2.0844	0.0000	0.0000	0.6076
Amino Acids	Tryptophan	2.0160	0.0000	0.0000	0.7117
Imidazoles	Imidazolepropionic acid	1.9056	0.0000	0.0000	1.0990
Carnitines	Tetradecanoylcarnitine	1.9053	0.0000	0.0000	0.5219
Amino Acids	L-Asparagine	1.8645	0.0000	0.0000	0.7673
Organic Acids	Oxalic acid	1.8409	0.0000	0.0000	0.6093
Amino Acids	Tyrosine	1.8267	0.0000	0.0000	0.7617
Amino Acids	N-Acetylserine	1.7805	0.0000	0.0001	1.5562
Carbohydrates	Gluconolactone	1.7324	0.0000	0.0001	1.8720
Benzoic Acids	4-Hydroxybenzoic acid	1.7311	0.0000	0.0001	2.4125
Organic Acids	alpha-Hydroxyisobutyric acid	1.7249	0.0000	0.0001	1.5466
Amino Acids	Homocitrulline	1.7249	0.0000	0.0001	1.5627
Carnitines	Methylmalonylcarnitine	1.7226	0.0000	0.0001	1.3214
Carbohydrates	N-Acetylneuraminic acid	1.7196	0.0000	0.0001	1.5755
Amino Acids	1-Methylhistidine	1.6838	0.0000	0.0001	1.5684
Organic Acids	Succinic acid	1.6740	0.0000	0.0001	0.7263
Fatty Acids	Dodecanoic acid	1.6502	0.0000	0.0002	0.5382
Carnitines	Hexanylcarnitine	1.5876	0.0001	0.0004	0.6719
Carnitines	Linoleylcarnitine	1.5868	0.0001	0.0004	0.6596
Amino Acids	Phenylacetylglutamine	1.5691	0.0001	0.0005	2.2548
Carbohydrates	Xylulose	1.5333	0.0001	0.0007	1.4261

<u>Organic Acids</u>	<u>Aconitic acid</u>	<u>1.5315</u>	<u>0.0001</u>	<u>0.0007</u>	<u>0.5668</u>
<u>Carnitines</u>	<u>Palmitoylcarnitine</u>	<u>1.5300</u>	<u>0.0001</u>	<u>0.0007</u>	<u>0.7264</u>
<u>Carnitines</u>	<u>Oleylcarnitine</u>	<u>1.5191</u>	<u>0.0001</u>	<u>0.0007</u>	<u>0.6539</u>
<u>Amino Acids</u>	<u>Arginine</u>	<u>1.5174</u>	<u>0.0001</u>	<u>0.0007</u>	<u>1.7947</u>
<u>Carnitines</u>	<u>Malonylcarnitine</u>	<u>1.5107</u>	<u>0.0001</u>	<u>0.0008</u>	<u>1.5117</u>
<u>Fatty Acids</u>	<u>Arachidonic acid</u>	<u>1.4879</u>	<u>0.0002</u>	<u>0.0010</u>	<u>1.7768</u>
<u>Carnitines</u>	<u>Stearyl carnitine</u>	<u>1.4688</u>	<u>0.0002</u>	<u>0.0012</u>	<u>0.6603</u>
<u>Amino Acids</u>	<u>L-aspartic acid</u>	<u>1.4468</u>	<u>0.0003</u>	<u>0.0014</u>	<u>3.3156</u>
<u>Carnitines</u>	<u>Adipoylcarnitine</u>	<u>1.4145</u>	<u>0.0004</u>	<u>0.0020</u>	<u>1.3193</u>
<u>Fatty Acids</u>	<u>Decanoic acid</u>	<u>1.4046</u>	<u>0.0004</u>	<u>0.0021</u>	<u>0.7900</u>
<u>Organic Acids</u>	<u>Pyruvic acid</u>	<u>1.4031</u>	<u>0.0004</u>	<u>0.0021</u>	<u>0.5252</u>
<u>Carbohydrates</u>	<u>Xylose</u>	<u>1.3945</u>	<u>0.0005</u>	<u>0.0023</u>	<u>1.6271</u>
<u>Amino Acids</u>	<u>Isoleucine</u>	<u>1.3707</u>	<u>0.0006</u>	<u>0.0028</u>	<u>1.2536</u>
<u>Organic Acids</u>	<u>Lactic acid</u>	<u>1.3484</u>	<u>0.0007</u>	<u>0.0035</u>	<u>0.8180</u>
<u>Organic Acids</u>	<u>3-Hydroxybutyric acid</u>	<u>1.3347</u>	<u>0.0009</u>	<u>0.0039</u>	<u>2.0921</u>
<u>Fatty Acids</u>	<u>Adrenic acid</u>	<u>1.3169</u>	<u>0.0010</u>	<u>0.0045</u>	<u>1.2120</u>
<u>Organic Acids</u>	<u>2-Hydroxybutyric acid</u>	<u>1.3021</u>	<u>0.0012</u>	<u>0.0051</u>	<u>1.3671</u>
<u>Peptides</u>	<u>Glycylproline</u>	<u>1.2887</u>	<u>0.0013</u>	<u>0.0055</u>	<u>1.2427</u>
<u>Benzoic Acids</u>	<u>4-Hydroxyhippuric acid</u>	<u>1.2876</u>	<u>0.0014</u>	<u>0.0055</u>	<u>1.2143</u>
<u>SCFAs</u>	<u>Isovaleric acid</u>	<u>1.2869</u>	<u>0.0014</u>	<u>0.0055</u>	<u>1.1855</u>
<u>Amino Acids</u>	<u>Ornithine</u>	<u>1.2695</u>	<u>0.0016</u>	<u>0.0063</u>	<u>0.6908</u>
<u>Organic Acids</u>	<u>Malic acid</u>	<u>1.2323</u>	<u>0.0023</u>	<u>0.0086</u>	<u>0.7325</u>
<u>Organic Acids</u>	<u>Methylmalonic acid</u>	<u>1.2269</u>	<u>0.0024</u>	<u>0.0089</u>	<u>0.8185</u>
<u>SCFAs</u>	<u>Acetic acid</u>	<u>1.2087</u>	<u>0.0028</u>	<u>0.0102</u>	<u>1.1259</u>
<u>Carbohydrates</u>	<u>Rhamnose</u>	<u>1.2024</u>	<u>0.0029</u>	<u>0.0106</u>	<u>1.8262</u>
<u>Phenols</u>	<u>p-Hydroxyphenylacetic acid</u>	<u>1.1971</u>	<u>0.0031</u>	<u>0.0108</u>	<u>2.1650</u>
<u>Carnitines</u>	<u>Isovalerylcarnitine</u>	<u>1.1959</u>	<u>0.0031</u>	<u>0.0108</u>	<u>1.5521</u>
<u>Amino Acids</u>	<u>L-Alanine</u>	<u>1.1888</u>	<u>0.0033</u>	<u>0.0112</u>	<u>0.8602</u>
<u>Carnitines</u>	<u>Glutaryl carnitine</u>	<u>1.1689</u>	<u>0.0039</u>	<u>0.0130</u>	<u>1.4990</u>
<u>Carnitines</u>	<u>2-Methylbutyroylcarnitine</u>	<u>1.1586</u>	<u>0.0043</u>	<u>0.0140</u>	<u>1.2297</u>
<u>Organic Acids</u>	<u>2-Hydroxyglutaric acid</u>	<u>1.1469</u>	<u>0.0047</u>	<u>0.0151</u>	<u>1.4411</u>
<u>Amino Acids</u>	<u>Glutamine</u>	<u>1.1427</u>	<u>0.0049</u>	<u>0.0154</u>	<u>0.8945</u>
<u>Fatty Acids</u>	<u>9E-tetradecenoic acid</u>	<u>1.1290</u>	<u>0.0054</u>	<u>0.0168</u>	<u>0.5030</u>
<u>Amino Acids</u>	<u>Citrulline</u>	<u>1.1256</u>	<u>0.0056</u>	<u>0.0168</u>	<u>1.3135</u>
<u>Carnitines</u>	<u>Butyrylcarnitine</u>	<u>1.1254</u>	<u>0.0056</u>	<u>0.0168</u>	<u>0.8157</u>

Abbreviations: NC, normal controls; DKD, diabetic kidney disease; VIP, variable importance in the projection; FDR, false discovery rate; FC, fold change.

Table S2. The serum metabolites differentially abundance between patients with DKD and DM.

<u>Class</u>	<u>Metabolite</u>	<u>VIP</u>	<u>P value</u>	<u>FDR</u>	<u>FC(DKD/D M)</u>
<u>Carnitines</u>	<u>Malonylcarnitine</u>	<u>2.7886</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.7581</u>
<u>Amino Acids</u>	<u>N-Acetylserine</u>	<u>2.7509</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.4915</u>
<u>Amino Acids</u>	<u>1-Methylhistidine</u>	<u>2.6596</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.7549</u>
<u>Carbohydrates</u>	<u>N-Acetylneuraminic acid</u>	<u>2.5196</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.3146</u>
<u>Carnitines</u>	<u>Methylmalonylcarnitine</u>	<u>2.4987</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.2097</u>
<u>Carbohydrates</u>	<u>Gluconolactone</u>	<u>2.4915</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.8192</u>
<u>Amino Acids</u>	<u>Homocitrulline</u>	<u>2.4489</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.6556</u>
<u>Carnitines</u>	<u>Adipoylcarnitine</u>	<u>2.4053</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.5224</u>
<u>Amino Acids</u>	<u>Phenylacetylglutamine</u>	<u>2.3517</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.9447</u>
<u>Amino Acids</u>	<u>N-Acetylaspartic acid</u>	<u>2.3185</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.1582</u>
<u>Carnitines</u>	<u>2-Methylbutyroylcarnitine</u>	<u>2.2766</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.9758</u>
<u>Carbohydrates</u>	<u>Glucaric acid</u>	<u>2.2262</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.3653</u>
<u>Indoles</u>	<u>Indolelactic acid</u>	<u>2.2031</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.3292</u>
<u>Carnitines</u>	<u>Glutaryl carnitine</u>	<u>2.1362</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.5605</u>
<u>Carbohydrates</u>	<u>Maltose/Lactose</u>	<u>2.0196</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.6993</u>
<u>Amino Acids</u>	<u>N-Acetylalanine</u>	<u>1.9789</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.4715</u>
<u>Carnitines</u>	<u>Hexanylcarnitine</u>	<u>1.9506</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.4471</u>
<u>Amino Acids</u>	<u>5-Aminolevulinic acid</u>	<u>1.9039</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.1506</u>
<u>Amino Acids</u>	<u>Citrulline</u>	<u>1.8765</u>	<u>0.0000</u>	<u>0.0000</u>	<u>1.3188</u>
<u>Amino Acids</u>	<u>Dimethylglycine</u>	<u>1.8382</u>	<u>0.0000</u>	<u>0.0001</u>	<u>1.3173</u>
<u>Imidazoles</u>	<u>Imidazolepropionic acid</u>	<u>1.8004</u>	<u>0.0000</u>	<u>0.0001</u>	<u>1.0866</u>
<u>Amino Acids</u>	<u>4-Hydroxyproline</u>	<u>1.7496</u>	<u>0.0000</u>	<u>0.0002</u>	<u>1.3695</u>
<u>Amino Acids</u>	<u>Tryptophan</u>	<u>1.7180</u>	<u>0.0000</u>	<u>0.0002</u>	<u>0.8574</u>
<u>Carbohydrates</u>	<u>Rhamnose</u>	<u>1.6907</u>	<u>0.0000</u>	<u>0.0003</u>	<u>1.7633</u>
<u>Carnitines</u>	<u>3-Hydroxyisovalerylcarnitine</u>	<u>1.6618</u>	<u>0.0001</u>	<u>0.0004</u>	<u>1.2120</u>
<u>Carnitines</u>	<u>Octanoylcarnitine</u>	<u>1.5666</u>	<u>0.0002</u>	<u>0.0012</u>	<u>1.6062</u>
<u>Carnitines</u>	<u>Decanoylcarnitine</u>	<u>1.5072</u>	<u>0.0003</u>	<u>0.0021</u>	<u>1.8783</u>
<u>Organic Acids</u>	<u>Isocitric acid</u>	<u>1.5057</u>	<u>0.0003</u>	<u>0.0021</u>	<u>1.6566</u>
<u>Phenylpropan-oic Acids</u>	<u>Phenyllactic acid</u>	<u>1.4743</u>	<u>0.0004</u>	<u>0.0027</u>	<u>0.8875</u>
<u>Organic Acids</u>	<u>Pyruvic acid</u>	<u>1.4274</u>	<u>0.0007</u>	<u>0.0042</u>	<u>1.3695</u>
<u>Carnitines</u>	<u>Acetylcarnitine</u>	<u>1.3495</u>	<u>0.0014</u>	<u>0.0084</u>	<u>1.5096</u>
<u>Carnitines</u>	<u>Propionyl carnitine</u>	<u>1.2854</u>	<u>0.0025</u>	<u>0.0141</u>	<u>1.3759</u>
<u>Organic Acids</u>	<u>alpha-Hydroxyisobutyric acid</u>	<u>1.2617</u>	<u>0.0031</u>	<u>0.0162</u>	<u>1.4726</u>
<u>Phenylpropan-oic Acids</u>	<u>3-(3-Hydroxyphenyl)-3-hydrox ypropanoic acid</u>	<u>1.2616</u>	<u>0.0031</u>	<u>0.0162</u>	<u>2.1778</u>
<u>Carnitines</u>	<u>Dodecanoylcarnitine</u>	<u>1.2527</u>	<u>0.0033</u>	<u>0.0169</u>	<u>1.5772</u>

<u>SCFAs</u>	<u>Isovaleric acid</u>	<u>1.2290</u>	<u>0.0040</u>	<u>0.0199</u>	<u>0.9100</u>
<u>Amino Acids</u>	<u>Tyrosine</u>	<u>1.1983</u>	<u>0.0051</u>	<u>0.0247</u>	<u>0.9077</u>
<u>Amino Acids</u>	<u>Kynurenine</u>	<u>1.1490</u>	<u>0.0074</u>	<u>0.0350</u>	<u>1.1826</u>
<u>Amino Acids</u>	<u>Pipecolic acid</u>	<u>1.1204</u>	<u>0.0091</u>	<u>0.0420</u>	<u>1.2310</u>

Abbreviations: DM, diabetic mellitus; DKD, diabetic kidney disease; VIP, variable importance in the projection; FDR, false discovery rate; FC, fold change.

Table S3. The serum metabolites differential abundance between DKD middle group and DKD early group.

<u>Class</u>	<u>Metabolite</u>	<u>VIP</u>	<u>P value</u>	<u>FDR</u>	<u>FC(DKD middle/DKD early)</u>
<u>Amino Acids</u>	<u>N-Acetylserine</u>	<u>2.3926</u>	<u>0.0000</u>	<u>0.0008</u>	<u>1.5482</u>
<u>Carnitines</u>	<u>Malonylcarnitine</u>	<u>2.3269</u>	<u>0.0000</u>	<u>0.0009</u>	<u>1.9843</u>
<u>Imidazoles</u>	<u>Imidazolepropionic acid</u>	<u>2.1186</u>	<u>0.0001</u>	<u>0.0064</u>	<u>1.1980</u>
<u>Amino Acids</u>	<u>Citrulline</u>	<u>2.0824</u>	<u>0.0002</u>	<u>0.0068</u>	<u>1.5575</u>
<u>Carnitines</u>	<u>Adipoylcarnitine</u>	<u>2.0358</u>	<u>0.0002</u>	<u>0.0084</u>	<u>1.4125</u>
<u>Amino Acids</u>	<u>Homocitrulline</u>	<u>1.9208</u>	<u>0.0006</u>	<u>0.0180</u>	<u>1.9598</u>
<u>Benzoic Acids</u>	<u>Phthalic acid</u>	<u>1.9085</u>	<u>0.0007</u>	<u>0.0180</u>	<u>1.2895</u>
<u>Fatty Acids</u>	<u>Methylsuccinic acid</u>	<u>1.7992</u>	<u>0.0016</u>	<u>0.0291</u>	<u>1.8154</u>
<u>Amino Acids</u>	<u>1-Methylhistidine</u>	<u>1.7946</u>	<u>0.0017</u>	<u>0.0291</u>	<u>1.8196</u>
<u>Carbohydrates</u>	<u>N-Acetylneuraminic acid</u>	<u>1.7922</u>	<u>0.0017</u>	<u>0.0291</u>	<u>1.3864</u>
<u>Organic Acids</u>	<u>2-Hydroxybutyric acid</u>	<u>1.7852</u>	<u>0.0018</u>	<u>0.0291</u>	<u>0.5054</u>
<u>Organic Acids</u>	<u>Ketoleucine</u>	<u>1.7583</u>	<u>0.0022</u>	<u>0.0313</u>	<u>0.7234</u>
<u>Amino Acids</u>	<u>Leucine</u>	<u>1.7512</u>	<u>0.0023</u>	<u>0.0313</u>	<u>0.7793</u>
<u>Carnitines</u>	<u>Methylmalonylcarnitine</u>	<u>1.7149</u>	<u>0.0029</u>	<u>0.0372</u>	<u>1.5458</u>
<u>Organic Acids</u>	<u>Glutaric acid</u>	<u>1.6924</u>	<u>0.0034</u>	<u>0.0403</u>	<u>1.4845</u>
<u>Amino Acids</u>	<u>alpha-Aminobutyric acid</u>	<u>1.6689</u>	<u>0.0039</u>	<u>0.0440</u>	<u>0.7235</u>
<u>Amino Acids</u>	<u>Valine</u>	<u>1.6204</u>	<u>0.0053</u>	<u>0.0562</u>	<u>0.8765</u>
<u>Amino Acids</u>	<u>5-Aminolevulinic acid</u>	<u>1.6039</u>	<u>0.0059</u>	<u>0.0571</u>	<u>1.1299</u>
<u>Carnitines</u>	<u>Glutaryl carnitine</u>	<u>1.5994</u>	<u>0.0060</u>	<u>0.0571</u>	<u>1.4616</u>
<u>Amino Acids</u>	<u>N-Acetylaspartic acid</u>	<u>1.5897</u>	<u>0.0064</u>	<u>0.0575</u>	<u>1.3046</u>
<u>Fatty Acids</u>	<u>Methylglutaric acid</u>	<u>1.5686</u>	<u>0.0072</u>	<u>0.0621</u>	<u>1.7127</u>
<u>Fatty Acids</u>	<u>Citraconic acid</u>	<u>1.5249</u>	<u>0.0093</u>	<u>0.0757</u>	<u>1.5620</u>
<u>Carbohydrates</u>	<u>Gluconolactone</u>	<u>1.5181</u>	<u>0.0097</u>	<u>0.0757</u>	<u>1.2954</u>

Abbreviations: DKD, diabetic kidney disease; VIP, variable importance in the projection; FDR, false discovery rate; FC, fold change.

Table S4. The bacteria differentially abundance between patients with DKD and NCs.

<u>Bacteria</u>	<u>Mean relative abundance</u>		<u>Lefse Analysis</u>	
	<u>NC</u>	<u>DKD</u>	<u>LDA value</u>	<u>P value</u>
<u>p Firmicutes.c Clostridia.o Oscillospirales.f Ruminococcaceae.g Subdoligranulum</u>	<u>1.09E+03</u>	<u>4.06E+02</u>	<u>3.6635</u>	<u>0.0188</u>
<u>p Fusobacteriota.c Fusobacteriia.o Fusobacteriales.f Fusobacteriaceae</u>	<u>1.70E-03</u>	<u>1.88E-02</u>	<u>3.8962</u>	<u>0.0000</u>
<u>p Proteobacteria</u>	<u>8.71E-02</u>	<u>2.39E-01</u>	<u>4.8522</u>	<u>0.0002</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Pasteurellales</u>	<u>9.89E-03</u>	<u>6.52E-04</u>	<u>3.6207</u>	<u>0.0043</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Burkholderiales.f Burkholderiaceae</u>	<u>5.60E-04</u>	<u>1.27E-02</u>	<u>3.7361</u>	<u>0.0341</u>
<u>p Fusobacteriota.c Fusobacteriia.o Fusobacteriales</u>	<u>1.73E-03</u>	<u>1.92E-02</u>	<u>3.9050</u>	<u>0.0000</u>
<u>p Bacteroidota.c Bacteroidia.o Bacteroidales.f Muribaculaceae.g Muribaculaceae</u>	<u>9.30E+01</u>	<u>5.39E+02</u>	<u>3.5233</u>	<u>0.0000</u>
<u>p Firmicutes.c Clostridia.o Oscillospirales.f Ruminococcaceae</u>	<u>2.14E-01</u>	<u>5.58E-02</u>	<u>4.8914</u>	<u>0.0000</u>
<u>p Firmicutes.c Clostridia.o Lachnospirales.f Lachnospiraceae.g Ruminococcus gnavus group</u>	<u>9.59E+01</u>	<u>8.01E+02</u>	<u>3.7908</u>	<u>0.0028</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Enterobacterales.f Enterobacteriaceae</u>	<u>6.86E-02</u>	<u>2.06E-01</u>	<u>4.8117</u>	<u>0.0002</u>
<u>p Fusobacteriota</u>	<u>1.73E-03</u>	<u>1.92E-02</u>	<u>3.9050</u>	<u>0.0000</u>
<u>p Firmicutes.c Clostridia.o Lachnospirales.f Lachnospiraceae.g Eubacterium ruminantium group</u>	<u>7.04E+02</u>	<u>2.21E+02</u>	<u>3.7925</u>	<u>0.0349</u>
<u>p Fusobacteriota.c Fusobacteriia.o Fusobacteriales.f Fusobacteriaceae.g Fusobacterium</u>	<u>9.75E+01</u>	<u>1.17E+03</u>	<u>3.8962</u>	<u>0.0000</u>
<u>p Firmicutes.c Clostridia.o Oscillospirales</u>	<u>3.09E-01</u>	<u>1.17E-01</u>	<u>4.9845</u>	<u>0.0000</u>
<u>p Firmicutes.c Clostridia.o Lachnospirales.f Lachnospiraceae.g Agathobacter</u>	<u>6.46E+02</u>	<u>1.35E+02</u>	<u>3.6795</u>	<u>0.0005</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Enterobacterales.f Enterobacteriaceae.g Escherichia Shigella</u>	<u>1.96E+03</u>	<u>7.91E+03</u>	<u>4.6135</u>	<u>0.0004</u>
<u>p Firmicutes.c Clostridia.o Lachnospirales.f Lachnospiraceae.g Eubacterium eligens group</u>	<u>1.02E+03</u>	<u>9.99E+01</u>	<u>3.8672</u>	<u>0.0001</u>
<u>p Fusobacteriota.c Fusobacteriia</u>	<u>1.73E-03</u>	<u>1.92E-02</u>	<u>3.9050</u>	<u>0.0000</u>
<u>p Bacteroidota.c Bacteroidia.o Bacteroidales.f Muribaculaceae</u>	<u>1.63E-03</u>	<u>8.62E-03</u>	<u>3.5305</u>	<u>0.0000</u>

<u>p Firmicutes.c Clostridia.o Oscillospirales.f Ruminococcaceae.g Faecalibacterium</u>	<u>1.04E+04</u>	<u>1.85E+03</u>	<u>4.8390</u>	<u>0.0000</u>
<u>p Firmicutes.c Clostridia.o Lachnospirales.f Lachnospiraceae.g Lachnospiraceae NK4A136_group</u>	<u>1.31E+03</u>	<u>3.07E+02</u>	<u>3.9244</u>	<u>0.0057</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Burkholderiales.f Burkholderiaceae.g Ralstonia</u>	<u>3.51E+01</u>	<u>9.09E+02</u>	<u>3.7361</u>	<u>0.0332</u>
<u>p Firmicutes</u>	<u>5.51E-01</u>	<u>3.53E-01</u>	<u>4.9914</u>	<u>0.0000</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Pasteurellales.f Pasteurellaceae</u>	<u>9.89E-03</u>	<u>6.52E-04</u>	<u>3.6207</u>	<u>0.0043</u>
<u>p Proteobacteria.c Alphaproteobacteria</u>	<u>1.52E-03</u>	<u>9.99E-03</u>	<u>3.6130</u>	<u>0.0371</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Pasteurellales.f Pasteurellaceae.g Haemophilus</u>	<u>6.46E+02</u>	<u>3.61E+01</u>	<u>3.6191</u>	<u>0.0007</u>
<u>p Bacteroidota.c Bacteroidia.o Bacteroidales.f Prevotellaceae.g Prevotella</u>	<u>5.38E+03</u>	<u>5.26E+02</u>	<u>4.5679</u>	<u>0.0016</u>
<u>p Firmicutes.c Clostridia</u>	<u>5.23E-01</u>	<u>3.10E-01</u>	<u>5.0315</u>	<u>0.0000</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Enterobacterales</u>	<u>6.92E-02</u>	<u>2.06E-01</u>	<u>4.8100</u>	<u>0.0002</u>
<u>p Bacteroidota.c Bacteroidia.o Bacteroidales.f Prevotellaceae</u>	<u>1.06E-01</u>	<u>1.18E-02</u>	<u>4.6447</u>	<u>0.0006</u>
<u>p Proteobacteria.c Gammaproteobacteria</u>	<u>8.56E-02</u>	<u>2.29E-01</u>	<u>4.8264</u>	<u>0.0003</u>
<u>p Firmicutes.c Bacilli.o Erysipelotrichales.f Erysipelotrichaceae.g Allobaculum</u>	<u>1.20E+00</u>	<u>0.00E+00</u>	<u>3.7556</u>	<u>0.0027</u>

Abbreviations: NC, normal controls; DKD, diabetic kidney disease; LDA, linear discriminant analysis.

Table S5. The bacteria differentially abundance between patients with DKD and DM

<u>Bacteria</u>	<u>Mean relative abundance</u>		<u>Lefse Analysis</u>	
	<u>DM</u>	<u>DKD</u>	<u>LDA value</u>	<u>P value</u>
<u>p Firmicutes.c Clostridia.o Peptostreptococcales Tissierellales.f Peptostreptococcaceae.g Romboutsia</u>	<u>7.56E-03</u>	<u>2.38E-03</u>	<u>3.4945</u>	<u>0.0138</u>
<u>p Firmicutes.c Clostridia.o Oscillospirales.f Ruminococcaceae.g Faecalibacterium</u>	<u>1.17E-01</u>	<u>3.02E-02</u>	<u>4.6349</u>	<u>0.0187</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Burkholderiales.f T34.g T34</u>	<u>4.10E-05</u>	<u>0.00E+00</u>	<u>3.0161</u>	<u>0.0106</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Pasteurellales</u>	<u>7.91E-03</u>	<u>6.52E-04</u>	<u>3.5996</u>	<u>0.0276</u>
<u>p Firmicutes.c Clostridia.o Lachnospirales.f Lachnospiraceae.g Eubacterium hallii group</u>	<u>1.78E-03</u>	<u>5.13E-03</u>	<u>3.2472</u>	<u>0.0144</u>
<u>p Firmicutes.c Clostridia.o Oscillospirales.f Ruminococcaceae</u>	<u>1.53E-01</u>	<u>5.58E-02</u>	<u>4.6983</u>	<u>0.0014</u>
<u>p Bacteroidota.c Bacteroidia.o Bacteroidales.f Muribaculaceae.g Muribaculaceae</u>	<u>3.22E-03</u>	<u>8.51E-03</u>	<u>3.3658</u>	<u>0.0036</u>
<u>p Firmicutes.c Clostridia.o Oscillospirales</u>	<u>2.11E-01</u>	<u>1.17E-01</u>	<u>4.6553</u>	<u>0.0246</u>
<u>p Firmicutes.c Clostridia.o Lachnospirales.f Lachnospiraceae.g Agathobacter</u>	<u>8.33E-03</u>	<u>2.04E-03</u>	<u>3.4146</u>	<u>0.0089</u>
<u>p Bacteroidota.c Bacteroidia.o Bacteroidales.f Muribaculaceae</u>	<u>3.22E-03</u>	<u>8.62E-03</u>	<u>3.3760</u>	<u>0.0022</u>
<u>p Firmicutes.c Bacilli.o Erysipelotrichales.f Erysipelotrichaceae.g Faecalitalea</u>	<u>2.86E-04</u>	<u>2.29E-03</u>	<u>3.0572</u>	<u>0.0076</u>
<u>p Bacteroidota.c Bacteroidia.o Bacteroidales.f Rikenellaceae.g Rikenella</u>	<u>0.00E+00</u>	<u>1.97E-05</u>	<u>3.1327</u>	<u>0.0054</u>
<u>p Proteobacteria.c Alphaproteobacteria.o Caulobacterales.f Caulobacteraceae.g uncultured</u>	<u>6.56E-03</u>	<u>1.55E-02</u>	<u>3.3905</u>	<u>0.0336</u>
<u>p Bacteroidota.c Bacteroidia.o Bacteroidales.f Tannerellaceae.g Parabacteroides</u>	<u>1.40E-02</u>	<u>3.77E-02</u>	<u>4.0990</u>	<u>0.0459</u>
<u>p Firmicutes.c Clostridia.o Clostridiales.f Clostridiaceae.g Clostridium sensu stricto 6</u>	<u>1.78E-05</u>	<u>0.00E+00</u>	<u>3.2094</u>	<u>0.0207</u>
<u>p Proteobacteria.c Alphaproteobacteria.o Caulobacterales.f Caulobacteraceae</u>	<u>9.21E-04</u>	<u>6.83E-03</u>	<u>3.3931</u>	<u>0.0314</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Pasteurellales.f Pasteurellaceae</u>	<u>7.91E-03</u>	<u>6.52E-04</u>	<u>3.5996</u>	<u>0.0276</u>
<u>p Proteobacteria.c Alphaproteobacteria</u>	<u>1.52E-03</u>	<u>9.99E-03</u>	<u>3.5668</u>	<u>0.0026</u>
<u>p Proteobacteria.c Gammaproteobacteria.o Pasteurellales.f Pasteurellaceae.g Haemophilus</u>	<u>7.86E-03</u>	<u>5.86E-04</u>	<u>3.6007</u>	<u>0.0166</u>

<u>p_Bacteroidota.c_Bacteroidia.o_Bacteroidales.f_Prevotellaceae.g_Prevotella</u>	<u>5.05E-02</u>	<u>8.12E-03</u>	<u>4.3814</u>	<u>0.0195</u>
<u>p_Firmicutes.c_Clostridia</u>	<u>4.01E-01</u>	<u>3.10E-01</u>	<u>4.6928</u>	<u>0.0493</u>
<u>p_Bacteroidota.c_Bacteroidia.o_Bacteroidales.f_Tannerellaceae</u>	<u>1.40E-02</u>	<u>3.77E-02</u>	<u>4.0990</u>	<u>0.0459</u>
<u>p_Bacteroidota.c_Bacteroidia.o_Bacteroidales.f_Marinifilaceae.g_Odoribacter</u>	<u>1.52E-03</u>	<u>3.35E-03</u>	<u>3.0531</u>	<u>0.0469</u>
<u>p_Proteobacteria.c_Alphaproteobacteria.o_Caulobacterales</u>	<u>9.21E-04</u>	<u>6.83E-03</u>	<u>3.3931</u>	<u>0.0314</u>

Abbreviations: DM, diabetic mellitus; DKD, diabetic kidney disease; LDA, linear discriminant analysis.

Table S6. The bacteria differentially abundance between DKD early group and DKD middle group

<u>Bacteria</u>	<u>Mean relative abundance</u>		<u>Lefse Analysis</u>	
	<u>DKD middle</u>	<u>DKD early</u>	<u>LDA value</u>	<u>P value</u>
<u>p_Firmicutes.c_Bacilli.o_Erysipelotrichales.f_Erysipelotrichaceae.g_Turicibacter</u>	<u>1.09E-04</u>	<u>2.64E-03</u>	<u>3.0955</u>	<u>0.0396</u>
<u>p_Firmicutes.c_Clostridia.o_Christensenellales.f_Christensenellaceae.g_Christensenellaceae_R_7_group</u>	<u>2.87E-03</u>	<u>1.13E-02</u>	<u>3.6373</u>	<u>0.0126</u>
<u>p_Firmicutes.c_Bacilli.o_RF39</u>	<u>3.90E-04</u>	<u>3.95E-04</u>	<u>2.5693</u>	<u>0.0077</u>
<u>p_Firmicutes.c_Negativicutes.o_Veillonellales_Selenomonadales.f_Selenomonadaceae</u>	<u>7.86E-05</u>	<u>5.13E-04</u>	<u>2.8203</u>	<u>0.0108</u>
<u>p_Firmicutes.c_Clostridia.o_Christensenellales</u>	<u>3.13E-03</u>	<u>1.16E-02</u>	<u>3.6352</u>	<u>0.0214</u>
<u>p_Synergistota.c_Synergistia.o_Synergistales</u>	<u>0.00E+00</u>	<u>3.27E-04</u>	<u>2.5031</u>	<u>0.0282</u>
<u>p_Firmicutes.c_Bacilli.o_RF39.f_RF39.g_RF39</u>	<u>3.90E-04</u>	<u>3.95E-04</u>	<u>2.5751</u>	<u>0.0077</u>
<u>p_Bacteroidota.c_Bacteroidia.o_Chitinophagales.f_Chitinophagaceae</u>	<u>8.65E-04</u>	<u>8.53E-05</u>	<u>2.6697</u>	<u>0.0422</u>
<u>p_Actinobacteriota.c_Coriobacteriia.o_Coriobacteriales.f_Eggerthellaceae.g_Adlercreutzia</u>	<u>4.32E-04</u>	<u>2.37E-04</u>	<u>3.1227</u>	<u>0.0351</u>
<u>p_Firmicutes.c_Clostridia.o_Monoglobales.f_Monoglobaceae</u>	<u>9.10E-04</u>	<u>1.38E-03</u>	<u>2.6835</u>	<u>0.0098</u>
<u>p_Synergistota.c_Synergistia.o_Synergistales.f_Synergistaceae</u>	<u>0.00E+00</u>	<u>3.27E-04</u>	<u>2.5121</u>	<u>0.0282</u>
<u>p_Firmicutes.c_Clostridia.o_Lachnospirales.f_Lachnospiraceae.g_Lachnospira</u>	<u>6.49E-04</u>	<u>3.64E-03</u>	<u>3.2118</u>	<u>0.0145</u>
<u>p_Firmicutes.c_Clostridia.o_Lachnospirales.f_Lachnospiraceae.g_Roseburia</u>	<u>6.43E-03</u>	<u>2.09E-02</u>	<u>3.8747</u>	<u>0.0152</u>
<u>p_Proteobacteria.c_Gammaproteobacteria.o_Enterobacterales.f_Enterobacteriaceae.g_Raoultella</u>	<u>0.00E+00</u>	<u>2.20E-04</u>	<u>2.4751</u>	<u>0.0282</u>
<u>p_Firmicutes.c_Clostridia.o_Monoglobales.f_Monoglobaceae.g_Monoglobus</u>	<u>9.10E-04</u>	<u>1.38E-03</u>	<u>2.6857</u>	<u>0.0098</u>
<u>p_Synergistota</u>	<u>0.00E+00</u>	<u>3.27E-04</u>	<u>2.5159</u>	<u>0.0282</u>
<u>p_Bacteroidota.c_Bacteroidia.o_Bacteroidales.f_Barnesiellaceae.g_Coprobacter</u>	<u>3.97E-06</u>	<u>5.86E-04</u>	<u>2.9853</u>	<u>0.0369</u>
<u>p_Firmicutes.c_Clostridia.o_Lachnospirales.f_Lachnospiraceae.g_Lachnospiraceae_ND3007_group</u>	<u>7.81E-05</u>	<u>2.61E-04</u>	<u>2.6867</u>	<u>0.0129</u>
<u>p_Proteobacteria.c_Alphaproteobacteria.o_Micropepsales</u>	<u>1.56E-05</u>	<u>7.72E-05</u>	<u>3.2038</u>	<u>0.0248</u>

<u>p_Firmicutes.c_Clostridia.o_Oscillospirales.f_Ruminococcaceae.g_Ruminococcus</u>	<u>2.93E-03</u>	<u>3.47E-03</u>	<u>2.9162</u>	<u>0.0372</u>
<u>p_Firmicutes.c_Clostridia.o_Oscillospirales.f_Ruminococcaceae.g_DTU089</u>	<u>0.00E+00</u>	<u>1.68E-04</u>	<u>3.1564</u>	<u>0.0099</u>
<u>p_Firmicutes.c_Clostridia.o_Oscillospirales.f_Ruminococcaceae.g_CAG_352</u>	<u>3.51E-04</u>	<u>4.56E-03</u>	<u>3.3501</u>	<u>0.0398</u>
<u>p_Synergistota.c_Synergistia</u>	<u>0.00E+00</u>	<u>3.27E-04</u>	<u>2.4726</u>	<u>0.0282</u>
<u>p_Proteobacteria.c_Gammaproteobacteria.o_Enterobacterales.f_Enterobacteriaceae.g_Klebsiella</u>	<u>4.29E-02</u>	<u>1.13E-01</u>	<u>4.5663</u>	<u>0.0158</u>
<u>p_Firmicutes.c_Clostridia.o_Lachnospirales.f_Lachnospiraceae.g_Eubacterium_eligens_group</u>	<u>3.18E-04</u>	<u>3.52E-03</u>	<u>3.1751</u>	<u>0.0009</u>
<u>p_Firmicutes.c_Clostridia.o_Oscillospirales.f_Oscillospirales.g_Hydrogenoanaerobacterium</u>	<u>0.00E+00</u>	<u>9.27E-05</u>	<u>2.7844</u>	<u>0.0282</u>
<u>p_Firmicutes.c_Bacilli.o_RF39.f_RF39</u>	<u>3.90E-04</u>	<u>3.95E-04</u>	<u>2.5909</u>	<u>0.0077</u>
<u>p_Firmicutes.c_Clostridia.o_Christensenellales.f_Christensenellaceae</u>	<u>3.13E-03</u>	<u>1.16E-02</u>	<u>3.6352</u>	<u>0.0214</u>
<u>p_Firmicutes</u>	<u>3.01E-01</u>	<u>4.31E-01</u>	<u>4.8156</u>	<u>0.0277</u>
<u>p_Firmicutes.c_Clostridia.o_Lachnospirales.f_Lachnospiraceae.g_CAG_56</u>	<u>0.00E+00</u>	<u>1.61E-04</u>	<u>2.7088</u>	<u>0.0282</u>
<u>p_Firmicutes.c_Clostridia.o_Monoglobales</u>	<u>9.10E-04</u>	<u>1.38E-03</u>	<u>2.6922</u>	<u>0.0098</u>
<u>p_Firmicutes.c_Negativicutes.o_Veillonellales.Selenomonadales.f.Selenomonadaceae.g_Anaerovibrio</u>	<u>0.00E+00</u>	<u>1.53E-05</u>	<u>3.9632</u>	<u>0.0282</u>
<u>p_Firmicutes.c_Clostridia</u>	<u>2.64E-01</u>	<u>3.79E-01</u>	<u>4.7740</u>	<u>0.0277</u>
<u>p_Firmicutes.c_Clostridia.o_Lachnospirales.f_Lachnospiraceae.g_Lachnospiraceae_UCG_001</u>	<u>5.64E-05</u>	<u>1.49E-03</u>	<u>2.9436</u>	<u>0.0007</u>
<u>p_Firmicutes.c_Clostridia.o_Lachnospirales.f_Lachnospiraceae.g_Eubacterium_ventriosum_group</u>	<u>6.07E-04</u>	<u>3.10E-03</u>	<u>3.1436</u>	<u>0.0113</u>
<u>p_Firmicutes.c_Clostridia.o_Oscillospirales.f_Oscillospirales</u>	<u>0.00E+00</u>	<u>9.27E-05</u>	<u>2.7790</u>	<u>0.0282</u>
<u>p_Desulfobacterota.c_Desulfovibrionia.o_Desulfovibrionales.f_Desulfovibrionaceae.g_Desulfovibrio</u>	<u>7.85E-04</u>	<u>5.34E-03</u>	<u>3.3434</u>	<u>0.0047</u>
<u>p_Proteobacteria.c_Alphaproteobacteria.o_Micropepsales.f_Micropepsaceae</u>	<u>1.56E-05</u>	<u>7.72E-05</u>	<u>3.1882</u>	<u>0.0248</u>
<u>p_Bacteroidota.c_Bacteroidia.o_Chitinophagales</u>	<u>8.65E-04</u>	<u>8.53E-05</u>	<u>2.6693</u>	<u>0.0422</u>

Abbreviations: DKD, diabetic kidney disease; LDA, linear discriminant analysis.