

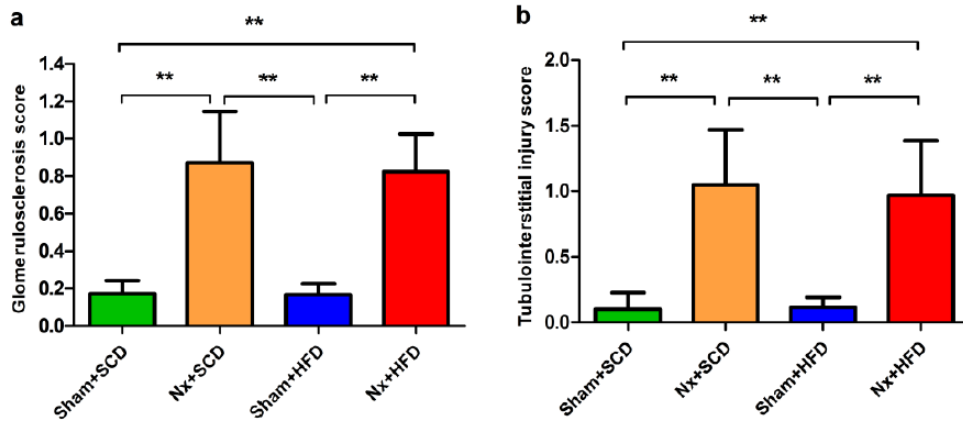
SUPPLEMENTARY MATERIAL

Metabonomic Profiling Reveals Difference in Altered Metabolic Pathways Between Chronic Kidney Disease and High-Fat-Induced Insulin Resistance in Rats

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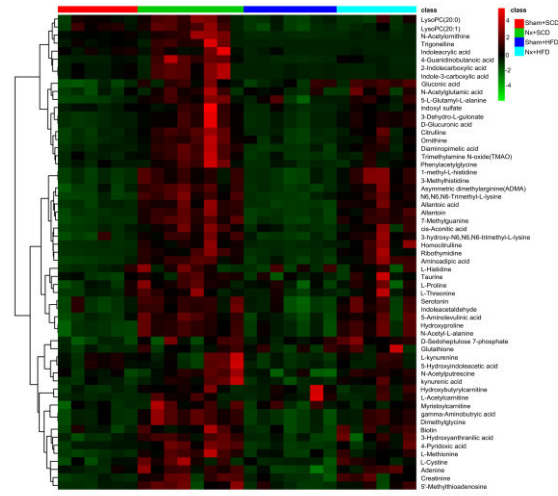
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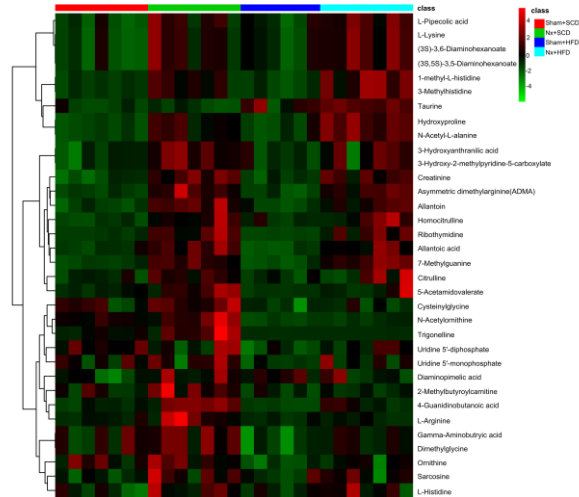
Suppl. Figure 1 Quantitative evaluation of renal histologic images in the study groups. (a) Examination of glomerulosclerosis scores *in* the Sham+SCD, Nx+SCD, Sham+HFD, and Nx+HFD groups. ** Differs from Sham+SCD and Sham+HFD $p < 0.01$; (b) An evaluation of tubulointerstitial injury scores in the Sham+SCD, Nx+SCD, Sham+HFD, and Nx+HFD groups. ** Differs from Sham+SCD and Sham+HFD $p < 0.01$.

Suppl. Fig. 2

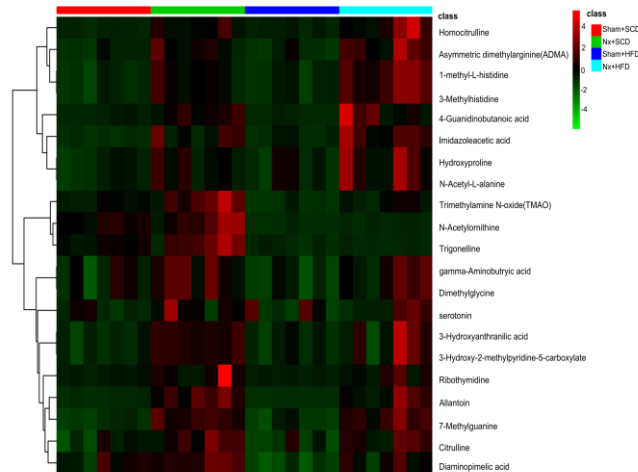
a



b



c



Suppl. Figure 2 Clustering heatmap representation of relative changes in metabolites in the four study groups. The clustering heatmap was used to visualize directly the results of the four study groups, including Sham+SCD, Nx+SCD, Sham+HFD, and Nx+HFD groups, in which each row represented a metabolite while each column represented a sample. Levels of metabolites altered significantly across the four different groups were projected on the clustering heatmap. (a) Serum metabolites; (b) Liver metabolites; (c) Muscle metabolites in the Sham+SCD, Nx+SCD, Sham+HFD and Nx+HFD study groups.

Suppl. Table 1 Biochemical changes of rats fed on SCD or HFD for 16 weeks in the four groups

| Biochemical tests | Sham+SCD | Nx+SCD | Sham+HFD | Nx+HFD |
|------------------------|-------------|----------------------------|-------------|----------------------------|
| Urea (mmol/L) | 5.01±0.83 | 12.67±5.09 ^{b,d} | 4.22±0.72 | 11.09±3.94 ^{b,d} |
| Creatinine (umol/L) | 35.01±9.25 | 89.47±19.61 ^{b,d} | 33.92±7.74 | 78.49±20.19 ^{b,d} |
| Uric acid (mmol/L) | 61.79±13.81 | 81.28±21.98 | 80.64±19.84 | 74.06±16.74 |
| Glucose (mmol/L) | 6.33±1.24 | 6.20±0.80 | 7.24±0.80 | 7.36±0.96 |
| Triglycerides (mmol/L) | 0.79±0.28 | 0.88±0.26 | 1.06±0.43 | 0.86±0.67 |
| Cholesterol (mmol/L) | 1.44±0.43 | 2.21±0.40 ^b | 1.79±0.23 | 2.28±0.47 ^{b,c} |
| LDL (mmol/L) | 0.37±0.14 | 0.72±0.21 ^{b,c} | 0.44±0.06 | 0.73±0.33 ^{b,c} |
| HDL (mmol/L) | 1.38±0.41 | 1.93±0.64 ^a | 1.47±0.22 | 1.92±0.78 ^a |
| Total protein (g/L) | 60.36±4.04 | 55.50±3.35 ^{a,c} | 60.03±2.51 | 57.41±2.91 |
| Albumin (g/L) | 35.07±2.66 | 29.43±3.62 ^{a,c} | 34.60±2.43 | 31.93±3.21 |

Note: ^a and ^b Differs from Sham+SCD p<0.05 and p<0.01, respectively; ^c and ^d Differs from Sham+HFD p<0.05 and p<0.01, respectively.

Suppl. Table 2 Food intake, the left/right kidney weight and visceral fat to the body weight ratio in the four study groups

| Parameters | Sham+SCD | Nx+SCD | Sham+HFD | Nx+HFD |
|-------------------------------|------------------------|------------------------|---------------------------|---------------------------|
| Food intake (g/day) | 25.85±1.41 | 26.73±1.07 | 19.67±1.71 ^{a,b} | 20.12±1.19 ^{a,b} |
| Visceral fat /Body weight (%) | 6.21±2.95 ^c | 3.96±2.20 ^c | 9.94±3.23 | 9.27±1.43 ^d |
| Left kidney/body weight (%) | 0.25±0.03 ^d | 0.34±0.06 | 0.24±0.03 ^d | 0.31±0.08 ^c |
| Right kidney/body weight (%) | 0.28±0.03 | | 0.24±0.03 | |

Note: ^aDiffers from Sham+SCD p<0.01; ^bDiffers from Nx+SCD p<0.01; ^cDiffers from Sham+HFD p<0.05; ^dDiffers from Nx+SCD p<0.05.

Suppl. Table 3. Serum metabolites significantly changed in both CKD and high-fat diet rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|--|------------------------------|----------------|--------------------------------|----------------|
| | Ratio Nx+SCD: Sham+SCD | <i>p</i> value | Ratio Sham+HFD: Sham+SCD | <i>p</i> value |
| Arginine and proline metabolism | | | | |
| 4-Guanidinobutanoic acid | 5.54 | 7.22E-03 | 0.41 | 7.05E-03 |
| Creatine | 0.45 | 2.97E-03 | 0.54 | 1.28E-02 |
| Glycerophospholipid metabolism | | | | |
| Glycerophosphocholine | 0.54 | 8.30E-03 | 0.43 | 2.62E-03 |
| LysoPC(20:0) | 1.89 | 1.72E-02 | 0.54 | 2.32E-02 |
| Pentose phosphate pathway | | | | |
| Gluconic acid(D-gluconate) | 2.38 | 2.14E-03 | 1.83 | 2.75E-02 |
| D-Sedoheptulose 7-phosphate | 1.72 | 3.17E-02 | 1.49 | 5.42E-03 |
| Vitamin B6 metabolism | | | | |
| 4-Pyridoxic acid | 2.52 | 6.05E-03 | 0.59 | 2.63E-02 |
| Butanoate metabolism | | | | |
| 2-Hydroxyglutarate | 1.63 | 4.96E-02 | 1.59 | 1.45E-02 |
| Arachidonic acid metabolism | | | | |
| Prostaglandin G2 | 0.52 | 1.82E-03 | 0.51 | 6.15E-03 |
| Lysine biosynthesis and degradation | | | | |
| L-Lysine | 1.64 | 9.78E-03 | 1.65 | 6.23E-03 |
| Diaminopimelic acid | 3.02 | 1.44E-03 | 0.72 | 3.34E-02 |
| L-Pipecolic acid | 1.45 | 1.17E-02 | 1.51 | 1.69E-03 |
| (3S)-3,6-Diaminohexanoate | 1.64 | 9.78E-03 | 1.65 | 6.23E-03 |
| (3S,5S)-3,5-Diaminohexanoate | 1.64 | 9.78E-03 | 1.65 | 6.23E-03 |
| Purine metabolism | | | | |
| 5-Aminoimidazole ribonucleotide | 0.57 | 1.01E-02 | 0.46 | 3.86E-03 |
| Adenine | 1.47 | 1.01E-02 | 0.68 | 1.66E-02 |
| Steroid hormone biosynthesis | | | | |
| Deoxycorticosterone | 0.51 | 1.02E-02 | 0.57 | 1.72E-02 |
| 17-Hydroxyprogesterone | 0.51 | 1.02E-02 | 0.57 | 1.72E-02 |
| Histidine metabolism | | | | |
| Imidazoleacetic acid | 2.67 | 1.99E-02 | 1.38 | 3.48E-02 |
| Arginine biosynthesis | | | | |
| N-Acetylmethionine | 2.58 | 4.02E-02 | 0.09 | 4.10E-02 |
| Indoles | | | | |
| 1H-Indole-3-carboxaldehyde | 0.62 | 8.61E-03 | 0.55 | 1.45E-02 |
| 2-Indolecarboxylic acid | 3.92 | 2.64E-02 | 0.35 | 3.92E-02 |
| Indole-3-carboxylic acid | 3.92 | 2.64E-02 | 0.35 | 3.92E-02 |
| Organonitrogen compounds-Guanidines | | | | |
| beta-Guanidinopropionic Acid | 0.45 | 2.97E-03 | 0.54 | 1.28E-02 |

| | | | | |
|--|------|----------|------|----------|
| Ubiquinone and other terpenoid-quinone biosynthesis | | | | |
| Alpha-Tocopherol | 0.38 | 7.98E-04 | 0.19 | 1.40E-03 |
| Carboxylic acids and derivatives-L-alpha-amino acids(ureas) | | | | |
| Homocitrulline | 8.51 | 3.51E-03 | 1.66 | 2.31E-02 |
| Methanemetabolism | | | | |
| Trimethylamine N-oxide(TMAO) | 3.05 | 4.76E-03 | 0.50 | 3.03E-02 |
| Biosynthesis of unsaturated fatty acids | | | | |
| Docosahexaenoic acid (DHA) | 0.69 | 1.30E-02 | 0.38 | 1.04E-03 |
| Ascorbate and aldarate metabolism | | | | |
| Ascorbic acid | 1.76 | 2.49E-02 | 1.57 | 4.68E-03 |
| monodehydroascorbate | 1.76 | 2.49E-02 | 1.57 | 4.68E-03 |

Suppl. Table 4. Hepatic metabolites significantly changed in both CKD and high-fat diet rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|---|------------------------------|----------------|--------------------------------|----------------|
| | Ratio Nx+SCD: Sham+SCD | <i>p</i> value | Ratio Sham+HFD: Sham+SCD | <i>p</i> value |
| Arginine and proline metabolism | | | | |
| 4-Guanidinobutanoic acid | 3.90 | 6.32E-04 | 0.39 | 1.36E-02 |
| Purine metabolism | | | | |
| Allantoic acid | 2.28 | 2.83E-04 | 0.63 | 2.71E-02 |
| Glutathione metabolism | | | | |
| Cysteinylglycine | 1.32 | 4.19E-02 | 0.62 | 3.03E-02 |
| Lysine degradation | | | | |
| Deoxycarnitine (4-Trimethylammoniobutanoate) | 4.30 | 2.87E-03 | 0.61 | 4.48E-02 |
| Carboxylic acids and derivatives-L-alpha-amino acids | | | | |
| Homocitrulline | 4.88 | 6.56E-03 | 2.27 | 3.52E-02 |
| Sphingolipids-Long-chain ceramides | | | | |
| N-Palmitoylsphingosine | 0.53 | 2.53E-02 | 0.52 | 1.49E-02 |
| Pyrimidine metabolism | | | | |
| orotate | 2.32 | 1.91E-02 | 2.39 | 3.46E-02 |
| Primary bile acid biosynthesis | | | | |
| Taurochenodeoxycholic acid | 0.64 | 1.99E-02 | 0.48 | 2.71E-02 |
| Nicotinate and nicotinamide metabolism | | | | |
| Trigonelline | 3.82 | 3.45E-02 | 0.02 | 7.05E-03 |

Suppl. Table 5. Muscle metabolites significantly changed in both CKD and high-fat diet rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|---|------------------------------|----------------|--------------------------------|----------------|
| | Ratio Nx+SCD: Sham+SCD | <i>p</i> value | Ratio Sham+HFD: Sham+SCD | <i>p</i> value |
| Carboxylic acids and derivatives-Alpha amino acids | | | | |
| 2-Phenylglycine | 4.60 | 3.68E-02 | 2.62 | 1.91E-03 |
| Allantoins | | | | |
| Allantoin | 10.44 | 1.30E-03 | 0.58 | 2.55E-02 |
| Lysine biosynthesis | | | | |
| Diaminopimelic acid | 1.41 | 2.70E-02 | 0.48 | 2.52E-03 |
| Nicotinate and nicotinamide metabolism | | | | |
| Trigonelline | 2.59 | 2.21E-02 | 0.25 | 9.87E-04 |
| Methanemetabolism | | | | |
| Trimethylamine N-oxide(TMAO) | 2.86 | 1.21E-02 | 0.31 | 1.67E-04 |

Suppl. Table 6. Serum metabolites significantly changed solely in Nx rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|---|------------------------------|----------------|--------------------------------|----------------|
| | Ratio Nx+SCD: Sham+SCD | <i>p</i> value | Ratio Sham+HFD: Sham+SCD | <i>p</i> value |
| Arginine and proline metabolism | | | | |
| Citrulline | 2.76 | 4.79E-04 | 0.97 | 8.11E-01 |
| L-Proline | 1.45 | 1.51E-02 | 1.06 | 7.51E-01 |
| Ornithine | 2.75 | 1.93E-03 | 1.10 | 6.02E-01 |
| Hydroxyproline | 2.01 | 1.30E-04 | 0.97 | 8.52E-01 |
| gamma-Aminobutyric acid | 2.07 | 2.96E-04 | 0.83 | 1.95E-01 |
| N-Acetylputrescine | 1.34 | 4.52E-02 | 0.86 | 2.81E-01 |
| Spermine | 0.75 | 8.26E-03 | 0.93 | 2.15E-01 |
| Creatinine | 1.70 | 1.50E-03 | 1.00 | 9.64E-01 |
| Arginine biosynthesis | | | | |
| N-Acetylglutamic acid | 2.31 | 2.71E-02 | 1.41 | 1.86E-01 |
| Tryptophan metabolism | | | | |
| 3-Hydroxyanthranilic acid | 2.29 | 1.03E-04 | 0.96 | 8.26E-01 |
| Serotonin | 1.46 | 2.02E-03 | 0.92 | 5.68E-01 |
| Indoleacetaldehyde | 1.46 | 4.76E-03 | 0.92 | 5.73E-01 |
| kynurenic acid | 2.26 | 1.95E-02 | 0.86 | 4.23E-01 |
| indoxyl sulfate | 2.12 | 1.81E-02 | 0.62 | 2.01E-01 |
| Acetyl-N-formyl-5-methoxykynurenamine | 0.69 | 4.87E-02 | 1.04 | 8.23E-01 |
| Steroid hormone biosynthesis | | | | |
| Pregnenolone | 0.44 | 1.60E-03 | 0.58 | 7.19E-01 |
| 17a-hydroxypregnenolone | 0.41 | 1.76E-02 | 0.64 | 1.09E-01 |
| Tetrahydrodeoxycorticosterone | 0.45 | 2.46E-02 | 0.84 | 4.56E-01 |
| Pentose and glucuronate interconversions | | | | |
| 3-Dehydro-L-gulonate | 3.27 | 1.33E-02 | 1.04 | 8.01E-01 |
| D-Glucuronic acid | 3.27 | 1.33E-02 | 1.04 | 8.01E-01 |
| Purine metabolism | | | | |
| Allantoic acid | 4.14 | 5.75E-04 | 0.69 | 9.26E-02 |
| Uric acid | 2.53 | 3.62E-02 | 2.63 | 5.75E-02 |
| Fatty acid metabolism | | | | |
| L-Palmitoylcarnitine | 1.87 | 7.36E-03 | 1.50 | 5.44E-02 |
| Palmitic acid | 0.75 | 1.08E-02 | 0.93 | 3.79E-01 |
| Biosynthesis of unsaturated fatty acids | | | | |
| Arachidonic Acid | 0.67 | 1.43E-02 | 0.74 | 5.51E-02 |
| Palmitic acid | 0.75 | 1.08E-02 | 0.93 | 3.79E-01 |
| Histidine metabolism | | | | |
| Carnosine | 0.40 | 3.73E-02 | 0.46 | 1.72E-01 |
| 1-methyl-L-histidine(3-Methylhistidine) | 2.60 | 8.99E-05 | 1.04 | 7.96E-01 |
| L-Histidine | 1.35 | 1.00E-02 | 1.11 | 2.34E-01 |

| | | | | |
|--|------|----------|------|----------|
| Lysine degradation | | | | |
| Amino adipic acid | 2.86 | 7.24E-05 | 1.06 | 7.15E-01 |
| N6,N6,N6-Trimethyl-L-lysine | 2.87 | 1.51E-05 | 1.20 | 1.22E-01 |
| 3-hydroxy-N6,N6,N6-trimethyl-L-lysine | 2.59 | 5.42E-03 | 0.80 | 6.39E-01 |
| Glutathione metabolism | | | | |
| Ornithine | 2.75 | 1.93E-03 | 1.10 | 6.02E-01 |
| Glutathione | 2.54 | 2.21E-02 | 1.10 | 7.54E-01 |
| 5-L-Glutamyl-L-alanine | 2.38 | 9.11E-04 | 1.22 | 3.50E-01 |
| Cysteine and methionine metabolism | | | | |
| L-Cystine | 1.81 | 2.30E-02 | 1.00 | 9.96E-01 |
| L-Methionine | 2.01 | 8.06E-04 | 1.13 | 2.28E-01 |
| 5'-Methylthioadenosine | 2.27 | 7.39E-03 | 1.06 | 7.57E-01 |
| Glycine, serine and threonine metabolism | | | | |
| L-Threonine | 1.69 | 2.66E-02 | 1.03 | 8.18E-01 |
| Dimethylglycine | 2.07 | 2.96E-04 | 0.83 | 1.95E-01 |
| 5-Aminolevulinic acid | 2.01 | 1.30E-04 | 0.97 | 8.52E-01 |
| Carboxylic acids and derivatives-N-acyl-L-alpha-amino acids | | | | |
| N-Acetyl-L-alanine | 2.99 | 5.23E-06 | 1.38 | 1.93E-01 |
| Biotin metabolism | | | | |
| Biotin | 1.64 | 4.49E-02 | 0.84 | 3.35E-01 |
| Amino sugar and nucleotide sugar metabolism | | | | |
| N-Acetyl-D-glucosamine | 2.91 | 1.74E-02 | 1.08 | 7.94E-01 |
| beta-Alanine metabolism | | | | |
| gamma-Aminobutyric acid | 2.07 | 2.96E-04 | 0.83 | 1.95E-01 |
| Spermine | 0.75 | 8.26E-03 | 0.93 | 2.15E-01 |
| beta-Alanine | 1.35 | 1.65E-02 | 1.08 | 5.26E-01 |
| Citrate cycle (TCA cycle) | | | | |
| cis-Aconitic acid | 4.41 | 1.40E-03 | 1.24 | 4.72E-01 |
| Porphyrin and chlorophyll metabolism | | | | |
| 5-Aminolevulinic acid | 2.01 | 1.30E-04 | 0.97 | 8.52E-01 |
| Tyrosine metabolism | | | | |
| Homovanillic acid | 2.34 | 2.44E-06 | 1.24 | 1.27E-01 |
| Hydroxyphenyllactic acid | 2.34 | 2.44E-06 | 1.24 | 1.27E-01 |
| Taurine and hypotaurine metabolism | | | | |
| Taurine | 1.37 | 8.95E-03 | 1.04 | 7.26E-01 |
| Allantoins | | | | |
| Allantoin | 3.14 | 4.06E-05 | 0.90 | 3.41E-01 |
| Pyrimidine nucleosides | | | | |
| Ribothymidine | 9.98 | 7.55E-04 | 1.02 | 9.44E-01 |
| Purines and purine derivatives-Hypoxanthines | | | | |
| 7-Methylguanine | 3.28 | 3.03E-06 | 0.99 | 9.26E-01 |
| Purines and purine derivatives-6-aminopurines | | | | |
| 1-Methyladenine | 2.98 | 1.03E-03 | 0.94 | 6.38E-01 |

| | | | | |
|---|-------|----------|-------|----------|
| 3-Methyladenine | 2.98 | 1.03E-03 | 0.94 | 6.38E-01 |
| 7-Methyladenine | 2.98 | 1.03E-03 | 0.94 | 6.38E-01 |
| Fatty acid esters -Acyl carnitines | | | | |
| Hydroxybutyrylcarnitine | 3.12 | 2.17E-02 | 3.48 | 1.26E-01 |
| Myristoylcarnitine | 1.72 | 3.50E-02 | 1.23 | 3.65E-01 |
| L-Acetylcarnitine | 12.66 | 1.93E-02 | 15.11 | 1.34E-01 |
| Phenylalanine metabolism | | | | |
| Phenylacetyl glycine | 3.56 | 2.04E-02 | 0.60 | 1.12E-01 |
| Purine nucleosides | | | | |
| 1-Methyladenosine | 1.50 | 6.72E-05 | 0.96 | 5.63E-01 |
| Phenylsulfates | | | | |
| 3-Methoxy-4-hydroxyphenylethyleneglycol sulfate | 2.51 | 2.36E-04 | 1.11 | 3.34E-01 |
| Amino acids, peptides, and analogues | | | | |
| Asymmetric dimethylarginine (ADMA) | 2.40 | 2.56E-05 | 1.03 | 8.57E-01 |
| Homoalanine (3-Aminobutanoic acid) | 2.07 | 2.96E-04 | 0.83 | 1.95E-01 |
| N-Acetyl glycine | 1.58 | 4.73E-03 | 1.09 | 3.19E-01 |
| Carboxylic acid derivatives-Acetamides | | | | |
| N1-Acetylspermidine | 1.81 | 1.15E-02 | 0.91 | 4.08E-01 |
| Diphenylethers | | | | |
| Thyroxine sulfate(T4) | 0.54 | 1.57E-02 | 1.13 | 4.61E-01 |

Suppl. Table 7. Hepatic metabolites significantly changed solely in Nx rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|--|---------------------|----------------|-----------------------|----------------|
| | Ratio | <i>p</i> value | Ratio | <i>p</i> value |
| | Nx+SCD: Sham+SCD | | Sham+HFD: Sham+SCD | |
| Arginine and proline metabolism | | | | |
| creatine | 0.57 | 2.27E-02 | 0.85 | 5.28E-01 |
| Creatinine | 2.92 | 3.89E-05 | 1.04 | 7.81E-01 |
| Hydroxyproline | 3.63 | 8.81E-04 | 1.44 | 4.55E-01 |
| L-Arginine | 2.83 | 4.45E-02 | 1.62 | 4.96E-01 |
| Sarcosine | 1.39 | 2.30E-02 | 0.98 | 8.73E-01 |
| Citrulline | 1.83 | 2.36E-03 | 1.18 | 5.60E-01 |
| Tryptophan metabolism | | | | |
| 3-Hydroxyanthranilic acid | 2.65 | 5.01E-04 | 1.22 | 4.73E-01 |
| 5-hydroxyindoleacetate | 1.77 | 2.44E-02 | 1.26 | 4.84E-01 |
| N-Acetyl-5-hydroxytryptamine | 1.50 | 2.25E-02 | 2.19 | 1.81E-01 |
| Purine metabolism | | | | |
| 5-aminoimidazole-4-carboxamide-1-beta-d-ribof | | | | |
| uranosyl 5'- | 0.51 | 3.66E-02 | 1.02 | 9.26E-01 |
| Cyclic AMP | 1.30 | 2.77E-03 | 1.06 | 8.38E-01 |
| L-Glutamine | 0.83 | 4.02E-02 | 0.91 | 5.37E-01 |
| Tyrosine metabolism | | | | |
| Epinephrine | 1.62 | 1.22E-02 | 1.83 | 1.48E-01 |
| 3-(4-hydroxyphenyl)lactate | 1.60 | 5.00E-02 | 0.89 | 1.23E-01 |
| Lysine degradation | | | | |
| (3S)-3,6-Diaminohexanoate | 1.34 | 1.03E-02 | 1.12 | 1.99E-01 |
| (3S,5S)-3,5-Diaminohexanoate | 1.34 | 1.03E-02 | 1.12 | 1.99E-01 |
| 5-Acetamidovalerate | 2.95 | 1.34E-02 | 1.10 | 8.69E-01 |
| glutarate | 1.35 | 1.07E-02 | 0.89 | 2.64E-01 |
| L-Pipecolic acid | 1.33 | 1.04E-02 | 1.11 | 2.08E-01 |
| L-Lysine | 1.34 | 1.03E-02 | 1.14 | 1.46E-01 |
| Purines and purine derivatives-6-aminopurines | | | | |
| 1-Methyladenine | 3.14 | 7.20E-03 | 1.56 | 5.45E-01 |
| 3-Methyladenine | 3.14 | 7.20E-03 | 1.56 | 5.45E-01 |
| 7-Methyladenine | 3.14 | 7.20E-03 | 1.56 | 5.45E-01 |
| Purine nucleosides | | | | |
| 1-methyladenosine | 1.50 | 1.15E-02 | 1.85 | 3.95E-01 |

| | | | | |
|--|------|----------|------|----------|
| Histidine metabolism | | | | |
| 1-methyl-L-histidine(3-Methylhistidine) | 2.20 | 5.66E-03 | 1.43 | 4.51E-01 |
| L-Histidine | 1.25 | 4.55E-02 | 0.98 | 8.73E-01 |
| Urocanic acid | 1.94 | 2.72E-02 | 2.50 | 2.60E-01 |
| Fatty Acyls-Acyl carnitines | | | | |
| 2-Methylbutyroylcarnitine | 1.92 | 3.25E-02 | 0.80 | 4.56E-01 |
| Carboxylic acids and derivatives- | | | | |
| Alpha amino acids | | | | |
| 2-Phenylglycine | 2.38 | 2.28E-02 | 0.70 | 1.64E-01 |
| Organonitrogen compounds-Guanidines | | | | |
| beta-Guanidinopropionic Acid | 0.85 | 3.75E-02 | 0.86 | 1.23E-01 |
| Vitamin B6 metabolism | | | | |
| 3-Hydroxy-2-methylpyridine-5-carboxylate | 2.65 | 5.01E-04 | 1.22 | 4.73E-01 |
| Benzene and substituted derivatives -Hippuric acids | | | | |
| 4-Aminohippuric acid | 4.38 | 3.56E-03 | 0.79 | 4.39E-01 |
| Cysteine and methionine metabolism | | | | |
| 5'-Methylthioadenosine | 1.95 | 4.65E-02 | 1.58 | 1.64E-01 |
| Imidazopyrimidines-Hypoxanthines | | | | |
| 7-Methylguanine | 2.10 | 8.16E-05 | 0.84 | 1.11E-01 |
| Starch and sucrose metabolism | | | | |
| ADP-glucose | 1.61 | 2.76E-02 | 1.18 | 6.51E-01 |
| Allantoins | | | | |
| Allantoin | 3.39 | 2.77E-04 | 1.58 | 2.91E-01 |
| Organooxygen compounds -Pentoses | | | | |
| Arabinose | 3.26 | 4.21E-05 | 1.70 | 2.71E-01 |
| Amino acids, peptides, and analogues | | | | |
| Asymmetric dimethylarginine(ADMA) | 2.41 | 2.06E-03 | 1.06 | 7.31E-01 |
| Lysine biosynthesis | | | | |
| Diaminopimelic acid | 1.48 | 4.11E-02 | 1.63 | 7.74E-02 |
| Galactose metabolism | | | | |
| Myoinositol | 1.34 | 8.15E-03 | 1.82 | 4.73E-01 |
| Glycine, serine and threonine metabolism | | | | |
| L-Cystathionine | 2.95 | 1.88E-02 | 1.23 | 5.47E-01 |
| Carboxylic acids and derivatives-N-acyl-L-alpha-amino acids | | | | |
| N-Acetyl-L-alanine | 3.63 | 8.81E-04 | 1.88 | 1.58E-01 |

| | | | | |
|---|------|----------|------|----------|
| Glycolysis / Gluconeogenesis | | | | |
| Oxalacetic acid | 1.31 | 2.13E-02 | 0.92 | 3.46E-01 |
| Pyruvic acid | 0.54 | 9.47E-03 | 2.43 | 3.87E-01 |
| beta-Alanine metabolism | | | | |
| Pantothenic Acid | 1.51 | 8.79E-03 | 1.45 | 3.36E-01 |
| beta-Alanine | 1.39 | 2.30E-02 | 0.98 | 8.73E-01 |
| Porphyrin and chlorophyll metabolism | | | | |
| Protoporphyrin IX | 0.61 | 4.87E-02 | 1.19 | 4.95E-01 |
| D-Glutamine and D-glutamate metabolism | | | | |
| Pyrrolidonecarboxylic acid | 0.91 | 4.29E-02 | 0.91 | 2.30E-01 |
| Pyrimidine nucleosides | | | | |
| Ribothymidine | 5.20 | 2.74E-03 | 1.04 | 9.45E-01 |
| others | | | | |
| 2-Pyrrolidinone | 2.44 | 1.45E-03 | 1.15 | 7.14E-01 |

Suppl. Table 8. Muscle metabolites significantly changed solely in Nx rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|--|------------------------------|----------------|--------------------------------|----------------|
| | Ratio Nx+SCD: Sham+SCD | <i>p</i> value | Ratio Sham+HFD: Sham+SCD | <i>p</i> value |
| Arginine and proline metabolism | | | | |
| Citrulline | 1.77 | 6.45E-03 | 0.91 | 6.64E-01 |
| 4-Guanidinobutanoic acid | 5.21 | 3.33E-03 | 0.49 | 6.05E-02 |
| gamma-Aminobutyric acid | 1.44 | 2.45E-02 | 0.82 | 1.82E-01 |
| Glutamic acid | 0.57 | 4.12E-02 | 0.86 | 3.53E-01 |
| Hydroxyproline | 2.54 | 2.09E-02 | 1.41 | 4.41E-01 |
| Tryptophan metabolism | | | | |
| 3-Hydroxyanthranilic acid | 2.86 | 8.98E-07 | 1.09 | 6.86E-01 |
| serotonin | 1.57 | 3.59E-02 | 0.85 | 1.23E-01 |
| Histidine metabolism | | | | |
| 1-methyl-L-histidine(3-Methylhistidine) | 2.03 | 8.66E-03 | 1.14 | 4.43E-01 |
| Imidazoleacetic acid | 4.28 | 2.37E-02 | 1.53 | 1.04E-01 |
| Purine nucleosides | | | | |
| 2'-O-Methyladenosine | 1.58 | 9.87E-04 | 1.15 | 3.23E-01 |
| Tyrosine metabolism | | | | |
| 3-(4-hydroxyphenyl)lactate | 0.68 | 2.53E-02 | 1.01 | 9.61E-01 |
| Vitamin B6 metabolism | | | | |
| 3-Hydroxy-2-methylpyridine-5-carboxylate | 2.86 | 8.98E-07 | 1.09 | 6.86E-01 |
| Purines and purine derivatives-Hypoxanthines | | | | |
| 7-Methylguanine | 2.80 | 2.59E-05 | 0.98 | 9.28E-01 |
| Organooxygen compounds -Pentoses | | | | |
| Arabinose | 2.31 | 8.21E-03 | 0.85 | 2.01E-01 |
| Amino acids, peptides, and analogues | | | | |
| Asymmetric dimethylarginine (ADMA) | 1.99 | 2.20E-02 | 0.97 | 8.96E-01 |
| L-Alpha-aminobutyric acid(homoal | 1.44 | 2.45E-02 | 0.82 | 1.82E-01 |
| Glycine, serine and threonine metabolism | | | | |
| Dimethylglycine | 1.44 | 2.45E-02 | 0.82 | 1.82E-01 |
| Carboxylic acids and derivatives-N-acyl-L-alpha-amino acids | | | | |
| N-Acetyl-L-alanine | 2.54 | 2.09E-02 | 1.41 | 4.41E-01 |
| Purine metabolism | | | | |
| dIMP | 0.50 | 1.77E-03 | 0.91 | 4.42E-01 |
| inosine 5'-phosphate | 0.64 | 3.68E-02 | 0.79 | 2.17E-01 |
| L-Glutamine | 0.59 | 9.25E-03 | 0.94 | 6.39E-01 |
| Xanthine | 3.27 | 8.31E-03 | 1.05 | 8.35E-01 |
| Glycine | 1.49 | 4.61E-02 | 0.77 | 2.72E-01 |

| | | | | |
|--|------|----------|------|----------|
| Methanemetabolism | | | | |
| Fructose 6-phosphate | 3.59 | 1.91E-02 | 6.85 | 2.64E-01 |
| Carboxylic acids and derivatives-L-alpha-amino acids(ureas) | | | | |
| Homocitrulline | 4.53 | 1.41E-02 | 1.34 | 1.97E-01 |
| Taurine and hypotaurine metabolism | | | | |
| hypotaurine | 0.51 | 8.95E-03 | 1.25 | 1.31E-01 |
| Organonitrogen compounds-N-acylethanolamines | | | | |
| LinoleoylEthanolamide | 0.47 | 5.74E-03 | 1.00 | 9.87E-01 |
| Citrate cycle (TCA cycle) | | | | |
| Malic acid | 0.76 | 2.68E-02 | 0.95 | 6.24E-01 |
| AMPK signaling pathway | | | | |
| Metformin | 0.43 | 1.94E-02 | 1.34 | 2.59E-01 |
| Galactose metabolism | | | | |
| Myoinositol | 1.53 | 2.14E-02 | 0.87 | 4.97E-01 |
| Riboflavin metabolism | | | | |
| FAD | 0.47 | 1.48E-02 | 1.67 | 7.05E-02 |
| Nicotinate and nicotinamide metabolism | | | | |
| NADP | 0.66 | 1.04E-02 | 1.19 | 1.81E-01 |
| Glutathione metabolism | | | | |
| Oxidized glutathione | 0.61 | 4.95E-03 | 0.99 | 9.49E-01 |
| NADP | 0.66 | 1.04E-02 | 1.19 | 1.81E-01 |
| Lysine degradation | | | | |
| pipecolate | 0.68 | 4.04E-02 | 0.97 | 8.31E-01 |
| Biosynthesis of terpenoids and steroids | | | | |
| Mevalonic Acid | 0.69 | 4.93E-02 | 1.01 | 9.46E-01 |
| Purines and purinederivatives-6-aminopurines | | | | |
| 1-Methyladenine | 2.52 | 1.74E-03 | 0.82 | 5.32E-02 |
| 3-Methyladenine | 2.52 | 1.74E-03 | 0.82 | 5.32E-02 |
| 7-Methyladenine | 2.52 | 1.74E-03 | 0.82 | 5.32E-02 |
| Benzene and substituted derivatives- Benzyl alcohols | | | | |
| 4-Hydroxybenzyl alcohol | 0.77 | 4.60E-02 | 1.08 | 5.05E-01 |
| Xanthines | | | | |
| Oxypurinol | 3.27 | 8.31E-03 | 1.05 | 8.35E-01 |

Suppl. Table 9. Serum metabolites significantly changed solely in HFD rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|---|------------------------------|----------------|--------------------------------|----------------|
| | Ratio Nx+SCD: Sham+SCD | <i>p</i> value | Ratio Sham+HFD: Sham+SCD | <i>p</i> value |
| Arginine and proline metabolism | | | | |
| Guanidoacetic acid | 0.94 | 6.35E-01 | 1.65 | 9.09E-03 |
| Tryptophan metabolism | | | | |
| Indoleacrylic acid | 1.88 | 2.76E-01 | 0.22 | 3.09E-03 |
| L-kynurenine | 1.29 | 3.63E-01 | 0.66 | 1.11E-02 |
| 5-Hydroxyindoleacetic acid | 1.33 | 3.65E-01 | 0.63 | 1.03E-02 |
| Histidine metabolism | | | | |
| Urocanic acid | 1.20 | 4.66E-01 | 1.54 | 2.25E-02 |
| Imidazoleacetic acid | 2.67 | 1.99E-02 | 1.38 | 3.48E-02 |
| Taurine and hypotaurine metabolism | | | | |
| Taurocholic acid | 1.01 | 9.85E-01 | 3.43 | 4.23E-02 |
| Glycine, serine and threonine metabolism | | | | |
| Betaine | 0.97 | 6.17E-01 | 0.83 | 1.75E-02 |
| Guanidoacetic acid | 1.14 | 4.63E-01 | 1.65 | 9.09E-03 |
| Biosynthesis of unsaturated fatty acids | | | | |
| Eicosapentaenoic acid | 0.66 | 1.39E-01 | 0.20 | 1.04E-02 |
| Lysine degradation | | | | |
| Pipecolic acid | 0.97 | 9.25E-01 | 2.00 | 2.97E-02 |
| Purine metabolism | | | | |
| Xanthine | 0.91 | 7.41E-01 | 1.91 | 3.05E-02 |
| Glycerophospholipid metabolism | | | | |
| LysoPC(20:1) | 1.47 | 7.58E-02 | 0.43 | 4.70E-03 |
| Steroid hormone biosynthesis | | | | |
| cholesterol sulfate | 0.97 | 7.65E-01 | 0.61 | 3.56E-04 |
| 3a-Hydroxy-5b-pregnane-20-one | 0.49 | 5.15E-01 | 0.38 | 2.74E-02 |
| Xanthines | | | | |
| Oxypurinol | 0.91 | 7.41E-01 | 1.91 | 3.05E-02 |
| Acyl carnitines | | | | |
| Decanoylcarnitine | 1.24 | 2.98E-01 | 1.76 | 1.56E-02 |
| Long-chain fatty acids | | | | |
| Pentadecanoic acid | 0.85 | 2.43E-01 | 0.44 | 1.25E-04 |
| 16(17)-EpDPE | 0.61 | 1.67E-01 | 0.29 | 2.17E-02 |
| Tetraalkylammonium salts | | | | |
| methacholine | 3.05 | 1.31E-01 | 0.40 | 3.62E-02 |
| Histidine metabolism | | | | |
| Ergothioneine | 0.85 | 6.39E-01 | 0.05 | 1.28E-03 |
| Carboxylic acids and derivatives-Alpha amino acids | | | | |
| N-Methyl-a-aminoisobutyric acid | 0.97 | 6.17E-01 | 0.83 | 1.75E-02 |

| | | | | |
|---|------|----------|------|----------|
| Arachidonic acid metabolism | | | | |
| Thromboxane B2 | 1.06 | 8.28E-01 | 1.49 | 1.81E-02 |
| Caprolactam degradation | | | | |
| Adipic acid | 1.06 | 5.51E-01 | 1.20 | 1.35E-02 |
| Nicotinate and nicotinamide metabolism | | | | |
| Trigonelline | 3.55 | 5.91E-02 | 0.02 | 6.19E-03 |

Suppl. Table 10. Hepatic metabolites significantly changed solely in HF rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|---|------------------------------|----------------|--------------------------------|----------------|
| | Ratio Nx+SCD: Sham+SCD | <i>p</i> value | Ratio Sham+HFD: Sham+SCD | <i>p</i> value |
| Arginine and proline metabolism | | | | |
| Gamma-Aminobutyric acid | 1.24 | 1.04E-01 | 0.71 | 3.60E-02 |
| Spermine | 0.98 | 8.96E-01 | 0.67 | 3.78E-02 |
| Ornithine | 1.10 | 4.39E-01 | 0.61 | 4.82E-03 |
| Pyrimidine metabolism | | | | |
| Uridine 5'-diphosphate | 2.05 | 6.30E-02 | 0.46 | 2.08E-03 |
| Uridine 5'-monophosphate | 1.24 | 3.57E-01 | 0.62 | 3.02E-02 |
| Uridinediphosphate glucose(UDP-glucose) | 0.99 | 9.56E-01 | 0.53 | 4.58E-03 |
| Phosphonate and phosphinate metabolism | | | | |
| (2-aminoethyl)phosphonate | 0.98 | 9.14E-01 | 1.97 | 1.36E-02 |
| Arachidonic acid metabolism | | | | |
| 15-Deoxy-d-12,14-PGJ2 | 1.30 | 2.08E-01 | 0.18 | 1.13E-03 |
| Nicotinate and nicotinamide metabolism | | | | |
| 1-methylnicotinamide | 1.40 | 1.86E-01 | 0.66 | 3.43E-02 |
| Nicotine | 1.94 | 1.67E-01 | 1.64 | 2.53E-02 |
| Phenylalanine metabolism | | | | |
| 3-(2-hydroxyphenyl)propanoate | 0.99 | 8.56E-01 | 0.92 | 2.83E-02 |
| Organooxygen compounds-Sugar acids and derivatives | | | | |
| 3-phosphoglycerate | 2.22 | 2.28E-01 | 1.78 | 3.20E-02 |
| Pyridines and derivatives-Aminopyridines and derivatives | | | | |
| 4-Aminopyridine | 1.12 | 7.31E-01 | 0.59 | 3.26E-02 |
| Purine metabolism | | | | |
| Adenosine 5'-monophosphate | 1.12 | 7.11E-01 | 0.46 | 2.75E-02 |
| Adenosine diphosphate ribose | 0.78 | 3.97E-01 | 0.60 | 4.23E-02 |
| Glycine, serine and threonine metabolism | | | | |
| Dimethylglycine | 1.24 | 1.04E-01 | 0.71 | 3.60E-02 |
| Biosynthesis of unsaturated fatty acids | | | | |
| Eicosapentaenoic acid | 1.09 | 7.64E-01 | 0.52 | 3.59E-03 |
| Histidine metabolism | | | | |
| Ergothioneine | 0.79 | 3.03E-01 | 0.07 | 4.54E-04 |
| Histamine | 1.15 | 7.01E-01 | 0.56 | 3.47E-02 |

| | | | | |
|--|------|----------|------|----------|
| Vitamin B6 metabolism | | | | |
| pyridoxal 5-phosphate (vitamin B6) | 0.92 | 6.26E-01 | 0.58 | 1.56E-03 |
| Taurine and hypotaurine metabolism | | | | |
| Taurine | 0.96 | 8.52E-01 | 2.39 | 1.22E-02 |
| Cysteine and methionine metabolism | | | | |
| Glutathione | 1.27 | 5.52E-02 | 0.63 | 2.70E-02 |
| S-Adenosylhomocysteine | 0.88 | 2.59E-01 | 0.72 | 4.52E-03 |
| Glycerophospholipid metabolism | | | | |
| LysoPC(20:0) | 0.89 | 6.69E-01 | 0.31 | 4.66E-03 |
| LysoPC(20:1) | 0.91 | 6.00E-01 | 0.37 | 7.38E-05 |
| Arginine biosynthesis | | | | |
| N-Acetylmethionine | 1.74 | 5.93E-02 | 0.17 | 6.83E-07 |
| Polycyclic aromatic hydrocarbon degradation | | | | |
| Phthalate | 0.98 | 6.34E-01 | 0.92 | 5.27E-03 |
| Thiamine metabolism | | | | |
| Thiamine | 1.01 | 9.51E-01 | 0.32 | 5.12E-04 |

Suppl. Table 11. Muscle metabolites significantly changed solely in HF rats

| Metabolite | CKD vs Sham | | HFD vs SCD | |
|---|------------------------------|----------------|--------------------------------|----------------|
| | Ratio Nx+SCD: Sham+SCD | <i>p</i> value | Ratio Sham+HFD: Sham+SCD | <i>p</i> value |
| Nicotinate and nicotinamide metabolism | | | | |
| 1-Methylnicotinamide | 1.21 | 4.39E-01 | 0.49 | 3.52E-02 |
| Synthesis and degradation of ketone bodies | | | | |
| acetoacetate | 1.06 | 4.94E-01 | 0.81 | 1.69E-02 |
| Caprolactam degradation | | | | |
| adipic acid | 1.23 | 9.56E-02 | 1.12 | 4.70E-02 |
| Glycine, serine and threonine metabolism | | | | |
| Betaine aldehyde | 0.88 | 2.69E-01 | 0.76 | 4.07E-02 |
| Betaine | 1.14 | 3.01E-01 | 0.63 | 2.92E-02 |
| L-Serine | 1.04 | 8.19E-01 | 1.37 | 4.32E-02 |
| Glycine | 1.04 | 9.16E-01 | 0.56 | 3.92E-02 |
| Carnitines | | | | |
| carnitine | 0.82 | 4.13E-01 | 0.66 | 3.70E-02 |
| Glycerophospholipid metabolism | | | | |
| CDP-ethanolamine | 1.04 | 8.48E-01 | 1.33 | 3.67E-02 |
| Cytidinediphosphate choline | 0.78 | 3.87E-01 | 0.53 | 4.21E-02 |
| Histidine metabolism | | | | |
| Ergothioneine | 0.76 | 3.74E-01 | 0.14 | 2.85E-03 |
| Tetraalkylammonium salts | | | | |
| methacholine | 2.05 | 7.97E-02 | 0.37 | 1.61E-02 |
| Arginine biosynthesis | | | | |
| N-Acetylornithine | 1.86 | 9.76E-02 | 0.07 | 2.29E-04 |
| Carboxylic acids and derivatives-Alpha amino acids | | | | |
| N-Methyl-a-aminoisobutyric acid | 1.14 | 3.01E-01 | 0.63 | 2.92E-02 |
| Pyrimidine nucleosides | | | | |
| Ribothymidine | 5.05 | 1.39E-01 | 0.60 | 1.94E-02 |
| Thiamine metabolism | | | | |
| Thiamine | 0.90 | 6.71E-01 | 0.43 | 1.16E-02 |
| Methane metabolism | | | | |
| trimethylamine | 0.87 | 4.90E-01 | 0.67 | 8.77E-03 |