**Supplemental Digital Content 1.** Associations between change in metabolites and change in cardiometabolic traits.

|  |  |  |  |
| --- | --- | --- | --- |
| ∆ Risk Factor | ∆ Metabolite | Beta Coefficient | p-Value |
| CRF | *N*-Acetyl-L-Glutamic Acid | -0.30 | 5.20×10-4 |
| (mL/kg/min) | Homogentisic Acid | -0.29 | 7.14×10-4 |
|  | Kynurenic Acid | -0.29 | 7.68×10-4 |
|  | Proline | -0.28 | 1.54×10-3 |
|  | Bilirubin | 0.24 | 3.63×10-3 |
|  | Tyrosine | -0.25 | 3.75×10-3 |
|  | Malic Acid | 0.24 | 4.02×10-3 |
|  | Pyroglutamic Acid | 0.23 | 4.41×10-3 |
|  | Kynurenic Acid | -0.24 | 4.65×10-3 |
|  | 1,5-Anhydroglucitol | -0.24 | 5.88×10-3 |
|  | 2-Hydroxyglutaric Acid | 0.22 | 6.95×10-3 |
|  | Glutamate | -0.24 | 7.20×10-3 |
|  | Ornithine | -0.22 | 9.78×10-3 |
|  | NMMA | -0.22 | 1.08×10-2 |
|  | Histidine | -0.22 | 1.11×10-2 |
|  | Alanine | -0.22 | 1.13×10-2 |
|  | ADMA/SDMA | -0.22 | 1.23×10-2 |
|  | Thyroxine | -0.21 | 1.26×10-2 |
|  | Methionine | -0.21 | 1.39×10-2 |
|  | Citrulline | -0.21 | 1.53×10-2 |
|  | Valine | -0.21 | 1.93×10-2 |
|  | C3-Carnitine | -0.20 | 2.09×10-2 |
|  | Lysine | -0.19 | 2.10×10-2 |
|  | Kynurenine | -0.19 | 2.76×10-2 |
|  | Carnitine | -0.19 | 2.86×10-2 |
|  | Creatine | -0.19 | 3.01×10-2 |
|  | Oxaloacetic Acid | -0.18 | 3.14×10-2 |
|  | Pyruvic Acid | -0.18 | 3.34×10-2 |
|  | Xanthurenic Acid | -0.18 | 3.41×10-2 |
|  | Glutathione Reduced | 0.18 | 3.49×10-2 |
|  | Niacinamide | -0.18 | 3.62×10-2 |
|  | Cyclic AMP | -0.16 | 4.64×10-2 |
|  | *cis/trans*-Hydroxyproline | -0.17 | 4.68×10-2 |
|  | Glutamine | -0.17 | 4.78×10-2 |
|  | C4-Methylmalonyl Carnitine | -0.17 | 4.83×10-2 |
| Weight | Proline | 0.27 | 1.06×10-3 |
|  | Kynurenic Acid | 0.26 | 2.00×10-3 |
|  | Pyroglutamic Acid | -0.26 | 2.08×10-3 |
|  | Methionine | 0.25 | 2.30×10-3 |
|  | Uridine | 0.24 | 4.44×10-3 |
|  | 3-Hydroxybutyric Acid | -0.23 | 7.10×10-3 |
|  | Niacinamide | 0.22 | 7.32×10-3 |
|  | Creatinine | 0.22 | 9.25×10-3 |
|  | Leucine | 0.22 | 9.35×10-3 |
|  | 1,5-Anhydroglucitol | 0.22 | 9.66×10-3 |
|  | Citric Acid/Isocitric Acid | -0.21 | 1.11×10-2 |
|  | C7-Carnitine | 0.21 | 1.11×10-2 |
|  | Isoleucine | 0.21 | 1.13×10-2 |
|  | Kynurenine | 0.21 | 1.15×10-2 |
|  | Histidine | 0.21 | 1.20×10-2 |
|  | Taurine | -0.20 | 1.65×10-2 |
|  | Acetoacetic Acid | -0.20 | 1.89×10-2 |
|  | Glycerol | 0.19 | 1.98×10-2 |
|  | Arginine | 0.19 | 2.22×10-2 |
|  | Thyroxine | 0.19 | 2.23×10-2 |
|  | Glycerol-3-Phosphate | 0.18 | 3.45×10-2 |
|  | Pyruvic Acid | 0.18 | 3.61×10-2 |
|  | Glutathione Reduced | -0.17 | 3.92×10-2 |
|  | Cyclic AMP | 0.17 | 4.02×10-2 |
|  | Kynurenic Acid | 0.17 | 4.07×10-2 |
|  | Oxaloacetic Acid | 0.17 | 4.09×10-2 |
|  | C14-Carnitine | 0.17 | 4.18×10-2 |
|  | Bilirubin | -0.17 | 4.35×10-2 |
|  | *N*-Acetyl-L-Glutamic Acid | 0.17 | 4.37×10-2 |
|  | Choline | 0.17 | 4.44×10-2 |
|  | Serine | -0.17 | 4.49×10-2 |
|  | Valine | 0.17 | 4.80×10-2 |
| WC | Alanine | 0.28 | 6.26×10-4 |
|  | Kynurenic Acid | 0.28 | 7.18×10-4 |
|  | Citric Acid/Isocitric Acid | -0.27 | 9.69×10-4 |
|  | Glutamate | 0.25 | 2.57×10-3 |
|  | Proline | 0.24 | 3.22×10-3 |
|  | Pyroglutamic Acid | -0.24 | 3.68×10-3 |
|  | Glutathione Reduced | -0.24 | 3.72×10-3 |
|  | Methionine | 0.23 | 4.30×10-3 |
|  | Carnitine | 0.24 | 4.49×10-3 |
|  | Leucine | 0.24 | 4.59×10-3 |
|  | Kynurenine | 0.23 | 4.79×10-3 |
|  | Arachidonoylglycerol | 0.23 | 4.89×10-3 |
|  | 3-Hydroxybutyric Acid | -0.22 | 8.36×10-3 |
|  | Creatinine | 0.22 | 8.72×10-3 |
|  | Thyroxine | 0.21 | 9.42×10-3 |
|  | Uridine | 0.21 | 1.19×10-2 |
|  | Arginine | 0.21 | 1.31×10-2 |
|  | Histidine | 0.21 | 1.37×10-2 |
|  | Homogentisic Acid | 0.20 | 1.54×10-2 |
|  | Kynurenic Acid | 0.19 | 2.16×10-2 |
|  | Isoleucine | 0.19 | 2.33×10-2 |
|  | C3-Carnitine | 0.19 | 2.36×10-2 |
|  | NMMA | 0.18 | 2.70×10-2 |
|  | Anthranilic-Acid | -0.18 | 3.16×10-2 |
|  | C7-Carnitine | 0.18 | 3.23×10-2 |
|  | C4-Methylmalonyl Carnitine | 0.17 | 3.73×10-2 |
|  | Oxaloacetic Acid | 0.17 | 3.93×10-2 |
|  | Glycerol-3-Phosphate | 0.17 | 4.08×10-2 |
|  | Pyruvic Acid | 0.17 | 4.24×10-2 |
|  | Serine | -0.17 | 4.41×10-2 |
|  | Alpha-Glycerophosphocholine | 0.23 | 4.41×10-2 |
|  | Maleic Acid | -0.17 | 4.74×10-2 |
|  | Bilirubin | -0.16 | 4.88×10-2 |
| BMI | Pyroglutamic Acid | -0.28 | 4.94×10-4 |
|  | Methionine | 0.26 | 1.05×10-3 |
|  | Uridine | 0.23 | 4.62×10-3 |
|  | 3-Hydroxybutyric Acid | -0.23 | 5.03×10-3 |
|  | Kynurenic Acid | 0.22 | 5.90×10-3 |
|  | Niacinamide | 0.22 | 5.95×10-3 |
|  | Leucine | 0.22 | 6.60×10-3 |
|  | Isoleucine | 0.22 | 6.73×10-3 |
|  | Histidine | 0.21 | 9.87×10-3 |
|  | Pyruvic Acid | 0.21 | 1.01×10-2 |
|  | Glycerol | 0.21 | 1.06×10-2 |
|  | Acetoacetic Acid | -0.20 | 1.23×10-2 |
|  | Kynurenine | 0.20 | 1.46×10-2 |
|  | Lactic Acid | 0.20 | 1.48×10-2 |
|  | Taurine | -0.19 | 2.09×10-2 |
|  | Oxaloacetic Acid | 0.18 | 2.11×10-2 |
|  | C7-Carnitine | 0.19 | 2.26×10-2 |
|  | Creatinine | 0.18 | 2.37×10-2 |
|  | Glycerol-3-Phosphate | 0.18 | 2.52×10-2 |
|  | Creatine | 0.18 | 2.63×10-2 |
|  | Citric Acid/Isocitric Acid | -0.18 | 2.73×10-2 |
|  | 1,5-Anhydroglucitol | 0.18 | 2.80×10-2 |
|  | Serine | -0.18 | 2.85×10-2 |
|  | Arginine | 0.18 | 2.87×10-2 |
|  | Orotic Acid | -0.18 | 3.13×10-2 |
|  | Thyroxine | 0.18 | 3.15×10-2 |
|  | Bilirubin | -0.17 | 3.17×10-2 |
|  | Valine | 0.18 | 3.20×10-2 |
|  | Glutathione Reduced | -0.18 | 3.20×10-2 |
|  | Homogentisic Acid | 0.17 | 4.16×10-2 |
|  | *N*-Acetyl-L-Glutamic Acid | 0.17 | 4.36×10-2 |
|  | Choline | 0.16 | 4.81×10-2 |
| Fasting Insulin | C8-Carnitine | -0.33 | 6.09×10-4 |
|  | Xanthurenic Acid | 0.30 | 1.91×10-3 |
|  | Creatine | 0.30 | 1.94×10-3 |
|  | Valine | 0.30 | 2.17×10-3 |
|  | C10-Carnitine | -0.29 | 2.58×10-3 |
|  | C12-Carnitine | -0.29 | 2.92×10-3 |
|  | ADP | -0.28 | 3.63×10-3 |
|  | Serine | -0.27 | 5.19×10-3 |
|  | Kynurenic Acid | 0.26 | 6.73×10-3 |
|  | Taurocholic Acid | 0.26 | 8.87×10-3 |
|  | C16-Carnitine | -0.25 | 9.21×10-3 |
|  | C6-Carnitine | -0.25 | 1.11×10-2 |
|  | Glutamate | 0.25 | 1.21×10-2 |
|  | Glycine | -0.24 | 1.39×10-2 |
|  | Tryptophan | 0.22 | 2.25×10-2 |
|  | Succinic Acid/Methylmalonic Acid | -0.22 | 2.42×10-2 |
|  | Thyroxine | 0.22 | 2.44×10-2 |
|  | C3-Carnitine | 0.21 | 3.03×10-2 |
|  | Tyrosine | 0.21 | 3.14×10-2 |
|  | C18:1-Carnitine | -0.20 | 3.72×10-2 |
|  | Kynurenic Acid | 0.20 | 3.89×10-2 |
|  | Indole-3-Propanoic Acid | -0.20 | 4.63×10-2 |
|  | Cystamine | 0.20 | 4.71×10-2 |
|  | Leucine | 0.19 | 4.76×10-2 |
| HOMA IR | UDP-GlcNAc | 0.33 | 6.01×10-4 |
|  | C8-Carnitine | -0.32 | 7.89×10-4 |
|  | Creatine | 0.30 | 1.98×10-3 |
|  | ADP | -0.29 | 2.86×10-3 |
|  | C10-Carnitine | -0.28 | 3.20×10-3 |
|  | C12-Carnitine | -0.28 | 3.32×10-3 |
|  | Xanthurenic Acid | 0.28 | 3.49×10-3 |
|  | Glucose Fructose Galactose | 0.27 | 5.21×10-3 |
|  | C16-Carnitine | -0.26 | 6.00×10-3 |
|  | Serine | -0.26 | 7.18×10-3 |
|  | Glycine | -0.26 | 7.41×10-3 |
|  | Kynurenic Acid | 0.26 | 7.56×10-3 |
|  | Valine | 0.26 | 8.23×10-3 |
|  | Glutamate | 0.25 | 1.09×10-2 |
|  | Taurocholic Acid | 0.24 | 1.42×10-2 |
|  | C6-Carnitine | -0.23 | 1.70×10-2 |
|  | C18:1-Carnitine | -0.22 | 2.18×10-2 |
|  | Succinic Acid/Methylmalonic Acid | -0.22 | 2.40×10-2 |
|  | Kynurenic Acid | 0.21 | 3.00×10-2 |
|  | Indole-3-Propanoic Acid | -0.21 | 3.05×10-2 |
|  | C18:2-Carnitine | -0.20 | 3.28×10-2 |
|  | Thyroxine | 0.20 | 3.77×10-2 |
|  | 2-Hydroxybutyric Acid | 0.20 | 4.06×10-2 |
|  | Hydroxyphenylpyruvic Acid | 0.20 | 4.34×10-2 |
| Insulin AUC | Kynurenic Acid | 0.34 | 9.36×10-4 |
|  | ADP | -0.33 | 1.31×10-3 |
|  | Kynurenic Acid | 0.31 | 2.42×10-3 |
|  | Creatine | 0.30 | 3.16×10-3 |
|  | Alanine | 0.28 | 6.53×10-3 |
|  | Thyroxine | 0.27 | 8.34×10-3 |
|  | Glycine | -0.27 | 1.06×10-2 |
|  | Serine | -0.26 | 1.20×10-2 |
|  | Citric Acid/Isocitric Acid | -0.26 | 1.26×10-2 |
|  | 2-Hydroxybutyric Acid | 0.26 | 1.29×10-2 |
|  | Aspartate | 0.24 | 1.79×10-2 |
|  | Indole-3-Propanoic Acid | -0.24 | 1.80×10-2 |
|  | Valine | 0.24 | 2.08×10-2 |
|  | Glutathione Reduced | -0.23 | 2.38×10-2 |
|  | Methionine | 0.22 | 3.66×10-2 |
|  | Indoxyl Sulfate | 0.21 | 3.80×10-2 |
|  | Leucine | 0.21 | 4.06×10-2 |
|  | Choline | 0.21 | 4.30×10-2 |
| 2-Hour Glucose | Glycerol | 0.25 | 5.25×10-3 |
|  | C7-Carnitine | 0.23 | 1.10×10-2 |
|  | Inosine | -0.22 | 1.35×10-2 |
|  | Kynurenine | -0.22 | 1.60×10-2 |
|  | Thyroxine | 0.22 | 1.62×10-2 |
|  | C14-Carnitine | 0.22 | 1.64×10-2 |
|  | Indole-3-Propanoic Acid | -0.21 | 1.95×10-2 |
|  | C2-Carnitine | 0.21 | 2.04×10-2 |
|  | Anandamide | 0.21 | 2.30×10-2 |
|  | Xanthosine | -0.20 | 2.33×10-2 |
|  | 2-Hydroxybutyric Acid | 0.20 | 2.84×10-2 |
|  | C6-Carnitine | 0.19 | 3.34×10-2 |
|  | Malic Acid | -0.19 | 3.51×10-2 |
|  | 3-Hydroxybutyric Acid | 0.19 | 3.69×10-2 |
|  | 2-Aminoadipic Acid | 0.19 | 3.86×10-2 |
|  | Leucine | 0.19 | 3.96×10-2 |
|  | Phosphocholine | 0.18 | 4.26×10-2 |
|  | Quinolinic Acid | -0.18 | 4.97×10-2 |
| SBP | Thymidine | 0.22 | 9.30×10-3 |
|  | Cysteamine | 0.21 | 1.26×10-2 |
|  | Taurine | -0.21 | 1.37×10-2 |
|  | Trimethylamine-*N-*Oxide | 0.20 | 1.52×10-2 |
|  | Citric Acid/Isocitric Acid | -0.20 | 1.96×10-2 |
|  | Anthranilic Acid | -0.19 | 2.36×10-2 |
|  | 1,5-Anhydroglucitol | 0.17 | 4.80×10-2 |
| DBP | Taurine | -0.20 | 2.03×10-2 |
|  | Aminoisobutyric Acid | -0.17 | 4.81×10-2 |

AUC, area under the curve; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; CRF, cardiorespiratory fitness. Multiple regression adjusted for age, sex and baseline risk factor.