Supplementary Online Content

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eFigure 5. Association Between Serum Mannose and Acute Respiratory Distress Syndrome (ARDS) Risk

eAppendix. Supplementary Methods

This supplementary material has been provided by the authors to give readers additional information about their work.
**eTable 1. Descriptions of mQTL Study**

| Study Procedure       | Study information | TwinsUK | KORA F4 |
|-----------------------|-------------------|---------|---------|
| **Sample description**| Country of origin | UK      | Germany |
|                       | Number of samples | 6,056   | 1,768   |
|                       | (Male/Female)     | (433/5,623) | (858/910) |
|                       | Age (years, mean±SD) | 53.4±14.0 | 60.8±8.8 |
|                       | BMI (kg/m², mean±SD) | 26.1±4.9 | 28.2±4.8 |
| **Metabolite measurements** | Platform | UPLC-MS/MS and GC-MS | UPLC-MS/MS and GC-MS |
|                       | Sample type (serum) | 1,052 | 1,768 |
|                       | Sample type (plasma) | 5,004 | 0 |
|                       | Number of metabolites (known/unknown) | 296/207 | 305/212 |
| **QC of samples**     | Outlier exclusion | outlier exclusion with high missing rate (one sample excluded) | |
| **QC metabolites**    | Data transformation | block correction, log-transformation | block correction, log-transformation |
|                       | Missing data      | 3 metabolites with <10 samples excluded | 4 metabolites with <10 samples excluded |
|                       | Outlier exclusion | >4 SD from mean | >4 SD from mean |
| **SNP genotyping**    | Platform | Illumina HumanHap300, 610Q, 1M-Duo, 1.2M-Duo 1M | Affymetrix Genome-Wide Human SNP Array 6.0 |
|                       | Calling algorithm | BeadStudio | Birdseed2 |
| **QC of SNPs**        | Sample Call Rate | 98% | 93% |
|                       | SNP Call Rate | 97% (MAF ≥5%) | 93% |
|                       | [99% (1≤ MAF ≤5%)] | | |
|                       | P value of HWE test | >10⁻⁶ | NA |
|                       | MAF               | >1% | NA |
| **Imputation of SNPs**| Number of autosomal SNPs | 489,767 | 655,658 |
|                       | Reference panel | NCBI Build 36 HapMap CEU HM2 rel22 | NCBI Build 36 |
|                       | Software          | IMPUTE v2 | IMPUTE |
|                       | MAF               | >1% | >1% |
| Study Procedure | Study information | TwinsUK | KORA F4 |
|-----------------|-------------------|---------|---------|
| **Study information** | | | |
| Imputation quality score | >0.4 | >0.4 |
| Imputation posterior probability | >90% | |
| **Statistical analysis** | | | |
| Number of samples with genotypes | 5,605 (MZ duplicated) | 1,768 |
| Number of SNPs | 3,039,184 | 2,163,597 |
| Number of metabolites | 293/207 | 301/212 |
| Model | Additive | Additive |
| Software | MERLIN | QUICKTEST |
| Adjustments | Age, sex, batch of specimen and zygosity | Age and sex |
| **Meta-analysis** | | | |
| Number of overlapped metabolites | | 486 |
| Model | | Inverse variance model |
| Software | | METAL |
**eTable 2. Annotation of Metabolites in mQTL Study**

| ID    | Metabolite         | Status  | Pathway                      | Super-pathway         | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|-------|--------------------|---------|------------------------------|-----------------------|----------|-------------|--------------|----------------|---------|---------|
| M32339| alanine            | Known   | Alanine and aspartate        | Amino acid            | GC/MS    |             |              | 13.40          | 7,788   |         |
|       |                    |         | metabolism                  |                       |          |             |              |                |         |         |
| M34283| asparagine         | Known   | Alanine and aspartate        | Amino acid            | GC/MS    |             |              | 27.90          | 7,761   |         |
|       |                    |         | metabolism                  |                       |          |             |              |                |         |         |
| M15996| aspartate          | Known   | Alanine and aspartate        | Amino acid            | GC/MS    |             |              | 29.00          | 7,721   |         |
|       |                    |         | metabolism                  |                       |          |             |              |                |         |         |
| M01585| N-acetylalanine    | Known   | Alanine and aspartate        | Amino acid            | LC/MS    | neg         |              | 12.10          | 7,720   |         |
|       |                    |         | metabolism                  |                       |          |             |              |                |         |         |
| M32348| 2-aminobutyrate    | Known   | Butanoate metabolism        | Amino acid            | LC/MS    | pos         |              | 9.60           | 7,814   |         |
|       |                    |         |                             |                       |          |             |              |                |         |         |
| M27718| creatine           | Known   | Creatine metabolism         | Amino acid            | LC/MS    | pos         |              | 5.70           | 7,822   |         |
|       |                    |         |                             |                       |          |             |              |                |         |         |
| M00513| creatinine         | Known   | Creatine metabolism         | Amino acid            | LC/MS    | pos         |              | 9.40           | 7,810   |         |
|       |                    |         |                             |                       |          |             |              |                |         |         |
| M21044| 2-hydroxybutyrate  | Known   | Cysteine, methionine,       | Amino acid            | GC/MS    |             |              | 7.40           | 7,815   |         |
|       | (AHB)              |         | SAM, taurine metabolism     |                       |          |             |              |                |         |         |
| M31453| cysteine           | Known   | Cysteine, methionine,       | Amino acid            | GC/MS    |             |              | 21.70          | 7,692   |         |
|       |                    |         | SAM, taurine metabolism     |                       |          |             |              |                |         |         |
| M31454| cystine            | Known   | Cysteine, methionine,       | Amino acid            | GC/MS    |             |              | NA             | 1,409   |         |
|       |                    |         | SAM, taurine metabolism     |                       |          |             |              |                |         |         |
| M01302| methionine         | Known   | Cysteine, methionine,       | Amino acid            | LC/MS    | neg         |              | 5.70           | 7,795   |         |
|       |                    |         | SAM, taurine metabolism     |                       |          |             |              |                |         |         |
| M32322| glutamate          | Known   | Glutamate metabolism        | Amino acid            | GC/MS    |             |              | 14.30          | 7,804   |         |
|       |                    |         |                             |                       |          |             |              |                |         |         |
| M00053| glutamine          | Known   | Glutamate metabolism        | Amino acid            | LC/MS    | pos         |              | 7.20           | 7,821   |         |
|       |                    |         |                             |                       |          |             |              |                |         |         |
| M32672| pyroglutamine*     | Known   | Glutamate metabolism        | Amino acid            | LC/MS    | pos         |              | 9.00           | 7,800   |         |
|       |                    |         |                             |                       |          |             |              |                |         |         |
| M01494| 5-oxoproline      | Known   | Glutathione metabolism      | Amino acid            | LC/MS    | pos         |              | 20.80          | 7,802   |         |
|       | cysteine-          |         |                             |                       |          |             |              |                |         |         |
|       | glutathione        |         | disulfide                   |                       |          |             |              |                |         |         |
| M35159|                   |         |                             |                       |          |             |              |                |         |         |
| M03141| betaine           | Known   | Glycine, serine and         | Amino acid            | LC/MS    | pos         |              | 8.50           | 7,806   |         |
|       |                    |         | threonine metabolism        |                       |          |             |              |                |         |         |
| M32338| glycine           | Known   | Glycine, serine and         | Amino acid            | GC/MS    |             |              | 13.90          | 7,802   |         |
|       |                    |         | threonine metabolism        |                       |          |             |              |                |         |         |
| M27710| N-acetylglycine    | Known   | Glycine, serine and         | Amino acid            | GC/MS    |             |              | 19.00          | 7,135   |         |
|       |                    |         | threonine metabolism        |                       |          |             |              |                |         |         |
| ID     | Metabolite                | Status  | Pathway                                      | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|---------------------------|---------|----------------------------------------------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M33939 | N-acetylthreonine         | Known   | Glycine, serine and threonine metabolism     | Amino acid    | LC/MS    | neg         |              | 24.50          | 6,909  |
| M32315 | serine                    | Known   | Glycine, serine and threonine metabolism     | Amino acid    | GC/MS    |              |              | 16.10          | 7,796  |
| M01284 | threonine                 | Known   | Glycine, serine and threonine metabolism     | Amino acid    | LC/MS    | pos         |              | 12.60          | 6,020  |
| M01558 | 4-acetamidobutanoate      | Known   | Guanidino and acetamido metabolism           | Amino acid    | LC/MS    | pos         |              | 17.30          | 6,930  |
| M15677 | 3-methylhistidine         | Known   | Histidine metabolism                         | Amino acid    | LC/MS    | neg         |              | 6.80           | 5,885  |
| M00059 | histidine                 | Known   | Histidine metabolism                         | Amino acid    | LC/MS    | neg         |              | 5.90           | 7,804  |
| M35439 | glutaroyl carnitine       | Known   | Lysine metabolism                            | Amino acid    | LC/MS    | pos         |              | 10.90          | 7,701  |
| M01301 | lysine                    | Known   | Lysine metabolism                            | Amino acid    | LC/MS    | pos         |              | 16.60          | 7,812  |
| M01444 | piperolate                | Known   | Lysine metabolism                            | Amino acid    | LC/MS    | pos         |              | 7.60           | 7,792  |
| M35635 | 3-(3-hydroxyphenyl)propiolate | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | neg         |              | 0.00           | 1,163  |
| M32197 | 3-(4-hydroxyphenyl)lactate| Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | neg         |              | 6.90           | 7,795  |
| M12017 | 3-methoxtyrosine          | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | pos         |              | 21.60          | 5,997  |
| M15749 | 2-phenylpropionate (hydrocinnamate) | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | neg         |              | 17.10          | 6,182  |
| M00541 | 4-hydroxyphenylacetate    | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | GC/MS    |              |              | 17.90          | 387    |
| M36103 | p-cresol sulfate          | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | neg         |              | 4.80           | 7,758  |
| M32553 | phenol sulfate            | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | neg         |              | 5.70           | 7,810  |
| M15958 | phenylacetate             | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | neg         |              | 20.30          | 4,754  |
| M35126 | phenylacetylglutamine     | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | pos         |              | 6.90           | 7,812  |
| M0064  | phenylalanine             | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | pos         |              | 5.90           | 7,803  |
| M22130 | phenyllactate (PLA)       | Known   | Phenylalanine & tyrosine metabolism          | Amino acid    | LC/MS    | neg         |              | 17.50          | 6,064  |
| ID     | Metabolite          | Status  | Pathway                                      | Super-pathway       | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|---------------------|---------|----------------------------------------------|---------------------|----------|-------------|--------------|----------------|--------|---------|
| M01299 | tyrosine            | Known   | Phenylalanine & tyrosine metabolism          | Amino acid          | LC/MS pos|            |              |                |        | 7,807   |
| M27672 | 3-indoxyl sulfate   | Known   | Tryptophan metabolism                        | Amino acid          | LC/MS neg|            |              |                |        | 7,787   |
| M32675 | C-glycosyltryptophan*| Known   | Tryptophan metabolism                        | Amino acid          | LC/MS pos|            |              |                |        | 7,786   |
| M27513 | indoleacetate       | Known   | Tryptophan metabolism                        | Amino acid          | LC/MS pos|            |              |                |        | 7,618   |
| M18349 | indolelactate       | Known   | Tryptophan metabolism                        | Amino acid          | LC/MS pos|            |              |                |        | 7,378   |
| M32405 | indolepropionate    | Known   | Tryptophan metabolism                        | Amino acid          | LC/MS pos|            |              |                |        | 7,803   |
| M15140 | kynurenine          | Known   | Tryptophan metabolism                        | Amino acid          | LC/MS pos|            |              |                |        | 7,816   |
| M02342 | serotonin (5HT)     | Known   | Tryptophan metabolism                        | Amino acid          | LC/MS pos|            |              |                |        | 6,139   |
| M00054 | tryptophan betaine  | Known   | Tryptophan metabolism                        | Amino acid          | LC/MS pos|            |              |                |        | 7,439   |
| M01638 | arginine            | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | LC/MS neg|            |              |                |        | 7,528   |
| M02132 | citrulline          | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | LC/MS pos|            |              |                |        | 7,773   |
| M36808 | dimethylarginine    | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | LC/MS pos|            |              |                |        | 7,347   |
| M22138 | homocitrulline      | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | LC/MS pos|            |              |                |        | 4,135   |
| M15630 | N-acetylornithine   | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | LC/MS pos|            |              |                |        | 7,574   |
| M01493 | ornithine           | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | LC/MS pos|            |              |                |        | 7,746   |
| M01493 | ornithine           | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | LC/MS pos|            |              |                |        | 7,746   |
| M01898 | proline             | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | LC/MS pos|            |              |                |        | 7,816   |
| M32319 | trans-4-hydroxyproline| Known | Urea cycle; arginine-, proline-, metabolism | Amino acid          | GC/MS    |            |              |                |        | 7,802   |
| M01670 | urea                | Known   | Urea cycle; arginine-, proline-, metabolism | Amino acid          | GC/MS    |            |              |                |        | 7,796   |
| M22030 | 2-hydroxyisobutyrate| Known   | Valine, leucine and isoleucine metabolism    | Amino acid          | GC/MS    |            |              |                |        | 6,539   |
| M35431 | 2-methylbutyroylcarnitine| Known | Valine, leucine and isoleucine metabolism   | Amino acid          | LC/MS pos|            |              |                |        | 7,420   |
| ID    | Metabolite                        | Status  | Pathway                                      | Super-pathway                  | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|-------|-----------------------------------|---------|----------------------------------------------|-------------------------------|----------|-------------|--------------|----------------|--------|---------|
| M32397| 3-hydroxy-2-methylpropionate      | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | GC/MS    |             |              | 18.90          | 889    |         |
| M21047| 3-methyl-2-oxobutyrate            | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS neg|             |              | 18.50          | 7,648  |         |
| M15676| 3-methyl-2-oxovalerate            | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS neg|             |              | 6.70           | 7,779  |         |
| M22116| 4-methyl-2-oxopentanoate          | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS neg|             |              | 7.10           | 7,776  |         |
| M33937| alpha-hydroxyisovalerate          | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS neg|             |              | 9.00           | 7,668  |         |
| M12129| beta-hydroxyisovalerate           | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS neg|             |              | 18.80          | 7,283  |         |
| M35433| hydroxyisovaleryl carnitine       | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS pos|             |              | 33.30          | 5,588  |         |
| M33441| isobutyrylcarnitine               | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS pos|             |              | 9.60           | 7,812  |         |
| M01125| isoleucine                        | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS pos|             |              | 6.20           | 7,801  |         |
| M34407| isovaleryl carnitine              | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS pos|             |              | 17.20          | 7,789  |         |
| M00060| leucine                           | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS pos|             |              | 6.10           | 7,799  |         |
| M22177| levulinate (4-oxovalerate)        | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS pos or neg|             |              | 28.60          | 6,982  |         |
| M35428| tiglyl carnitine                  | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS pos|             |              | 24.30          | 1,328  |         |
| M01649| valine                            | Known   | Valine, leucine and isoleucine metabolism    | Amino acid                    | LC/MS pos|             |              | 6.20           | 7,808  |         |
| M33477| erythronate*                      | Known   | Aminosugars metabolism                       | Carbohydrate                  | GC/MS    |             |              | 13.80          | 7,752  |         |
| M27722| erythrose                         | Known   | Fructose, mannose, galactose, starch, and sucrose metabolism | Carbohydrate                  | GC/MS    |             |              | 40.70          | 7,263  |         |
| M00577| fructose                          | Known   | Fructose, mannose, galactose, starch, and sucrose metabolism | Carbohydrate                  | GC/MS    |             |              | 22.58          | 7,781  |         |
| M15335| mannitol                          | Known   | Fructose, mannose, galactose, starch, and sucrose metabolism | Carbohydrate                  | GC/MS    |             |              | 30.45          | 5917   |         |
| M00584| mannose                           | Known   | Fructose, mannose, galactose, starch, and sucrose metabolism | Carbohydrate                  | GC/MS    |             |              | 17.24          | 7,793  |         |
| ID      | Metabolite                        | Status    | Pathway                                                                 | Super-pathway                              | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|---------|-----------------------------------|-----------|-------------------------------------------------------------------------|--------------------------------------------|----------|-------------|--------------|----------------|---------|----------|
| M20675  | 1,5-anhydroglucitol (1,5-AG)      | Known     | Glycolysis, gluconeogenesis, pyruvate metabolism                        | Carbohydrate                               | LC/MS neg |             |              | 6.70            |         | 7,746    |
| M21049  | 1,6-anhydroglucose               | Known     | Glycolysis, gluconeogenesis, pyruvate metabolism                        | Carbohydrate                               | GC/MS    |             |              | 17.81           |         | 3663     |
| M20489  | glucose                           | Known     | Glycolysis, gluconeogenesis, pyruvate metabolism                        | Carbohydrate                               | GC/MS    |             |              | 12.70           |         | 7,773    |
| M01572  | glycerate                         | Known     | Glycolysis, gluconeogenesis, pyruvate metabolism                        | Carbohydrate                               | GC/MS    |             |              | 10.84           |         | 7778     |
| M00527  | lactate                           | Known     | Glycolysis, gluconeogenesis, pyruvate metabolism                        | Carbohydrate                               | GC/MS    |             |              | 6.70            |         | 7,814    |
| M00599  | pyruvate                          | Known     | Glycolysis, gluconeogenesis, pyruvate metabolism                        | Carbohydrate                               | GC/MS    |             |              | 30.31           |         | 7682     |
| M00575  | arabinose                         | Known     | Nucleotide sugars, pentose metabolism                                  | Carbohydrate                               | GC/MS    |             |              | 25.70           |         | 5,889    |
| M15964  | arabitol                          | Known     | Nucleotide sugars, pentose metabolism                                  | Carbohydrate                               | GC/MS    |             |              | 18.91           |         | 1744     |
| M35854  | threitol                          | Known     | Nucleotide sugars, pentose metabolism                                  | Carbohydrate                               | GC/MS    |             |              | 23.00           |         | 7,381    |
| M01640  | threitol-ascorbate (Vitamin C)    | Known     | Ascorbate and aldarate metabolism                                      | Cofactors and vitamins                      | GC/MS    |             |              | 0.00            |         | 2085     |
| M27738  | threonate                         | Known     | Ascorbate and aldarate metabolism                                      | Cofactors and vitamins                      | GC/MS    |             |              | 13.90           |         | 7,782    |
| M32586  | bilirubin (E,E)*                  | Known     | Hemoglobin and porphyrin metabolism                                   | Cofactors and vitamins                      | LC/MS pos|             |              | 24.80           |         | 7748     |
| M34106  | bilirubin (E,Z or Z,E)*           | Known     | Hemoglobin and porphyrin metabolism                                   | Cofactors and vitamins                      | LC/MS pos|             |              | 29.20           |         | 5,295    |
| M27716  | bilirubin (Z,Z)                   | Known     | Hemoglobin and porphyrin metabolism                                   | Cofactors and vitamins                      | LC/MS neg|             |              | 36.80           |         | 6,812    |
| M32593  | heme*                             | Known     | Hemoglobin and porphyrin metabolism                                   | Cofactors and vitamins                      | LC/MS pos|             |              | 24.40           |         | 6,380    |
| M02137  | biliverdin                        | Known     | Hemoglobin and porphyrin metabolism                                   | Cofactors and vitamins                      | LC/MS neg|             |              | 18.65           |         | 6686     |
| M32401  | trigonelline (N'-methylnicotinate) | Known   | Nicotinate and nicotinamide metabolism                               | Cofactors and vitamins                      | LC/MS pos|             |              | 13.90           |         | 739      |
| M01508  | pantothenate and/or CoA metabolism| Known     | Pantothenate and CoA metabolism                                       | Cofactors and vitamins                      | LC/MS pos|             |              | 15.03           |         | 7604     |
| M01827  | riboflavin (Vitamin B2)           | Known     | Riboflavin metabolism                                                | Cofactors and vitamins                      | LC/MS pos|             |              | NA              |         | 305      |
| ID     | Metabolite                  | Status | Pathway                   | Super-pathway        | Platform | Compo. ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|-----------------------------|--------|---------------------------|----------------------|----------|-----------|-------------|----------------|--------|---------|
| M01561 | alpha-tocopherol            | Known  | Tocopherol metabolism    | Cofactors and vitamins | GC/MS    |           |             | 16.71          | 7725   |         |
| M33420 | gamma-tocopherol            | Known  | Tocopherol metabolism    | Cofactors and vitamins | GC/MS    |           |             | 19.70          | 6,226  |         |
| M31555 | pyridoxate                  | Known  | Vitamin B6 metabolism   | Cofactors and vitamins | LC/MS    |           |             | 10.94          | 7703   |         |
| M33453 | alpha-ketoglutarate         | Known  | Krebs cycle              | Energy               | GC/MS    |           |             | 27.10          | 6,130  |         |
| M01564 | citrate                     | Known  | Krebs cycle              | Energy               | GC/MS    |           |             | 8.01           | 7813   |         |
| M01303 | malate                      | Known  | Krebs cycle              | Energy               | GC/MS    |           |             | 20.80          | 7,384  |         |
| M37058 | succinylcarnitine           | Known  | Krebs cycle              | Energy               | LC/MS pos|           |             | 28.12          | 6948   |         |
| M15488 | acetylphosphate             | Known  | Oxidative phosphorylation| Energy              | GC/MS    |           |             | 22.10          | 7,789  |         |
| M11438 | phosphate                   | Known  | Oxidative phosphorylation| Energy              | GC/MS    |           |             | 7.22           | 7789   |         |
| M22842 | cholate                     | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 28.90          | 5,929  |         |
| M01114 | deoxycholate                | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 24.70          | 5194   |         |
| M32346 | glycochenodeoxycholate      | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 12.10          | 7,087  |         |
| M18476 | glycocholate                | Known  | Bile acid metabolism     | Lipid                | LC/MS pos|           |             | 12.37          | 5995   |         |
| M18477 | glycodeoxycholate           | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 18.80          | 1,477  |         |
| M39379 | glycoursodeoxycholate       | Known  | Bile acid metabolism     | Lipid                | LC/MS Neg|           |             | 7.02           | 4675   |         |
| M27531 | hyodeoxycholate             | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 13.00          | 6,025  |         |
| M18494 | taurochenodeoxycholate      | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 16.24          | 5716   |         |
| M18497 | taurocholate                | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 23.30          | 4,032  |         |
| M12261 | taurodeoxycholate           | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 21.24          | 1564   |         |
| M36850 | taurolithocholate 3-sulfate | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 23.80          | 6,904  |         |
| M01605 | ursodeoxycholate            | Known  | Bile acid metabolism     | Lipid                | LC/MS neg|           |             | 13.53          | 5477   |         |
| M35472 | 2-tetradeconoylcarnitine    | Known  | Carnitine metabolism    | Lipid                | LC/MS pos|           |             | 25.20          | 6,998  |         |
| ID     | Metabolite                                | Status     | Pathway                        | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|-------------------------------------------|------------|--------------------------------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M32654 | 3-dehydrocarnitine*                        | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 13.50          | 7809   |         |
| M32198 | acetylcarnitine                           | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 8.40           | 7,805  |         |
| M15500 | carnitine                                 | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 5.22           | 7797   |         |
| M38170 | cis-4-decenoylcarnitine                   | Known      | Carnitine metabolism          | Lipid         | LC/MS Pos|             |              | 9.70           | 7,660  |         |
| M33941 | decanoylcarnitine                         | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 14.23          | 7766   |         |
| M32328 | hexanoylcarnitine                         | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 14.30          | 7,786  |         |
| M34534 | laurylcarnitine                           | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 27.87          | 5170   |         |
| M33936 | octanoylcarnitine                         | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 12.50          | 7,790  |         |
| M35160 | oleoylcarnitine                           | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 20.54          | 7708   |         |
| M22189 | palmitoylcarnitine                        | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 24.90          | 7,701  |         |
| M34409 | stearoylcarnitine                         | Known      | Carnitine metabolism          | Lipid         | LC/MS pos|             |              | 25.46          | 7183   |         |
| M35718 | dihomo-linolenate (20:3n3 or n6)          | Known      | Essential fatty acid          | Lipid         | LC/MS neg|             |              | 10.30          | 7,805  |         |
| M19323 | docosahexaenoate (DHA; 22:6n3)             | Known      | Essential fatty acid          | Lipid         | LC/MS neg|             |              | 11.47          | 7818   |         |
| M32504 | docosapentaenoate (n3 DPA; 22:5n3)         | Known      | Essential fatty acid          | Lipid         | LC/MS neg|             |              | 14.10          | 7,821  |         |
| M18467 | eicosapentaenoate (EPA; 20:5n3)            | Known      | Essential fatty acid          | Lipid         | LC/MS neg|             |              | 11.50          | 7816   |         |
| M01105 | linoleate (18:2n6)                         | Known      | Essential fatty acid          | Lipid         | LC/MS neg|             |              | 7.90           | 7,780  |         |
| M34035 | linolenate [alpha or gamma; (18:3n3 or 6)]| Known      | Essential fatty acid          | Lipid         | LC/MS neg|             |              | 9.28           | 7786   |         |
| M34732 | isovalerate                               | Known      | Fatty acid metabolism         | Lipid         | LC/MS neg|             |              | 14.10          | 7,080  |         |
| M32412 | butyrylcarnitine                          | Known      | Fatty acid metabolism (also BCAA metabolism) | Lipid | LC/MS pos|             |              | 13.67          | 7796   |         |
| M32452 | propionylcarnitine                        | Known      | Fatty acid metabolism (also BCAA metabolism) | Lipid | LC/MS pos|             |              | 9.40           | 7,813  |         |
| ID     | Metabolite                                      | Status | Pathway                  | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|------------------------------------------------|--------|--------------------------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M32455 | linoleamide (18:2n6)                           | Known  | Fatty acid, amide        | Lipid         | LC/MS pos| NA          | 1767         | NA             |        |         |
| M32458 | oleamide                                       | Known  | Fatty acid, amide        | Lipid         | LC/MS pos| 83.40       | 1,765        | NA             |        |         |
| M38768 | 15-methyl/palmitate (isobar with 2- methyl/palmitate) | Known  | Fatty acid, branched     | Lipid         | LC/MS Neg| 16.98       | 7371         | NA             |        |         |
| M37253 | 2-hydroxyglutarate                             | Known  | Fatty acid, dicarboxylate| Lipid         | GC/MS    | 27.30       | 6,287        | NA             | 27.30  | 6,287   |
| M31787 | 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF) | Known  | Fatty acid, dicarboxylate| Lipid         | LC/MS neg| 7.96        | 7812         | NA             |        |         |
| M32388 | dodecanedioate                                 | Known  | Fatty acid, dicarboxylate| Lipid         | LC/MS neg| 22.60       | 6,478        | NA             |        |         |
| M35678 | hexadecanedioate                               | Known  | Fatty acid, dicarboxylate| Lipid         | LC/MS neg| 12.40       | 6887         | NA             | 12.40  | 6887    |
| M36754 | octadecanedioate                               | Known  | Fatty acid, dicarboxylate| Lipid         | LC/MS neg| 19.50       | 7,300        | NA             | 19.50  | 7,300   |
| M32398 | sebacate (decanedioate)                        | Known  | Fatty acid, dicarboxylate| Lipid         | LC/MS neg| NA          | 398          | NA             |        |         |
| M35669 | tetradecanedioate                               | Known  | Fatty acid, dicarboxylate| Lipid         | LC/MS neg| 12.80       | 6,046        | NA             | 12.80  | 6,046   |
| M36802 | n-Butyl Oleate                                 | Known  | Fatty acid, ester        | Lipid         | GC/MS    | 28.89       | 4542         | NA             | 28.89  | 4542    |
| M35675 | 2-hydroxypalmitate                             | Known  | Fatty acid, monohydroxy  | Lipid         | LC/MS neg| 14.30       | 7,797        | NA             | 14.30  | 7,797   |
| M17945 | 2-hydroxystearate                              | Known  | Fatty acid, monohydroxy  | Lipid         | LC/MS neg| 16.40       | 7763         | NA             | 16.40  | 7763    |
| M15506 | choline                                        | Known  | Glycerolipid metabolism  | Lipid         | LC/MS pos| 8.10        | 7,750        | NA             | 8.10   | 7,750   |
| M15122 | glycerol                                       | Known  | Glycerolipid metabolism  | Lipid         | GC/MS    | 8.23        | 7800         | NA             | 8.23   | 7800    |
| M15365 | glycerol 3-phosphate (G3P)                      | Known  | Glycerolipid metabolism  | Lipid         | GC/MS    | 14.50       | 7,781        | NA             | 14.50  | 7,781   |
| M15990 | glycerophosphorylcholine (GPC)                 | Known  | Glycerolipid metabolism  | Lipid         | LC/MS pos| 10.26       | 7156         | NA             | 10.26  | 7156    |
| M37112 | chiro-inositol                                 | Known  | Inositol metabolism      | Lipid         | GC/MS    | 20.80       | 2,729        | NA             | 20.80  | 2,729   |
| M01481 | inositol 1-phosphate (I1P)                     | Known  | Inositol metabolism      | Lipid         | GC/MS    | NA          | 1379         | NA             |        |         |
| M19934 | myo-inositol                                   | Known  | Inositol metabolism      | Lipid         | GC/MS    | 15.30       | 7,803        | NA             | 15.30  | 7,803   |
| M32379 | scyllo-inositol                                | Known  | Inositol metabolism      | Lipid         | GC/MS    | 33.87       | 6500         | NA             | 33.87  | 6500    |
| M00542 | 3-hydroxybutyrate (BHBA)                       | Known  | Ketone bodies            | Lipid         | GC/MS    | 7.40        | 7,820        | NA             | 7.40   | 7,820   |

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| ID       | Metabolite                                  | Status  | Pathway             | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N  |
|----------|---------------------------------------------|---------|---------------------|---------------|----------|-------------|--------------|----------------|--------|----------|
| M33971   | 10-heptadecenoate (17:1n7)                  | Known   | Long chain fatty acid | Lipid         | LC/MS neg|             | 11.55        | 7795           |        |          |
| M33972   | 10-nonadecenoate (19:1n9)                   | Known   | Long chain fatty acid | Lipid         | LC/MS neg|             | 12.60        | 7,789          |        |          |
| M32980   | arachidonate (20:4n6)                       | Known   | Long chain fatty acid | Lipid         | LC/MS neg|             | 23.17        | 7778           |        |          |
| M01110   | eicosenoate (20:1n9 or 11)                  | Known   | Long chain fatty acid | Lipid         | LC/MS neg|             | 9.10         | 7,816          |        |          |
| M17805   | docosahexaenoylglycerophosphocholine*       | Known   | Lysolipid           | Lipid         | LC/MS pos|             | 39.04        | 7507           |        |          |
| M33822   | 1-docosahexaenoylglycerophosphoethanolamine*| Known   | Lysolipid           | Lipid         | LC/MS neg|             | 33.70        | 7,798          |        |          |
| M34214   | 1-docosahexaenoylglycerophosphoinositol*    | Known   | Lysolipid           | Lipid         | LC/MS neg|             | 22.38        | 7797           |        |          |
| M33969   | stearidonate (18:4n3)                       | Known   | Long chain fatty acid | Lipid         | LC/MS neg|             | 14.90        | 7,775          |        |          |
| ID     | Metabolite                    | Status      | Pathway | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|------------------------------|-------------|---------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M33871 | 1-aceodylphosphocholine*      | Known       | Lysolipid | Lipid         | LC/MS pos|             | 73.34        | 6892           |        |         |
| M33821 | 1-aceodylphosphocholine*      | Known       | Lysolipid | Lipid         | LC/MS pos|             | 39.90        | 7,809          |        |         |
| M33957 | 1-heptadecanoylphosphocholine | Known       | Lysolipid | Lipid         | LC/MS pos|             | 83.43        | 7422           |        |         |
| M34419 | 1-oleoylglycerophosphocholine | Known       | Lysolipid | Lipid         | LC/MS pos|             | 35.00        | 7,795          |        |         |
| M32635 | 1-oleoylglycerophosphoinositol | Known       | Lysolipid | Lipid         | LC/MS neg|             | 30.97        | 7,817          |        |         |
| M35626 | 1-oleoylglycerophosphoethanolamine | Known       | Lysolipid | Lipid         | LC/MS pos|             | 42.80        | 7,812          |        |         |
| M33960 | 1-oleoylglycerophosphocholine | Known       | Lysolipid | Lipid         | LC/MS pos|             | 39.88        | 7812           |        |         |
| M35628 | 1-oleoylglycerophosphoethanolamine | Known       | Lysolipid | Lipid         | LC/MS neg|             | 33.00        | 7,749          |        |         |
| M33230 | 1-palmitoylglycerophosphocholine* | Known       | Lysolipid | Lipid         | LC/MS pos|             | 41.93        | 7812           |        |         |
| M33955 | 1-palmitoylglycerophosphocholine | Known       | Lysolipid | Lipid         | LC/MS pos|             | 24.30        | 7,803          |        |         |
| M35631 | 1-palmitoylglycerophosphoethanolamine | Known       | Lysolipid | Lipid         | LC/MS neg|             | 28.76        | 7763           |        |         |
| M35305 | 1-palmitoylglycerophosphoinositol* | Known       | Lysolipid | Lipid         | LC/MS neg|             | 23.30        | 6,282          |        |         |
| M39270 | 1-palmitoylplasmenyl ethanolamine* | Known       | Lysolipid | Ethanolamine  | LC/MS Neg|             | 31.63        | 4948           |        |         |
| M33961 | 1-stearylglycerophosphocholine | Known       | Lysolipid | Lipid         | LC/MS pos|             | 84.90        | 7,817          |        |         |
| M34416 | 1-stearylglycerophosphoethanolamine | Known       | Lysolipid | Lipid         | LC/MS neg|             | 38.48        | 7369           |        |         |
| ID     | Metabolite                                    | Status    | Pathway             | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|-----------------------------------------------|-----------|---------------------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M19324 | 1-stearoylglycerophosphoinositol              | Known     | Lysolipid           | Lipid         | LC/MS    | neg         | 21.30        | 7,694          |        |         |
| M35257 | 2-linoleoylglycerophosphocholine*            | Known     | Lysolipid           | Lipid         | LC/MS    | pos         | 45.91        | 6894           |        |         |
| M35253 | 2-palmitoylglycerophosphocholine*            | Known     | Lysolipid           | Lipid         | LC/MS    | pos         | 113.14       | 7524           |        |         |
| M35255 | 2-stearoylglycerophosphocholine*             | Known     | Lysolipid           | Lipid         | LC/MS    | pos         | 96.63        | 7730           |        |         |
| M32497 | 10-undecenoate (11:1n1)                      | Known     | Medium chain fatty acid | Lipid     | LC/MS    | neg         | 15.90        | 7,806          |        |         |
| M33968 | 5-dodecenoate (12:1n7)                       | Known     | Medium chain fatty acid | Lipid     | LC/MS    | neg         | 12.54        | 7770           |        |         |
| M10642 | caprate (10:0)                                | Known     | Medium chain fatty acid | Lipid     | LC/MS    | Neg         | NA           | 7,799          |        |         |
| M32489 | caproate (6:0)                                | Known     | Medium chain fatty acid | Lipid     | LC/MS    | neg         | 11.93        | 7811           |        |         |
| M32492 | caprylate (8:0)                               | Known     | Medium chain fatty acid | Lipid     | LC/MS    | neg         | 9.60         | 7,802          |        |         |
| M01644 | heptanoate (7:0)                              | Known     | Medium chain fatty acid | Lipid     | LC/MS    | neg         | 11.27        | 7802           |        |         |
| M01645 | laurate (12:0)                                | Known     | Medium chain fatty acid | Lipid     | LC/MS    | neg         | 8.60         | 7,793          |        |         |
| M12035 | pelargonate (9:0)                             | Known     | Medium chain fatty acid | Lipid     | LC/MS    | neg         | 9.62         | 7803           |        |         |
| M12067 | undecanoate (11:0)                            | Known     | Medium chain fatty acid | Lipid     | LC/MS    | neg         | 15.50        | 7,500          |        |         |
| M27447 | 1-linoleoylglycerol (1-monolinolein)          | Known     | Monoacylglycerol    | Lipid        | LC/MS    | neg         | 75.01        | 2797           |        |         |
| M21184 | 1-oleoylglycerol (1-monolein)                 | Known     | Monoacylglycerol    | Lipid        | LC/MS    | pos         | 111.40       | 5,717          |        |         |
| M21127 | 1-palmitoylglycerol (1-monopalmitin)          | Known     | Monoacylglycerol    | Lipid        | GC/MS    |              | 19.92        | 7429           |        |         |
| M21188 | 1-stearoylglycerol (1-monostearin)            | Known     | Monoacylglycerol    | Lipid        | GC/MS    |              | 22.20        | 6,965          |        |         |
| ID     | Metabolite                      | Status  | Pathway                  | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|--------------------------------|---------|--------------------------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M33443 | valerate                       | Known   | Short chain fatty acid   | Lipid         | LC/MS neg|             |              |                | 26.05  | 4102    |
| M37506 | palmitoyl sphingomyelin        | Known   | Sphingolipid             | Lipid         | GC/MS    |             |              |                | 12.00  | 7,814   |
| M37202 | 4-androsten-3beta,17beta-diol diisulfate 1* | Known | Sterol, Steroid          | Lipid         | LC/MS Neg|             |              |                | 5.83   | 7804    |
| M37203 | 4-androsten-3beta,17beta-diol diisulfate 2* | Known | Sterol, Steroid          | Lipid         | LC/MS Neg|             |              |                | 6.50   | 7,776   |
| M37190 | alpha-androstan-3beta,17beta-diol diisulfate | Known | Sterol, Steroid          | Lipid         | LC/MS Neg|             |              |                | 7.45   | 7345    |
| M37198 | alpha-pregnan-3beta,20alpha-diol diisulfate | Known | Sterol, Steroid          | Lipid         | LC/MS Neg|             |              |                | 32.22  | 7784    |
| M36776 | 7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca) | Known | Sterol, Steroid          | Lipid         | LC/MS neg|             |              |                | 30.26  | 5457    |
| M31591 | androsterone sulfate           | Known   | Sterol, Steroid          | Lipid         | LC/MS neg|             |              |                | 7.40   | 7,785   |
| M00063 | cholesterol                    | Known   | Sterol, Steroid          | Lipid         | GC/MS    |             |              |                | 9.27   | 7813    |
| M01712 | cortisol                       | Known   | Sterol, Steroid          | Lipid         | LC/MS pos|             |              |                | 7.20   | 7,795   |
| M01769 | cortisone                      | Known   | Sterol, Steroid          | Lipid         | LC/MS pos|             |              |                | 15.26  | 7575    |
| M32425 | dehydroisoandrosterone sulfate (DHEA-S) | Known | Sterol, Steroid          | Lipid         | LC/MS neg|             |              |                | 6.00   | 7,793   |
| M33973 | epiandrosterone sulfate        | Known   | Sterol, Steroid          | Lipid         | LC/MS neg|             |              |                | 6.88   | 7769    |
| M18474 | estrone 3-sulfate              | Known   | Sterol, Steroid          | Lipid         | LC/MS neg|             |              |                | 22.80  | 957     |
| M33488 | lathosterol                    | Known   | Sterol, Steroid          | Lipid         | GC/MS    |             |              |                | 30.26  | 5457    |
| M03127 | hypoxanthine                   | Known   | Purine metabolism, (hypo)xanthine, inosine containing | Nucleotide    | LC/MS neg|             |              |                | 29.00  | 7,287   |
| M01123 | inosine                        | Known   | Purine metabolism, (hypo)xanthine, inosine containing | Nucleotide    | LC/MS neg|             |              |                | NA     | 2675    |
| M03147 | xanthine                       | Known   | Purine metabolism, (hypo)xanthine, inosine containing | Nucleotide    | LC/MS pos|             |              |                | 33.80  | 6,845   |
| M00555 | adenosine                      | Known   | Purine metabolism, adenine containing | Nucleotide    | LC/MS pos|             |              |                | NA     | 406     |
| ID      | Metabolite                  | Status | Pathway                                      | Super-pathway          | Platform | Compound ID | Quant. | Mass. | Retention Time | CV (%) | Total N |
|---------|-----------------------------|--------|----------------------------------------------|------------------------|----------|-------------|--------|-------|----------------|--------|---------|
| M15650  | N1-methyladenosine          | Known  | Purine metabolism, adenine containing        | Nucleotide             | LC/MS pos|             | 13.10 | 7,813 |
| M35114  | 7-methylguanine             | Known  | Purine metabolism, guanine containing        | Nucleotide             | LC/MS pos|             | 43.28 | 6091 |
| M01573  | guanosine                   | Known  | Purine metabolism, guanine containing        | Nucleotide             | LC/MS pos|             | NA    | 2,343 |
| M35137  | N2,N2-dimethylguanosine     | Known  | Purine metabolism, guanine containing        | Nucleotide             | LC/MS pos|             | 18.37 | 5228 |
| M01107  | allantoin                   | Known  | Purine metabolism, urate metabolism          | Nucleotide             | GC/MS    |             | 27.90 | 5,705 |
| M01604  | urate                      | Known  | Purine metabolism, urate metabolism          | Nucleotide             | LC/MS neg|             | 5.15  | 7819 |
| M33442  | pseudouridine               | Known  | Pyrimidine metabolism, uracil containing     | Nucleotide             | LC/MS pos|             | 12.60 | 7,785 |
| M00606  | uridine                     | Known  | Pyrimidine metabolism, uracil containing     | Nucleotide             | LC/MS neg|             | 6.26  | 7800 |
| M22175  | aspartylphenylalanine       | Known  | Dipeptide                                    | Peptide                | LC/MS pos|             | 22.50 | 3,948 |
| M37104  | cyclo(leu-pro)              | Known  | Dipeptide                                    | Peptide                | LC/MS Pos|             | 27.35 | 4833 |
| M18357  | glycylylvaline              | Known  | Dipeptide                                    | Peptide                | LC/MS pos|             | NA    | 2,108 |
| M36756  | eucylleucine                | Known  | Dipeptide                                    | Peptide                | LC/MS pos|             | 10.60 | 3386 |
| M38150  | phenylalanylphenylalanine   | Known  | Dipeptide                                    | Peptide                | LC/MS Pos|             | 26.40 | 4,961 |
| M35127  | pro-hydroxy-pro             | Known  | Dipeptide                                    | Peptide                | LC/MS pos|             | 18.62 | 7787 |
| M31522  | pyroglutamylglycine         | Known  | Dipeptide                                    | Peptide                | LC/MS neg|             | 8.20  | 1,586 |
| M33801  | ADpSGEGDFXAE GGVRC*         | Known  | Fibrinogen cleavage peptide                  | Peptide                | LC/MS pos|             | 22.23 | 3939 |
| M33084  | ADSGEGDFXAE GGVRC*          | Known  | Fibrinogen cleavage peptide                  | Peptide                | LC/MS pos|             | 11.90 | 5,588 |
| M31548  | DSGEGDFXAE GGVRC*          | Known  | Fibrinogen cleavage peptide                  | Peptide                | LC/MS pos|             | 17.82 | 5371 |
| M36738  | gamma-glutamylglutamate     | Known  | gamma-glutamyl                               | Peptide                | LC/MS pos|             | 20.10 | 931  |
| M02730  | gamma-glutamylglutamine     | Known  | gamma-glutamyl                               | Peptide                | LC/MS pos|             | 29.73 | 7662 |
| M34456  | gamma-glutamylisoleucine*   | Known  | gamma-glutamyl                               | Peptide                | LC/MS pos|             | 12.80 | 5,522 |
| ID     | Metabolite                          | Status    | Pathway               | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|-------------------------------------|-----------|-----------------------|---------------|----------|-------------|--------------|----------------|---------|---------|
| M18369 | gamma-glutamylleucine               | Known     | gamma-glutamyl        | Peptide       | LC/MS pos|             | 9.25         | 7802           |         |         |
| M33363 | gamma-glutamylmethionine*           | Known     | gamma-glutamyl        | Peptide       | LC/MS pos|             | 23.10        | 2,240          |         |         |
| M33422 | gamma-glutamylphenylalanine         | Known     | gamma-glutamyl        | Peptide       | LC/MS pos|             | 13.29        | 7753           |         |         |
| M33364 | gamma-glutamylthreonine*            | Known     | gamma-glutamyl        | Peptide       | LC/MS pos|             | 24.30        | 4,016          |         |         |
| M02734 | gamma-glutamyltyrosine              | Known     | gamma-glutamyl        | Peptide       | LC/MS pos|             | 14.13        | 7468           |         |         |
| M32393 | gamma-glutamylvaline                | Known     | gamma-glutamyl        | Peptide       | LC/MS pos|             | 9.30         | 7,753          |         |         |
| M34420 | bradykinin, des-arg(9)              | Known     | Polypeptide           | Peptide       | LC/MS pos|             | 9.58         | 4570           |         |         |
| M32836 | HWESASXX*                           | Known     | Polypeptide           | Peptide       | LC/MS pos|             | 11.90        | 7,700          |         |         |
| M18281 | 2-hydroxyhippurate (salicylurate)   | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS neg|             | 22.61        | 2592           |         |         |
| M36848 | 3-ethylphenylsulfate*               | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS neg|             | 24.90        | 165            |         |         |
| M36099 | 4-ethylphenylsulfate                | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS neg|             | 15.46        | 6012           |         |         |
| M35527 | 4-hydroxyhippurate                  | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS Neg |             | 20.90        | 4,368          |         |         |
| M36098 | 4-vinylphenol sulfate               | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS neg|             | 6.75         | 7483           |         |         |
| M15778 | benzoate                            | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS neg|             | 8.90         | 7,756          |         |         |
| M35320 | catechol sulfate                    | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS neg|             | 5.77         | 7807           |         |         |
| M15753 | hippurate                           | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS pos|             | 11.60        | 7,806          |         |         |
| M27728 | glycerol 2-phosphate                | Known     | Benzoate metabolism  | Xenobiotics   | LC/MS pos|             | 17.81        | 5912           |         |         |
| M33173 | 2-hydroxyacetaminophen sulfate*     | Known     | Drug                 | Xenobiotics   | LC/MS neg|             | 14.20        | 1,688          |         |         |
| M33178 | 2-methoxyacetaminophen sulfate*     | Known     | Drug                 | Xenobiotics   | LC/MS neg|             | 10.26        | 1086           |         |         |
| M34365 | 3-(cystein-S-)acetaminophen*        | Known     | Drug                 | Xenobiotics   | LC/MS pos|             | 0.00         | 1,024          |         |         |
| ID       | Metabolite                  | Status       | Pathway          | Super-pathway | Platform  | Compo und ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|----------|-----------------------------|--------------|------------------|---------------|-----------|--------------|--------------|----------------|--------|---------|
| M12032  | 4-acetamidophenol           | Known        | Drug             | Xenobiotics   | GC/MS     |              |              | 0.00           |        | 756     |
| M36097  | 4-acetaminophen sulfate     | Known        | Drug             | Xenobiotics   | LC/MS neg |              |              | 8.60           |        | 498     |
| M38658  | atenolol                    | Known        | Drug             | Xenobiotics   | LC/MS Pos |              |              | NA             |        | 182     |
| M37033  | carbamazepine*              | Known        | Drug             | Xenobiotics   | LC/MS pos |              |              | NA             |        | 24      |
| M35322  | hydroquinone sulfate        | Known        | Drug             | Xenobiotics   | LC/MS neg |              |              | 7.19           |        | 451     |
| M33085  | hydroxypioglitazon*         | Known        | Drug             | Xenobiotics   | LC/MS pos |              |              | NA             |        | 8       |
| M17799  | ibuprofen                   | Known        | Drug             | Xenobiotics   | LC/MS neg |              |              | 11.23          |        | 1976    |
| M18037  | metoprolol                  | Known        | Drug             | Xenobiotics   | LC/MS pos |              |              | NA             |        | 69      |
| M34109  | metoprolol acid metabolite* | Known        | Drug             | Xenobiotics   | LC/MS pos |              |              | NA             |        | 286     |
| M12122  | naproxen                    | Known        | Drug             | Xenobiotics   | LC/MS neg |              |              | NA             |        | 36      |
| M33423  | p-aminobenzoic acid         | Known        | Drug             | Xenobiotics   | LC/MS pos |              |              | 31.56          |        | 1494    |
| M33339  | piroglibazone*              | Known        | Drug             | Xenobiotics   | LC/MS pos |              |              | NA             |        | 8       |
| M01518  | salicylate                  | Known        | Drug             | Xenobiotics   | GC/MS     |              |              | 27.34          |        | 2374    |
| M33384  | salicylic acid              | Known        | Drug             | Xenobiotics   | LC/MS neg |              |              | 0.00           |        | 832     |
| M37459  | ergothioneine               | Known        | Food component, Plant | Xenobiotics | LC/MS Pos |              |              | 29.15          |        | 4453    |
| M33009  | homostachydrine*            | Known        | Food component, Plant | Xenobiotics | LC/MS Pos |              |              | 15.90          |        | 3,003   |
| M31536  | N-(2-furoyl)glycine         | Known        | Food component, Plant | Xenobiotics | LC/MS Pos |              |              | 23.19          |        | 604     |
| M33935  | piperine                    | Known        | Food component, Plant | Xenobiotics | LC/MS pos |              |              | 16.60          |        | 7,173   |
| M18335  | quinate                     | Known        | Food component, Plant | Xenobiotics | GC/MS     |              |              | 23.80          |        | 6265    |
| M21151  | saccharin                   | Known        | Food component, Plant | Xenobiotics | LC/MS neg |              |              | NA             |        | 2,449   |
| M34384  | stachydrine                 | Known        | Food component, Plant | Xenobiotics | LC/MS pos |              |              | 6.95           |        | 6745    |
| M36095  | thymol sulfate              | Known        | Food component, Plant | Xenobiotics | LC/MS neg |              |              | 14.30          |        | 4,172   |
| ID       | Metabolite                  | Status   | Pathway                      | Super-pathway     | Platform | Compound | Quant. Mass. | Retention Time | CV (%) | Total N |
|----------|-----------------------------|----------|------------------------------|-------------------|----------|----------|-------------|----------------|--------|---------|
| M20699   | erythritol                  | Known    | Sugar, sugar substitute, starch | Xenobiotics       | GC/MS    |          |             | 12.86          |        | 7776    |
| M00553   | cotinine                    | Known    | Tobacco metabolite           | Xenobiotics       | LC/MS    | pos      | 7776        | 12.10          | 1,270  |
| M34404   | 1,3,7-trimethylurate        | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | neg      |             | 32.28          |        | 796     |
| M34400   | 1,7-dimethylurate           | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | neg      |             | 19.30          |        | 6,057   |
| M34395   | 1-methylurate               | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | pos      |             | 36.38          |        | 5520    |
| M34389   | 1-methylxanthine            | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | pos      |             | 30.60          |        | 5,504   |
| M32445   | 3-methylxanthine            | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | pos      |             | 34.89          |        | 5396    |
| M34390   | 7-methylxanthine            | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | pos      |             | 29.20          |        | 5,901   |
| M00569   | caffeine                    | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | pos      |             | 12.51          |        | 7719    |
| M18254   | paraxanthine                | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | pos      |             | 14.40          |        | 7,504   |
| M18392   | theobromine                 | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | pos      |             | 8.61           |        | 7768    |
| M18394   | theophylline                | Known    | Xanthine metabolism          | Xenobiotics       | LC/MS    | neg      |             | 19.30          |        | 7,393   |
| M32735   | X-01911                     | Unknown  |                             |                   | LC/MS    | Pos      | 32735       | 464.1          | 4.26   | 6360    |
| M32587   | X-02249                     | Unknown  |                             |                   | LC/MS    | Neg      | 32587       | 267,200        | 4.030  | 7,818   |
| M32549   | X-02269                     | Unknown  |                             |                   | LC/MS    | Neg      | 32549       | 255.1          | 1.55   | 7,701   |
| M12593   | X-02973                     | Unknown  |                             |                   | GC/MS    |          |             | 21.70          |        | 7,759   |
| M12626   | X-03003                     | Unknown  |                             |                   | GC/MS    |          |             | 25.79          |        | 7689    |
| M32709   | X-03056--N-[3-(2-Oxopyrrolidin-1-yl)propyl]acetamid | Identified | Polyamine metabolism | Amino acid | LC/MS | Pos | 11.80 | 7,812 |
| M12768   | X-03088                     | Unknown  |                             |                   | GC/MS    |          |             | 25.82          |        | 7474    |
| M12770   | X-03090                     | Unknown  |                             |                   | GC/MS    |          |             | 47.50          |        | 1,394   |
| M12774   | X-03094                     | Unknown  |                             |                   | GC/MS    |          | 12774       | 299            | 11.55  | 7804    |
| M16634   | X-04357                     | Unknown  |                             |                   | GC/MS    |          |             | 32.30          |        | 7,502   |
| M16816   | X-04494                     | Unknown  |                             |                   | GC/MS    |          |             | 27.07          |        | 5007    |
| M16818   | X-04495                     | Unknown  |                             |                   | GC/MS    |          |             | 17.10          |        | 7,490   |
| ID       | Metabolite                  | Status     | Pathway                      | Super-pathway          | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|----------|-----------------------------|------------|------------------------------|------------------------|----------|-------------|--------------|----------------|--------|---------|
| M16821   | X-04498                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 18.69  | 7160    |
| M16822   | X-04499-3,4-dihydroxybutyrate | Identified | Butanoate metabolism        | Amino acid             | GC/MS    | 16822       | 189.000      | 7.220          | 21.10  | 6,948   |
| M16823   | X-04500                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 19.51  | 3647    |
| M17059   | X-04621                     | Unknown    |                              |                        | GC/ms    | 16822       | 189.000      | 7.220          | 0.00   | 8       |
| M18283   | X-05426                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 22.38  | 6357    |
| M18929   | X-05907                     | Unknown    |                              |                        | LC/MS    | 16822       | 189.000      | 7.220          | 24.70  | 7,734   |
| M32557   | X-06126                     | Unknown    |                              |                        | LC/MS    | 16822       | 189.000      | 7.220          | 6.71   | 7785    |
| M19362   | X-06226                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 23.50  | 7,623   |
| M19363   | X-06227                     | Unknown    |                              |                        | GC/ms    | 16822       | 189.000      | 7.220          | 30.70  | 1690    |
| M19364   | X-06246                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 25.00  | 7,358   |
| M19368   | X-06267                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 29.03  | 7075    |
| M19396   | X-06307                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 31.90  | 6,774   |
| M19414   | X-06350                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 29.78  | 5161    |
| M19415   | X-06351                     | Unknown    |                              |                        | LC/MS    | 16822       | 189.000      | 7.220          | 24.20  | 4,791   |
| M32560   | X-07765                     | Unknown    |                              |                        | LC/MS    | 16822       | 189.000      | 7.220          | 5.82   | 2170    |
| M21630   | X-08402                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 21.20  | 7,726   |
| M22032   | X-08766                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 26.90  | 6050    |
| M22481   | X-08988                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 58.40  | 7,776   |
| M22548   | X-09026                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 26.44  | 7627    |
| M22649   | X-09108                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 28.30  | 6,910   |
| M24074   | X-09706                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 22.41  | 7697    |
| M32753   | X-09789                     | Unknown    |                              |                        | LC/MS    | 16822       | 189.000      | 7.220          | 7.20   | 7,805   |
| M33782   | X-10346                     | Unknown    |                              |                        | LC/MS    | 16822       | 189.000      | 7.220          | 17.76  | 4207    |
| M25459   | X-10395                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 18.60  | 7,784   |
| M25599   | X-10429                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 24.60  | 6807    |
| M27256   | X-10500                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 15.90  | 7,751   |
| M27273   | X-10506                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 23.90  | 7710    |
| M27278   | X-10510                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 19.10  | 7,792   |
| M28354   | X-10675                     | Unknown    |                              |                        | GC/ms    | 16822       | 189.000      | 7.220          | 33.15  | 1241    |
| M30805   | X-10810                     | Unknown    |                              |                        | GC/MS    | 16822       | 189.000      | 7.220          | 31.50  | 7,232   |
| ID     | Metabolite     | Status    | Pathway                                      | Super-pathway                  | Platform ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|----------------|-----------|----------------------------------------------|--------------------------------|-------------|--------------|----------------|--------|---------|
| M32518 | X-11204        | Unknown   |                                              |                                | LC/MS Pos   | 12.28        | 7799           |        |         |
| M32564 | X-11247        | Unknown   |                                              |                                | LC/MS Neg   | 15.30        | 7,403          |        |         |
| M32576 | X-11261        | Unknown   |                                              |                                | LC/MS Pos   | 3.69         | 7,771          |        |         |
| M32616 | X-11299        | Unknown   |                                              |                                | LC/MS Neg   | 7.60         | 7,347          |        |         |
| M32632 | X-11315        | Unknown   |                                              |                                | LC/MS Pos   | 7.79         | 7,785          |        |         |
| M32634 | X-11317        | Unknown   |                                              |                                | LC/MS Neg   | 14.70        | 7,811          |        |         |
| M32644 | X-11327        | Unknown   |                                              |                                | LC/MS Pos   | 15.99        | 7671           |        |         |
| M32651 | X-11334        | Unknown   |                                              |                                | LC/MS Pos   | 18.00        | 5,462          |        |         |
| M32689 | X-11372        | Unknown   |                                              |                                | LC/MS Neg   | 11.69        | 6043           |        |         |
| M32691 | X-11374        | Unknown   |                                              |                                | LC/MS Pos   | 52.80        | 2,609          |        |         |
| M32698 | X-11381        | Unknown   |                                              |                                | LC/MS Pos   | 32698        | 186.2          | 16.06  | 7,753  |
| M32729 | X-11412        | Unknown   | Purine metabolism, (hypo)xanthine/inosine containing Nucleotide | LC/MS Pos | 20.70        | 6,935          |        |         |
| M32739 | X-11422--xanthine | Identified | Purine metabolism, (hypo)xanthine/inosine containing Nucleotide | LC/MS Pos | 30.67        | 6346           |        |         |
| M32740 | X-11423--O-sulfo-L-tyrosine | Identified | Phenylalanine & tyrosine metabolism Amino acid | LC/MS Neg | 8.60         | 7,765          |        |         |
| M32754 | X-11437        | Unknown   |                                              |                                | LC/MS Neg   | 7.21         | 6782           |        |         |
| M32755 | X-11438        | Unknown   |                                              |                                | LC/MS Neg   | 32755        | 241.200        | 14.10  | 7,084  |
| M32757 | X-11440        | Unknown   |                                              |                                | LC/MS Neg   | 32757        | 246.3          | 8.04   | 7,686  |
| M32758 | X-11441        | Unknown   |                                              |                                | LC/MS Neg   | 32758        | 331.100        | 10.90  | 7,072  |
| M32759 | X-11442        | Unknown   |                                              |                                | LC/MS Neg   | 32759        | 331.1          | 9.03   | 7142   |
| M32761 | X-11444        | Unknown   |                                              |                                | LC/MS Neg   | 32761        | 541.200        | 8.10   | 7,758  |
| M32762 | X-11445--5-alpha-pregn- | Identified | Sterol/Steroid Lipid | LC/MS Neg | 10.28        | 2570          |        |         |
| ID     | Metabolite                  | Status   | Pathway                      | Super-pathway | Platform | Component ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|-----------------------------|----------|------------------------------|---------------|----------|--------------|--------------|----------------|--------|---------|
| M32769 | 3beta,20alpha-disulfate     | Unknown  |                             |               | LC/MS Neg | 32910        | 189.2        | 0.79            | 11.62  | 7788    |
| M32786 |                             | Unknown  | LC/MS Pos                    | 32786         | 239.1    | 3.82         | 38.22        | 7779           |
| M32787 |                             | Unknown  | LC/MS Neg                    | 32787         | 525.200  | 4.160        | 12.00        | 7271           |
| M32795 |                             | Unknown  | LC/MS Neg                    | 32795         | 165.2    | 4.3          | 16.81        | 6593           |
| M32800 |                             | Unknown  | LC/MS Neg                    | 32800         | 32786    | 239.1        | 3.82         | 12.50          | 4608   |
| M32802 |                             | Unknown  | LC/MS Neg                    | 32802         | 32787    | 525.200      | 4.160        | 12.00          | 7271   |
| M32814 |                             | Unknown  | LC/MS Neg                    | 32814         | 32795    | 165.2        | 4.3          | 16.81          | 6593   |
| M32838 |                             | Unknown  | LC/MS Pos                    | 32838         | 32800    | 239.1        | 3.82         | 12.50          | 4608   |
| M32846 |                             | Unknown  | LC/MS Neg                    | 32846         | 32802    | 32787        | 525.200      | 4.160          | 12.00  | 7271   |
| M32847 |                             | Unknown  | LC/MS Neg                    | 32847         | 32802    | 32787        | 525.200      | 4.160          | 12.00  | 7271   |
| M32854 |                             | Unknown  | LC/MS Pos                    | 32854         | 32802    | 32787        | 525.200      | 4.160          | 12.00  | 7271   |
| M32855 |                             | Unknown  | LC/MS Neg                    | 32855         | 32802    | 32787        | 525.200      | 4.160          | 12.00  | 7271   |
| M32863 |                             | Unknown  | LC/MS Neg                    | 32863         | 32802    | 32787        | 525.200      | 4.160          | 12.00  | 7271   |
| M32867 |                             | Unknown  | LC/MS Pos                    | 32867         | 32802    | 32787        | 525.200      | 4.160          | 12.00  | 7271   |
| M32869 |                             | Unknown  | LC/MS Pos                    | 32869         | 32802    | 32787        | 525.200      | 4.160          | 12.00  | 7271   |
| M32910 |                             | Identified| Ascorbate and aldarate   |               | LC/MS Neg | 32910        | 189.2        | 0.79            | 11.62  | 7788    |
| M33131 |                             | Identified| Cysteine, methionine,     |               | LC/MS Pos | 33132        | 148.1        | 1.13            | 9.53   | 7811    |
| M33132 |                             | Unknown  | Amino acid                   |               | LC/MS Pos | 33132        | 148.1        | 1.13            | 9.53   | 7811    |
| ID       | Metabolite                       | Status      | Pathway                                | Super-pathway                      | Platform | Compo ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|----------|----------------------------------|-------------|----------------------------------------|------------------------------------|----------|----------|-------------|----------------|--------|---------|
| M33137   | X-11792                          | Unknown     |                                        |                                    | LC/MS    | 33137    | 989.800     | 3.570          | 21.80  | 2,442   |
| M33138   | X-11793--oxidized bilirubin*      | Identified  | Hemoglobin and porphyrin metabolism    | Cofactors and vitamins              | LC/MS    | 33138    | 601.1       | 3.570          | 20.18  | 7111    |
| M33140   | X-11795                          | Unknown     |                                        |                                    | LC/MS    | 33144    | 226         | 1.58           | 16.95  | 5038    |
| M33144   | X-11799                          | Unknown     |                                        |                                    | LC/MS    | 33145    | 25.60       | NA             | 2.814  |         |
| M33150   | X-11805                          | Unknown     |                                        |                                    | LC/MS    | 33150    | 948.3       | 4.68           | 33.16  | 7710    |
| M33165   | X-11820                          | Unknown     |                                        |                                    | LC/MS    | 33165    | 33165       | 4.68           | 33.16  | 7710    |
| M33183   | X-11838                          | Unknown     |                                        |                                    | LC/MS    | 33183    | 33183       | 4.68           | 33.16  | 7710    |
| M33188   | X-11843                          | Unknown     |                                        |                                    | LC/MS    | 33188    | 33188       | 4.68           | 33.16  | 7710    |
| M33190   | X-11845                          | Unknown     |                                        |                                    | LC/MS    | 33190    | 33190       | 4.68           | 33.16  | 7710    |
| M33192   | X-11847                          | Unknown     |                                        |                                    | LC/MS    | 33192    | 33192       | 4.68           | 33.16  | 7710    |
| M33194   | X-11849                          | Unknown     |                                        |                                    | LC/MS    | 33194    | 33194       | 4.68           | 33.16  | 7710    |
| M33195   | X-11850                          | Unknown     |                                        |                                    | LC/MS    | 33195    | 33195       | 4.68           | 33.16  | 7710    |
| M33197   | X-11852                          | Unknown     |                                        |                                    | LC/MS    | 33197    | 33197       | 4.68           | 33.16  | 7710    |
| M33203   | X-11858                          | Unknown     |                                        |                                    | LC/MS    | 33203    | 33203       | 4.68           | 33.16  | 7710    |
| M33204   | X-11859                          | Unknown     |                                        |                                    | LC/MS    | 33204    | 33204       | 4.68           | 33.16  | 7710    |
| M33221   | X-11876                          | Unknown     |                                        |                                    | LC/MS    | 33221    | 33221       | 4.68           | 33.16  | 7710    |
| M33225   | X-11880                          | Unknown     |                                        |                                    | LC/MS    | 33225    | 33225       | 4.68           | 33.16  | 7710    |
| M33250   | X-11905                          | Unknown     |                                        |                                    | LC/MS    | 33250    | 33250       | 4.68           | 33.16  | 7710    |
| M33353   | X-12007                          | Unknown     |                                        |                                    | LC/MS    | 33353    | 33353       | 4.68           | 33.16  | 7710    |
| ID     | Metabolite               | Status       | Pathway                  | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|--------------------------|--------------|--------------------------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M33359 | X-12013                  | Unknown      |                          |               | LC/MS Neg | 33359       | 245.3        | 5.82           | 16.44  | 7758    |
| M33380 | X-12029                  | Unknown      |                          |               | LC/MS Neg | 33380       | 243.3        | 6.02           | 16.44  | 7758    |
| M33389 | X-12038                  | Unknown      |                          |               | LC/MS Neg | 33389       | 245.3        | 5.82           | 16.44  | 7758    |
| M33390 | X-12039                  | Unknown      |                          |               | LC/MS Neg | 33390       | 245.3        | 5.82           | 16.44  | 7758    |
| M33391 | X-12040                  | Unknown      |                          |               | LC/MS Neg | 33391       | 245.3        | 5.82           | 16.44  | 7758    |
| M33408 | X-12056                  | Unknown      |                          |               | LC/MS Pos | 33408       | 245.3        | 5.82           | 16.44  | 7758    |
| M33415 | X-12063                  | Unknown      |                          |               | LC/MS Neg | 33415       | 245.3        | 5.82           | 16.44  | 7758    |
| M33507 | X-12092                  | Unknown      |                          |               | LC/MS Pos | 33507       | 245.3        | 5.82           | 16.44  | 7758    |
| M33508 | X-12093                  | Unknown      |                          |               | LC/MS Pos | 33508       | 245.3        | 5.82           | 16.44  | 7758    |
| M33509 | X-12094                  | Unknown      |                          |               | LC/MS Pos | 33509       | 245.3        | 5.82           | 16.44  | 7758    |
| M33510 | X-12095--N1-methyl-3-pyridone-4-carboxamide | Identified | NAD metabolism | Nucleotide | LC/MS Pos | 33510       | 245.3        | 5.82           | 16.44  | 7758    |
| M33515 | X-12100--hydroxytryptophan* | Identified | Tryptophan metabolism | Amino acid | LC/MS Pos | 33515       | 245.3        | 5.82           | 16.44  | 7758    |
| M33531 | X-12116                  | Unknown      |                          |               | LC/MS Pos | 33531       | 245.3        | 5.82           | 16.44  | 7758    |
| M33609 | X-12188                  | Unknown      |                          |               | LC/MS Neg | 33609       | 245.3        | 5.82           | 16.44  | 7758    |
| M33610 | X-12189                  | Unknown      |                          |               | LC/MS Neg | 33610       | 245.3        | 5.82           | 16.44  | 7758    |
| M33616 | X-12195                  | Unknown      |                          |               | LC/MS Neg | 33616       | 245.3        | 5.82           | 16.44  | 7758    |
| M33627 | X-12206                  | Unknown      |                          |               | LC/MS Neg | 33627       | 245.3        | 5.82           | 16.44  | 7758    |
| M33633 | X-12212                  | Unknown      |                          |               | LC/MS Neg | 33633       | 245.3        | 5.82           | 16.44  | 7758    |
| M33637 | X-12216                  | Unknown      |                          |               | LC/MS Neg | 33637       | 245.3        | 5.82           | 16.44  | 7758    |
| M33638 | X-12217                  | Unknown      |                          |               | LC/MS Neg | 33638       | 245.3        | 5.82           | 16.44  | 7758    |
| M33652 | X-12230                  | Unknown      |                          |               | LC/MS Neg | 33652       | 245.3        | 5.82           | 16.44  | 7758    |
| ID      | Metabolite                        | Status     | Pathway       | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|---------|-----------------------------------|------------|---------------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M33653  | X-12231                           | Unknown    |               |               | LC/MS Neg|             |              | 15.40          | 5,111  |
| M33658  | X-12236                           | Unknown    |               |               | LC/MS Neg|             |              | NA             | 1924   |
| M33666  | X-12244--N-acetylcarnosine        | Identified | Dipeptide     | Peptide       | LC/MS Pos|             |              | 14.40          | 6,608  |
| M33675  | X-12253                           | Unknown    |               |               | LC/MS Neg|             |              | 8.98           | 6004   |
| M33683  | X-12261                           | Unknown    |               |               | LC/MS Neg|             |              | 14.60          | 1,050  |
| M33685  | X-12263                           | Unknown    |               |               | LC/MS Neg|             |              | 18.19          | 247    |
| M33751  | X-12329                           | Unknown    |               |               | LC/MS Neg|             |              | 31.30          | 867    |
| M33833  | X-12405                           | Unknown    |               |               | LC/MS Neg|             |              | 17.52          | 6676   |
| M33835  | X-12407                           | Unknown    |               |               | LC/MS Neg|             |              | 18.60          | 2,814  |
| M33864  | X-12428                           | Unknown    |               |               | LC/MS Neg|             |              | 16.74          | 1439   |
| M33877  | X-12435                           | Unknown    |               |               | LC/MS Neg|             |              | NA             | 231    |
| M33883  | X-12441--12-hydroxyeicosatetraenoate (12-HETE) | Identified | Eicosanoid | Lipid | LC/MS Neg | 33884 | 223.400 | 5.280 | 14.80 | 7,780 |
| M33884  | X-12442--5,8-tetradecadienoate    | Identified | Long chain fatty acid | Lipid | LC/MS Neg | 33884 | 223.400 | 5.280 | 14.80 | 7,780 |
| M33885  | X-12443                           | Unknown    |               |               | LC/MS Neg|             |              | 132.93         | 5357   |
| M33892  | X-12450                           | Unknown    |               |               | LC/MS Neg|             |              | 25.60          | 6,432  |
| M33901  | X-12456                           | Unknown    |               |               | LC/MS Neg| 33901 | 427.2  | 4.34  | 18.29 | 4774  |
| M33910  | X-12465                           | Unknown    |               |               | LC/MS Pos|             |              | 13.80          | 5,883  |
| M34040  | X-12510--2-aminoocotanoic acid    | Identified | Amino fatty acid | Amino acid | LC/MS Pos|             |              | 16.82          | 7566   |
| M34062  | X-12524                           | Unknown    |               |               | LC/MS Neg|             |              | 13.00          | 7,809  |
| M34102  | X-12539                           | Unknown    |               |               | LC/MS Neg|             |              | 29.53          | 1000   |
| M34112  | X-12544                           | Unknown    |               |               | LC/MS Pos|             |              | 9.50           | 5,893  |
| ID    | Metabolite | Status  | Pathway | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|-------|------------|---------|---------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M34123| X-12556    | Unknown |         |               | GC/MS    | 34123       | 116.9        | 6.61            | 20.76  | 7483    |
| M34221| X-12627    | Unknown |         |               | LC/MS Neg| 34221       | 357.400      | 5.840           | 27.90  | 7,419   |
| M34244| X-12644    | Unknown |         |               | LC/MS Neg| 34244       |              | 41.19           | 7795   |         |
| M34245| X-12645    | Unknown |         |               | LC/MS Neg| 34245       |              | 64.10           | 5,254  |         |
| M34289| X-12680    | Unknown |         |               | LC/MS Pos| 34289       |              | 22.01           | 2311   |         |
| M34306| X-12696    | Unknown |         |               | LC/MS Neg| 34306       |              | 12.40           | 7,409  |         |
| M34314| X-12704    | Unknown |         |               | LC/MS Neg| 34314       |              | 0.00            | 1813   |         |
| M34321| X-12711    | Unknown |         |               | LC/MS Neg| 34321       |              | 14.70           | 393    |         |
| M34322| X-12712    | Unknown |         |               | LC/MS Neg| 34322       |              | 0.00            | 260    |         |
| M34327| X-12717    | Unknown |         |               | LC/MS Neg| 34327       |              | NA              | 1,632  |         |
| M34329| X-12719    | Unknown |         |               | LC/MS Neg| 34329       |              | NA              | 1539   |         |
| M34336| X-12726    | Unknown |         |               | LC/MS Neg| 34336       |              | 29.00           | 5,495  |         |
| M34338| X-12728    | Unknown |         |               | LC/MS Neg| 34338       |              | 12.05           | 537    |         |
| M34339| X-12729    | Unknown |         |               | LC/MS Neg| 34339       |              | 17.00           | 1,753  |         |
| M34344| X-12734    | Unknown |         |               | LC/MS Neg| 34344       |              | 21.64           | 5616   |         |
| M34350| X-12740    | Unknown |         |               | LC/MS Neg| 34350       |              | 12.40           | 3,731  |         |
| M34359| X-12749    | Unknown |         |               | LC/MS Pos| 34359       | 262.1         | 1.51            | 13.16  | 7,178   |
| M34369| X-12759    | Unknown |         |               | LC/MS Pos| 34369       |              | NA              | 63     |         |
| M34441| X-12771    | Unknown |         |               | GC/MS    | 34441       |              | 35.16           | 4734   |         |
| M34453| X-12776    | Unknown |         |               | LC/MS Neg| 34453       |              | 13.90           | 7,764  |         |
| M34469| X-12786    | Unknown |         |               | GC/MS    | 34469       |              | 28.89           | 6566   |         |
| M34481| X-12798    | Unknown |         |               | LC/MS Pos| 34481       | 240.100       | 1.840           | 17.80  | 7,552   |
| ID       | Metabolite                  | Status        | Pathway          | Superpathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|----------|-----------------------------|---------------|------------------|--------------|----------|-------------|--------------|----------------|--------|---------|
| M34499   | X-12816                     | Unknown       |                  |              | LC/MS Neg |             |              |                |        |         |
| M34513   | X-12830                     | Unknown       |                  |              | LC/MS Neg |             |              |                |        |         |
| M34516   | X-12833                     | Unknown       |                  |              | LC/MS Neg | 34527       | 539.300      | 4.120          | 9.30   |         |
| M34527   | X-12844                     | Unknown       |                  |              | LC/MS Neg |             |              |                |        |         |
| M34530   | X-12847                     | Unknown       |                  |              | LC/MS Neg |             |              |                | 15.86  | 4036    |
| M34533   | X-12850                     | Unknown       |                  |              | LC/MS Neg | 34533       | 263.800      | 4.820          | 11.10  |         |
| M34535   | X-12851                     | Unknown       |                  |              | LC/MS Neg |             |              |                | 11.09  | 4808    |
| M34539   | X-12855                     | Unknown       |                  |              | LC/MS Pos |             |              |                | 25.70  | 5,120   |
| M34674   | X-12990--docosapentaenoic acid (n6-DPA) | Identified  | Essential fatty acid | Lipid | LC/MS Neg |             |              |                | 13.67  | 2581    |
| M34761   | X-13069                     | Unknown       |                  |              | LC/MS Neg |             |              |                | 21.00  | 6,770   |
| M34826   | X-13134                     | Unknown       |                  |              | LC/MS Neg |             |              |                | 36.71  | 975     |
| M34878   | X-13183--stearamide        | Identified    | Fatty acid amide  | Lipid | LC/MS Pos | 34912       | 149.2        | 5.2            | 18.56  | 6305    |
| M34912   | X-13215                     | Unknown       |                  |              | LC/MS Neg |             |              |                |        |         |
| M35072   | X-13372                     | Unknown       |                  |              | LC/MS Neg |             |              |                | 18.40  | 1,500   |
| M35187   | X-13429                     | Unknown       |                  |              | LC/MS Neg | 35187       | 263.7        | 4.84           | 13.51  | 6344    |
| M35189   | X-13431--nonanoylcarnitine* | Identified    | Carnitine metabolism | Lipid | LC/MS Pos | 35189       | 302.300      | 4.180          | 25.80  | 6,591   |
| M35193   | X-13435                     | Unknown       |                  |              | LC/MS Pos | 35193       | 314.3        | 4.61           | 15.21  | 6970    |
| M35240   | X-13477                     | Unknown       |                  |              | LC/MS Pos | 35240       | 176.200      | 0.850          | 21.10  | 5,952   |
| M35270   | X-13496                     | Unknown       |                  |              | GC/MS     |             |              |                | 17.73  | 7656    |
| M35326   | X-13548                     | Unknown       |                  |              | LC/MS Pos | 35326       | 295.100      | 2.330          | 19.90  | 6,022   |
| M35327   | X-13549                     | Unknown       |                  |              | LC/MS Pos |             |              |                | 18.78  | 7330    |
| ID     | Metabolite         | Status   | Pathway       | Super-pathway | Platform   | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|--------|--------------------|----------|---------------|---------------|------------|-------------|--------------|----------------|--------|---------|
| M35331 | X-13553            | Unknown  |               |               | LC/MS      | 35464       | 315.300      | 5.290       | 13.20  | 7,311   |
| M35397 | X-13619            | Unknown  |               |               | GC/MS      |             | 3085         |              | 20.87  | 7791    |
| M35422 | X-13640            | Unknown  |               |               | LC/MS      |             | 0.00         |             | 0.00   | 660     |
| M35451 | X-13658            | Unknown  |               |               | LC/MS      |             | 23.08        |             | 1412   |         |
| M35464 | X-13671            | Unknown  |               |               | LC/MS      | 35464       | 315.300      | 5.290       | 13.20  | 7,311   |
| M35508 | X-13699            | Unknown  |               |               | LC/MS      |             | 11.86        |             | 146    |         |
| M35551 | X-13741            | Unknown  |               |               | LC/MS      |             | 10.10        |             | 5.325  |         |
| M35754 | X-13859            | Unknown  |               |               | LC/MS      |             | 31.24        |             | 7002   |         |
| M35977 | X-14056            | Unknown  |               |               | LC/MS      |             | 20.90        |             | 7,259  |         |
| M35978 | X-14057            | Unknown  |               |               | LC/MS      |             | 33.14        |             | 4716   |         |
| M36009 | X-14086            | Unknown  |               |               | LC/MS      |             | NA           |             | 2,686  |         |
| M36115 | X-14189--leucylalanine | Identified | Dipeptide       | Peptide     | LC/MS      |             | 8.28         |             | 2745   |         |
| M36131 | X-14205--alpha-glutamyltyrosine | Identified | Dipeptide       | Peptide     | LC/MS      |             | 13.50        |             | 1,789  |         |
| M36134 | X-14208--phenylalanylsereine | Identified | Dipeptide       | Peptide     | LC/MS      |             | 20.68        |             | 2455   |         |
| M36230 | X-14304--leucylalanine | Identified | Dipeptide       | Peptide     | LC/MS      |             | 13.20        |             | 2,434  |         |
| M36300 | X-14374            | Unknown  |               |               | LC/MS      |             | 20.61        |             | 7627   |         |
| M36376 | X-14450--phenylalanylleucine | Identified | Dipeptide       | Peptide     | LC/MS      |             | 16.00        |             | 2,555  |         |
| M36394 | X-14468            | Unknown  |               |               | LC/MS      |             | NA           |             | 368    |         |
| M36399 | X-14473            | Unknown  |               |               | LC/MS      | 36399       | 211.200      | 3.270       | 24.20  | 6,884   |
| M36468 | X-14541            | Unknown  |               |               | LC/MS      |             | NA           |             | 1941   |         |
| M36515 | X-14588            | Unknown  |               |               | LC/MS      |             | 9.20         |             | 7,777  |         |
| ID    | Metabolite       | Status  | Pathway | Super-pathway | Platform | Compound ID | Quant. Mass. | Retention Time | CV (%) | Total N |
|-------|------------------|---------|---------|---------------|----------|-------------|--------------|----------------|--------|---------|
| M36552 X-14625 | Unknown |         |         |               | LC/MS Neg | 36552       | 308.1        | 0.72            | 14.88  | 7511    |
| M36553 X-14626 | Unknown |         |         |               | LC/MS Neg | 36553       | 288.800      | 4.800           | 26.20  | 6,904   |
| M36559 X-14632 | Unknown |         |         |               | LC/MS Neg |             |              |                 |        |         |
| M36585 X-14658 | Unknown |         |         |               | LC/MS Neg |             |              |                 |        |         |
| M36589 X-14662 | Unknown |         |         |               | LC/MS Neg |             |              |                 |        |         |
| M36590 X-14663 | Unknown |         |         |               | LC/MS Neg |             |              |                 |        |         |
| M36673 X-14745 | Unknown |         |         |               | GC/MS    |             |              |                 |        |         |
| M37004 X-14977--vanillin | Identified | Food component/Plant | Xenobiotics | LC/MS Pos  | 22.10     | 1,789        |              |                 |        |         |
| M17807 X-18601 | Unknown |         |         |               | LC/MS neg |             |              |                 |        |         |
### eTable 3. Association Results Derived From mQTL Analysis of SNPs on Mannose With P Value<5×10^{-8}

| Chr | Position (hg19) | SNP | Major allele | Minor allele | MAF  | Coefficient | Standard Error | P     |
|-----|----------------|-----|--------------|--------------|------|-------------|----------------|-------|
| 2   | 27544285       | rs1122227 | T             | C            | 0.2050 | 0.0148      | 0.0026         | 8.81E-09 |
| 2   | 27873326       | rs8731 | C             | G            | 0.7955 | -0.0169     | 0.0026         | 4.02E-11 |
| 2   | 27504312       | rs1992291 | A             | G            | 0.7845 | -0.0153     | 0.0026         | 2.03E-09 |
| 2   | 27825715       | rs12467476 | T             | G            | 0.7355 | 0.0336      | 0.0025         | 1.03E-42 |
| 2   | 28418189       | rs13000936 | A             | G            | 0.3138 | 0.0135      | 0.0024         | 3.27E-08 |
| 2   | 28225861       | rs11692105 | T             | G            | 0.2450 | 0.0141      | 0.0025         | 1.74E-08 |
| 2   | 28199424       | rs12465000 | A             | G            | 0.7840 | -0.0152     | 0.0026         | 2.85E-09 |
| 2   | 28344285       | rs4401177 | A             | G            | 0.1204 | -0.0201     | 0.0036         | 2.56E-08 |
| 2   | 27853245       | rs13002853 | C             | G            | 0.7434 | 0.0327      | 0.0025         | 1.69E-40 |
| 2   | 27893939       | rs2068834 | T             | C            | 0.7229 | 0.0324      | 0.0024         | 2.29E-40 |
| 2   | 27688601       | rs1647276 | T             | C            | 0.3894 | 0.0248      | 0.0024         | 6.91E-25 |
| 2   | 27508710       | rs11686131 | T             | C            | 0.2051 | 0.0148      | 0.0026         | 7.45E-09 |
| 2   | 27579231       | rs6760828 | T             | C            | 0.6099 | -0.0257     | 0.0024         | 5.09E-27 |
| 2   | 27743154       | rs780092 | A             | G            | 0.8479 | -0.0226     | 0.0032         | 3.54E-12 |
| 2   | 27519153       | rs13404327 | T             | G            | 0.2530 | 0.0193      | 0.0025         | 1.09E-14 |
| 2   | 27961344       | rs1317580 | C             | G            | 0.2568 | -0.0167     | 0.0025         | 2.91E-11 |
| 2   | 28088580       | rs4666028 | A             | T            | 0.1739 | 0.0152      | 0.0026         | 5.99E-09 |
| 2   | 27811722       | rs12478841 | A             | G            | 0.7347 | 0.0336      | 0.0025         | 9.05E-43 |
| 2   | 27528692       | rs4665963 | T             | C            | 0.7462 | -0.0194     | 0.0025         | 9.29E-15 |
| 2   | 27767107       | rs1972669 | T             | G            | 0.5182 | 0.0132      | 0.0024         | 3.61E-08 |
| 2   | 28107692       | rs6708889 | T             | C            | 0.7928 | -0.0152     | 0.0026         | 2.60E-09 |
| 2   | 27644464       | rs1728922 | A             | C            | 0.6098 | -0.0253     | 0.0024         | 4.32E-26 |
| 2   | 27995931       | rs3792252 | A             | G            | 0.7527 | -0.0176     | 0.0025         | 2.11E-12 |
| 2   | 27722416       | rs1260320 | A             | G            | 0.3855 | 0.0249      | 0.0024         | 2.45E-25 |
| 2   | 27855397       | rs10173720 | A             | T            | 0.7974 | -0.0181     | 0.0025         | 1.05E-12 |
| 2   | 27550967       | rs1049817 | A             | G            | 0.6106 | -0.0251     | 0.0024         | 9.82E-26 |
| 2   | 27750546       | rs2911711 | A             | T            | 0.5511 | 0.0363      | 0.0024         | 2.37E-53 |
| Chr | Position (hg19) | SNP | Major allele | Minor allele | MAF | Coefficient | Standard Error | P       |
|-----|----------------|-----|--------------|--------------|-----|-------------|----------------|---------|
| 2   | 27933642       | rs4616435 | T           | C            | 0.2107 | -0.0291     | 0.0025         | 8.41E-31 |
| 2   | 27715207       | rs8395  | A            | T            | 0.3838 | 0.0256      | 0.0024         | 2.91E-26 |
| 2   | 28200152       | rs2337374 | A          | G            | 0.7840 | -0.0152     | 0.0026         | 2.84E-09 |
| 2   | 28367761       | rs6751559 | T          | G            | 0.8993 | 0.0183      | 0.0034         | 4.96E-08 |
| 2   | 28301540       | rs937813 | T            | C            | 0.9025 | 0.0271      | 0.0039         | 2.65E-12 |
| 2   | 27801418       | rs1919126 | A          | C            | 0.4816 | -0.0132     | 0.0024         | 3.48E-08 |
| 2   | 28281545       | rs6547820 | A            | G            | 0.7939 | -0.0150     | 0.0026         | 4.43E-09 |
| 2   | 28523834       | rs12617913 | T          | C            | 0.5964 | -0.0131     | 0.0024         | 4.68E-08 |
| 2   | 28232279       | rs2839791 | A            | C            | 0.2158 | 0.0150      | 0.0026         | 4.01E-09 |
| 2   | 27839832       | rs7571558 | C          | G            | 0.7974 | -0.0200     | 0.0026         | 5.09E-15 |
| 2   | 27789861       | rs965813 | A            | T            | 0.2018 | 0.0192      | 0.0026         | 5.14E-14 |
| 2   | 28396483       | rs7586645 | A          | G            | 0.3229 | 0.0134      | 0.0024         | 4.02E-08 |
| 2   | 27910706       | rs13023094 | A          | C            | 0.7918 | 0.0298      | 0.0025         | 2.74E-32 |
| 2   | 27995781       | rs3736594 | A            | C            | 0.2560 | 0.0179      | 0.0025         | 9.02E-13 |
| 2   | 28090059       | rs10171517 | T          | C            | 0.2015 | 0.0174      | 0.0025         | 7.85E-12 |
| 2   | 28079344       | rs4233719 | A            | C            | 0.2159 | 0.0153      | 0.0025         | 2.06E-09 |
| 2   | 27802805       | rs3811644 | A            | G            | 0.7989 | -0.0192     | 0.0026         | 5.28E-14 |
| 2   | 27741237       | rs780094 | T            | C            | 0.3977 | -0.0428     | 0.0024         | 6.89E-73  |
| 2   | 27952406       | rs12994085 | T          | C            | 0.7705 | -0.0180     | 0.0025         | 1.07E-12 |
| 2   | 27840640       | rs4666002 | C            | G            | 0.2757 | -0.0386     | 0.0042         | 9.98E-20  |
| 2   | 27801759       | rs1919128 | A            | G            | 0.7347 | 0.0336      | 0.0024         | 8.39E-43  |
| 2   | 27574953       | rs4665969 | T            | C            | 0.6105 | -0.0256     | 0.0024         | 1.01E-26  |
| 2   | 27706640       | rs2272417 | T            | C            | 0.5930 | -0.0224     | 0.0024         | 2.75E-20  |
| 2   | 27663416       | rs1260342 | T            | G            | 0.3894 | 0.0248      | 0.0024         | 6.93E-25  |
| 2   | 27488432       | rs6547521 | C            | G            | 0.2826 | 0.0167      | 0.0025         | 1.32E-11  |
| 2   | 27846645       | rs1528403 | C            | G            | 0.5290 | 0.0138      | 0.0024         | 1.19E-08  |
| 2   | 27895073       | rs2178198 | T            | C            | 0.1351 | -0.0254     | 0.0033         | 1.98E-14  |
| 2   | 28082494       | rs4578809 | A            | G            | 0.1739 | 0.0152      | 0.0026         | 5.99E-09  |
| 2   | 27426878       | rs1275522 | T            | C            | 0.7113 | -0.0167     | 0.0025         | 1.29E-11  |
| 2   | 27721971       | rs813592  | T            | C            | 0.6118 | -0.0254     | 0.0024         | 3.51E-26  |
| Chr | Position (hg19) | SNP      | Major allele | Minor allele | MAF     | Coefficient | Standard Error | P        |
|-----|----------------|----------|--------------|--------------|---------|-------------|----------------|----------|
| 2   | 28256831       | rs9309658| A            | G            | 0.2157  | 0.0150      | 0.0026         | 4.26E-09 |
| 2   | 27637235       | rs2010087| T            | C            | 0.3855  | 0.0255      | 0.0024         | 3.01E-26 |
| 2   | 27613617       | rs11891554| A           | G            | 0.0427  | 0.0337      | 0.0055         | 1.18E-09 |
| 2   | 27424636       | rs1395   | A            | G            | 0.7024  | -0.0170     | 0.0025         | 5.97E-12 |
| 2   | 27455726       | rs13399758| T           | C            | 0.9349  | -0.0275     | 0.0049         | 1.47E-08 |
| 2   | 27449293       | rs7934488| C            | G            | 0.7116  | -0.0169     | 0.0025         | 7.32E-12 |
| 2   | 27731212       | rs3817588| T            | C            | 0.8135  | -0.0239     | 0.0026         | 1.08E-19 |
| 2   | 28418031       | rs6712705| T            | C            | 0.6814  | -0.0135     | 0.0024         | 3.31E-08 |
| 2   | 27783801       | rs4665382| T            | C            | 0.7353  | 0.0336      | 0.0024         | 7.91E-43 |
| 2   | 27393030       | rs1659689| A            | G            | 0.2752  | 0.0166      | 0.0025         | 1.92E-11 |
| 2   | 27958855       | rs6753736| C            | G            | 0.2214  | 0.0193      | 0.0025         | 2.78E-14 |
| 2   | 27975394       | rs6547796| T            | C            | 0.2557  | 0.0178      | 0.0025         | 1.00E-12 |
| 2   | 28520083       | rs10189899| A           | G            | 0.4003  | 0.0137      | 0.0024         | 1.15E-08 |
| 2   | 27659491       | rs780102  | T            | C            | 0.6099  | -0.0248     | 0.0024         | 6.94E-25 |
| 2   | 28162861       | rs4390729| T            | C            | 0.2161  | 0.0152      | 0.0026         | 2.89E-09 |
| 2   | 27746832       | rs8179252| A            | C            | 0.6073  | -0.0252     | 0.0024         | 1.26E-25 |
| 2   | 27604279       | rs4582   | A            | G            | 0.6103  | -0.0253     | 0.0024         | 4.81E-26 |
| 2   | 28162274       | rs13416434| T           | C            | 0.2161  | 0.0152      | 0.0026         | 2.89E-09 |
| 2   | 27742603       | rs780093  | T            | C            | 0.3985  | -0.0433     | 0.0024         | 1.48E-75 |
| 2   | 27703495       | rs1260345| A            | G            | 0.5881  | -0.0223     | 0.0024         | 3.53E-20 |
| 2   | 27611469       | rs7594812| A            | G            | 0.6097  | -0.0253     | 0.0024         | 4.63E-26 |
| 2   | 27452784       | rs6717980| T            | C            | 0.7122  | -0.0169     | 0.0025         | 7.43E-12 |
| 2   | 27519254       | rs13404446| A          | G            | 0.2530  | 0.0194      | 0.0025         | 8.83E-15 |
| 2   | 27841305       | rs6756238| A            | G            | 0.4721  | -0.0133     | 0.0024         | 2.77E-08 |
| 2   | 27852637       | rs6547738| A            | G            | 0.5281  | 0.0132      | 0.0024         | 2.89E-08 |
| 2   | 28530720       | rs4666052| A            | G            | 0.4003  | 0.0137      | 0.0024         | 1.17E-08 |
| 2   | 28113911       | rs2305929| A            | G            | 0.8169  | 0.0260      | 0.0025         | 2.05E-24 |
| 2   | 27443196       | rs4665958| A            | G            | 0.7125  | -0.0169     | 0.0025         | 7.01E-12 |
| 2   | 27987046       | rs12477908| A           | C            | 0.2557  | 0.0178      | 0.0025         | 9.97E-13 |
| 2   | 28443050       | rs7349418| T            | C            | 0.5484  | 0.0154      | 0.0024         | 1.85E-10 |
| Chr | Position (hg19) | SNP    | Major allele | Minor allele | MAF   | Coefficient | Standard Error | P       |
|-----|----------------|--------|--------------|--------------|-------|-------------|----------------|---------|
| 2   | 27652153       | rs780100 | T            | G            | 0.3894 | 0.0248      | 0.0024         | 6.99E-25|
| 2   | 28144067       | rs1870325 | A            | G            | 0.7922 | -0.0152     | 0.0026         | 2.84E-09|
| 2   | 27471025       | rs1561535 | T            | C            | 0.2818 | 0.0163      | 0.0025         | 4.13E-11|
| 2   | 28255302       | rs937812 | T            | C            | 0.7843 | -0.0150     | 0.0026         | 4.26E-09|
| 2   | 27851918       | rs3749147 | A            | G            | 0.2755 | -0.0363     | 0.0043         | 1.72E-17|
| 2   | 27932587       | rs6727388 | A            | G            | 0.7893 | 0.0291      | 0.0025         | 8.35E-31|
| 2   | 27801493       | rs1919127 | T            | C            | 0.7340 | 0.0336      | 0.0024         | 8.37E-43|
| 2   | 28213424       | rs10175508 | T           | C            | 0.7840 | -0.0144     | 0.0026         | 1.69E-08|
| 2   | 27748624       | rs1260333 | A            | G            | 0.4501 | -0.0363     | 0.0024         | 2.37E-53|
| 2   | 28018293       | rs4666012 | A            | G            | 0.8018 | -0.0152     | 0.0026         | 3.43E-09|
| 2   | 28258027       | rs7593127 | A            | G            | 0.7843 | -0.0150     | 0.0026         | 4.27E-09|
| 2   | 28517861       | rs4666051 | A            | G            | 0.4003 | 0.0137      | 0.0024         | 1.16E-08|
| 2   | 28140349       | rs2337372 | A            | G            | 0.1736 | 0.0144      | 0.0026         | 3.96E-08|
| 2   | 28219941       | rs1458398 | A            | G            | 0.2159 | 0.0151      | 0.0026         | 3.40E-09|
| 2   | 27968454       | rs9967838 | A            | C            | 0.2494 | 0.0178      | 0.0025         | 1.01E-12|
| 2   | 27818721       | rs1919129 | C            | G            | 0.7974 | -0.0200     | 0.0026         | 5.11E-15|
| 2   | 27536380       | rs4665965 | T            | C            | 0.7468 | -0.0184     | 0.0025         | 2.41E-13|
| 2   | 27693485       | rs1647266 | T            | C            | 0.6106 | -0.0248     | 0.0024         | 6.91E-25|
| 2   | 27450724       | rs3769143 | A            | G            | 0.2889 | 0.0170      | 0.0025         | 5.12E-12|
| 2   | 27648726       | rs4665978 | T            | C            | 0.5993 | -0.0311     | 0.0024         | 1.28E-39|
| 2   | 27432547       | rs1275530 | A            | G            | 0.2878 | 0.0170      | 0.0025         | 4.62E-12|
| 2   | 27755825       | rs4665987 | A            | G            | 0.2653 | -0.0336     | 0.0024         | 8.06E-43|
| 2   | 27441397       | rs1275538 | A            | G            | 0.2574 | 0.0153      | 0.0025         | 6.67E-10|
| 2   | 28094270       | rs13016573 | C            | G            | 0.8258 | -0.0154     | 0.0026         | 2.84E-09|
| 2   | 27430781       | rs1275528 | A            | G            | 0.2878 | 0.0169      | 0.0025         | 6.79E-12|
| 2   | 27812252       | rs6760250 | A            | G            | 0.2653 | -0.0336     | 0.0025         | 9.09E-43|
| 2   | 27567407       | rs6743819 | T            | G            | 0.3901 | 0.0257      | 0.0024         | 5.25E-27|
| 2   | 27791555       | rs4665383 | C            | G            | 0.7335 | 0.0334      | 0.0025         | 1.63E-41|
| 2   | 27600239       | rs13472   | A            | G            | 0.3844 | 0.0261      | 0.0024         | 1.93E-27|
| 2   | 27972833       | rs12104449 | A            | G            | 0.8737 | 0.0253      | 0.0033         | 3.24E-14|
| Chr | Position (hg19) | SNP   | Major allele | Minor allele | MAF   | Coefficient | Standard Error | P    |
|-----|----------------|-------|--------------|--------------|-------|-------------|----------------|------|
| 2   | 27398196       | rs2580754 | A            | T            | 0.7098 | -0.0166     | 0.0025         | 1.45E-11 |
| 2   | 27566520       | rs11689803 | A            | T            | 0.2661 | 0.0251      | 0.0025         | 6.04E-24 |
| 2   | 27860258       | rs2141371 | A            | G            | 0.6820 | -0.0198     | 0.0024         | 3.27E-16 |
| 2   | 28202936       | rs898032  | C            | G            | 0.2160 | 0.0152      | 0.0026         | 2.84E-09 |
| 2   | 28124171       | rs10177845 | A            | G            | 0.7839 | -0.0152     | 0.0025         | 2.60E-09 |
| 2   | 27416702       | rs1275504 | A            | T            | 0.2976 | 0.0168      | 0.0025         | 9.83E-12 |
| 2   | 28101938       | rs6706209 | T            | C            | 0.7857 | -0.0148     | 0.0025         | 6.05E-09 |
| 2   | 27589810       | rs2280737 | T            | C            | 0.6215 | -0.0255     | 0.0024         | 1.67E-25 |
| 2   | 27772777       | rs2293572 | C            | G            | 0.6148 | -0.0264     | 0.0024         | 1.17E-27 |
| 2   | 27635582       | rs1060525 | A            | G            | 0.6112 | -0.0257     | 0.0024         | 5.82E-27 |
| 2   | 28529165       | rs10165668 | A            | G            | 0.5997 | -0.0137     | 0.0024         | 1.16E-08 |
| 2   | 28085311       | rs7595986 | A            | G            | 0.7834 | -0.0153     | 0.0025         | 2.06E-09 |
| 2   | 27839369       | rs4666000 | T            | C            | 0.7221 | 0.0323      | 0.0024         | 4.85E-40 |
| 2   | 28276643       | rs1395324 | C            | G            | 0.2157 | 0.0150      | 0.0026         | 4.29E-09 |
| 2   | 27389195       | rs1275541 | A            | G            | 0.2833 | 0.0166      | 0.0025         | 1.92E-11 |
| 2   | 27743215       | rs814295  | A            | G            | 0.8452 | -0.0217     | 0.0032         | 1.94E-11 |
| 2   | 27830067       | rs6719960 | A            | G            | 0.7982 | -0.0201     | 0.0026         | 3.16E-15 |
| 2   | 27848397       | rs4665384 | A            | G            | 0.5280 | 0.0133      | 0.0024         | 2.66E-08 |
| 2   | 28085347       | rs13021285 | T            | C            | 0.8261 | -0.0152     | 0.0026         | 5.99E-09 |
| 2   | 28019175       | rs4666014 | A            | G            | 0.2072 | 0.0146      | 0.0026         | 1.33E-08 |
| 2   | 27778091       | rs6706610 | A            | G            | 0.4818 | -0.0132     | 0.0024         | 3.51E-08 |
| 2   | 28168415       | rs7577437 | A            | G            | 0.2161 | 0.0152      | 0.0026         | 2.89E-09 |
| 2   | 28087205       | rs13004096 | T            | C            | 0.1732 | 0.0152      | 0.0026         | 5.99E-09 |
| 2   | 28080214       | rs13025314 | A            | G            | 0.1739 | 0.0152      | 0.0026         | 5.99E-09 |
| 2   | 27685388       | rs780110  | A            | G            | 0.4424 | 0.0306      | 0.0024         | 4.06E-38 |
| 2   | 28081630       | rs4578808 | T            | G            | 0.1739 | 0.0152      | 0.0026         | 5.99E-09 |
| 2   | 27420690       | rs1659685 | T            | C            | 0.7025 | -0.0165     | 0.0025         | 2.25E-11 |
| 2   | 27542041       | rs1975384 | T            | C            | 0.2051 | 0.0148      | 0.0026         | 8.80E-09 |
| 2   | 28086765       | rs11902158 | A            | G            | 0.8261 | -0.0152     | 0.0026         | 5.99E-09 |
| 2   | 27657167       | rs704791  | T            | C            | 0.6106 | -0.0248     | 0.0024         | 6.94E-25 |
| Chr | Position (hg19) | SNP       | Major allele | Minor allele | MAF   | Coefficient | Standard Error | P       |
|-----|----------------|-----------|--------------|--------------|-------|-------------|----------------|---------|
| 2   | 28271435       | rs13402420| T            | G            | 0.2150| 0.0150      | 0.0026         | 4.29E-09|
| 2   | 27515105       | rs4665962 | A            | G            | 0.7949| -0.0148     | 0.0026         | 7.43E-09|
| 2   | 27847606       | rs6749426 | T            | C            | 0.5280| 0.0133      | 0.0024         | 2.70E-08|
| 2   | 27981655       | rs12471347| C            | G            | 0.2455| 0.0170      | 0.0025         | 1.10E-11|
| 2   | 28199736       | rs12465103| C            | G            | 0.7840| -0.0152     | 0.0026         | 2.85E-09|
| 2   | 27677691       | rs780104  | A            | G            | 0.3894| 0.0248      | 0.0024         | 6.92E-25|
| 2   | 27830990       | rs6547734 | T            | G            | 0.4808| -0.0131     | 0.0024         | 3.87E-08|
| 2   | 27718474       | rs78090   | T            | C            | 0.0854| -0.0282     | 0.0041         | 8.28E-12|
| 2   | 28209283       | rs10209126| T            | C            | 0.7840| -0.0152     | 0.0026         | 2.96E-09|
| 2   | 28023120       | rs11127125| T            | C            | 0.7947| -0.0146     | 0.0026         | 1.38E-08|
| 2   | 28098724       | rs13411592| A            | G            | 0.7844| -0.0152     | 0.0025         | 2.29E-09|
| 2   | 28118662       | rs7607546 | A            | G            | 0.8264| -0.0151     | 0.0026         | 7.21E-09|
| 2   | 27934731       | rs6727215 | A            | G            | 0.2100| -0.0291     | 0.0025         | 8.53E-31|
| 2   | 28090820       | rs898034  | T            | C            | 0.2015| 0.0174      | 0.0025         | 7.85E-12|
| 2   | 27980944       | rs10209020| T            | C            | 0.7443| -0.0178     | 0.0025         | 9.99E-13|
| 2   | 27774702       | rs2384628 | T            | G            | 0.5304| 0.0141      | 0.0024         | 4.03E-09|
| 2   | 27684734       | rs780107  | A            | G            | 0.6106| -0.0248     | 0.0024         | 6.92E-25|
| 2   | 27558252       | rs11684134| A            | G            | 0.5674| -0.0250     | 0.0024         | 1.04E-25|
| 2   | 27568565       | rs10205219| T            | C            | 0.6099| -0.0257     | 0.0024         | 5.22E-27|
| 2   | 28020966       | rs3935148 | A            | T            | 0.1966| 0.0152      | 0.0026         | 3.64E-09|
| 2   | 27796526       | rs10165098| T            | C            | 0.4810| -0.0132     | 0.0024         | 3.43E-08|
| 2   | 28136351       | rs1458396 | A            | G            | 0.2160| 0.0152      | 0.0025         | 2.68E-09|
| 2   | 27460968       | rs1141313 | A            | G            | 0.7122| -0.0169     | 0.0025         | 7.46E-12|
| 2   | 27730817       | rs8179219 | A            | G            | 0.0381| 0.0343      | 0.0062         | 2.76E-08|
| 2   | 27712408       | rs7583698 | T            | C            | 0.0483| 0.0338      | 0.0049         | 8.55E-12|
| 2   | 27613031       | rs12476704| A            | C            | 0.3843| 0.0261      | 0.0024         | 1.79E-27|
| 2   | 27951658       | rs867282  | T            | C            | 0.2214| 0.0167      | 0.0025         | 3.43E-11|
| 2   | 27715416       | rs2303369 | T            | C            | 0.3838| 0.0256      | 0.0024         | 2.91E-26|
| 2   | 28189280       | rs1902966 | A            | G            | 0.7839| -0.0152     | 0.0026         | 2.87E-09|
| 2   | 27892023       | rs2272406 | A            | T            | 0.7912| 0.0293      | 0.0025         | 2.19E-31|
| Chr | Position (hg19) | SNP | Major allele | Minor allele | MAF   | Coefficient | Standard Error | P      |
|-----|----------------|-----|--------------|--------------|-------|-------------|----------------|--------|
| 2   | 28155195       | rs6547815 | A            | T            | 0.7924 | -0.0152     | 0.0026         | 3.28E-09 |
| 2   | 27698343       | rs780117 | C            | G            | 0.6106 | -0.0248     | 0.0024         | 6.90E-25 |
| 2   | 27988821       | rs13013484 | A            | G            | 0.7379 | -0.0186     | 0.0025         | 9.33E-14 |
| 2   | 27772879       | rs6749052 | A            | T            | 0.5182 | 0.0132      | 0.0024         | 3.56E-08 |
| 2   | 28268467       | rs6738887 | T            | C            | 0.7846 | -0.0149     | 0.0025         | 4.61E-09 |
| 2   | 27631191       | rs7563162 | T            | C            | 0.3896 | 0.0247      | 0.0024         | 4.15E-24 |
| 2   | 27681598       | rs780106 | A            | C            | 0.6106 | -0.0248     | 0.0024         | 6.92E-25 |
| 2   | 27646770       | rs6547626 | T            | C            | 0.3902 | 0.0253      | 0.0024         | 4.32E-26 |
| 2   | 28394293       | rs17759746 | T            | C            | 0.9007 | 0.0184      | 0.0034         | 4.96E-08 |
| 2   | 28235184       | rs7602328 | A            | G            | 0.7842 | -0.0150     | 0.0026         | 4.09E-09 |
| 2   | 27663215       | rs1260341 | A            | T            | 0.3894 | 0.0248      | 0.0024         | 6.93E-25 |
| 2   | 27441302       | rs1275537 | C            | G            | 0.2766 | 0.0157      | 0.0025         | 1.93E-10 |
| 2   | 277743423      | rs11681351 | A            | G            | 0.3941 | 0.0259      | 0.0024         | 5.45E-27 |
| 2   | 28261163       | rs6731650 | A            | C            | 0.7843 | -0.0150     | 0.0026         | 4.27E-09 |
| 2   | 27608115       | rs1647284 | T            | C            | 0.3896 | 0.0253      | 0.0024         | 4.71E-26 |
| 2   | 27808154       | rs6734059 | T            | C            | 0.7991 | -0.0189     | 0.0025         | 1.18E-13 |
| 2   | 27595756       | rs1528533 | C            | G            | 0.3897 | 0.0253      | 0.0024         | 5.15E-26 |
| 2   | 28143017       | rs10173848 | T            | G            | 0.7975 | -0.0155     | 0.0026         | 1.89E-09 |
| 2   | 28003174       | rs13030345 | T            | G            | 0.1794 | -0.0257     | 0.0025         | 6.33E-24 |
| 2   | 28029649       | rs4665392 | A            | G            | 0.7946 | -0.0146     | 0.0026         | 1.35E-08 |
| 2   | 27640325       | rs4665976 | A            | G            | 0.6098 | -0.0253     | 0.0024         | 4.33E-26 |
| 2   | 27844601       | rs1881396 | T            | G            | 0.7975 | -0.0187     | 0.0025         | 1.71E-13 |
| 2   | 27725761       | rs715326 | T            | C            | 0.3789 | 0.0313      | 0.0041         | 1.78E-14 |
| 2   | 27667297       | rs4803  | A            | G            | 0.6106 | -0.0254     | 0.0024         | 4.15E-26 |
| 2   | 27462405       | rs2014252 | A            | T            | 0.2878 | 0.0169      | 0.0025         | 7.46E-12 |
| 2   | 28079775       | rs4233720 | A            | G            | 0.8261 | -0.0152     | 0.0026         | 5.99E-09 |
| 2   | 27851120       | rs12615690 | T            | C            | 0.5272 | 0.0133      | 0.0024         | 2.51E-08 |
| 2   | 27642734       | rs11675428 | A            | C            | 0.8181 | -0.0235     | 0.0026         | 2.23E-19 |
| 2   | 27584666       | rs7586601 | A            | G            | 0.5621 | -0.0311     | 0.0024         | 2.29E-39 |
| 2   | 27796927       | rs6704596 | A            | G            | 0.7982 | -0.0192     | 0.0026         | 5.26E-14 |
| Chr | Position (hg19) | SNP       | Major allele | Minor allele | MAF    | Coefficient | Standard Error | P       |
|-----|----------------|-----------|--------------|--------------|--------|-------------|----------------|---------|
| 2   | 27847364       | rs2384654 | T            | C            | 0.4830 | -0.0131     | 0.0024         | 4.49E-08|
| 2   | 27592423       | rs7602534 | T            | C            | 0.3844 | 0.0261      | 0.0024         | 2.09E-27|
| 2   | 28164553       | rs10170872 | T            | C            | 0.7839 | -0.0152     | 0.0026         | 2.89E-09|
| 2   | 27716494       | rs704795  | A            | G            | 0.3881 | 0.0248      | 0.0024         | 6.89E-25|
| 2   | 27876866       | rs4666010 | T            | C            | 0.7926 | -0.0162     | 0.0026         | 2.62E-10|
| 2   | 27832055       | rs2384656 | A            | G            | 0.7348 | 0.0335      | 0.0025         | 1.17E-42|
| 2   | 27733452       | rs4425043 | A            | G            | 0.3851 | 0.0267      | 0.0024         | 1.86E-28|
| 2   | 27766284       | rs465991  | A            | G            | 0.2653 | -0.0336     | 0.0024         | 7.98E-43|
| 2   | 28078994       | rs7426295 | A            | G            | 0.2159 | 0.0153      | 0.0025         | 2.06E-09|
| 2   | 28151354       | rs10185472 | T            | C            | 0.7915 | -0.0152     | 0.0026         | 2.89E-09|
| 2   | 27831607       | rs6547735 | T            | C            | 0.8120 | -0.0171     | 0.0029         | 3.24E-09|
| 2   | 28121190       | rs7592580 | T            | C            | 0.1736 | 0.0144      | 0.0026         | 3.90E-08|
| 2   | 27794150       | rs4260197 | C            | G            | 0.5326 | 0.0138      | 0.0024         | 8.09E-09|
| 2   | 27827196       | rs2141372 | T            | G            | 0.2026 | 0.0200      | 0.0026         | 4.63E-15|
| 2   | 27419282       | rs1275501 | T            | G            | 0.2864 | 0.0168      | 0.0025         | 1.25E-11|
| 2   | 27729480       | rs2293571 | A            | G            | 0.3843 | 0.0263      | 0.0024         | 1.01E-27|
| 2   | 27807624       | rs1026621 | A            | G            | 0.4816 | -0.0132     | 0.0024         | 3.55E-08|
| 2   | 27626945       | rs2911712 | A            | T            | 0.6104 | -0.0253     | 0.0024         | 4.57E-26|
| 2   | 27730940       | rs1260326 | T            | C            | 0.4088 | -0.0439     | 0.0024         | 1.30E-77|
| 2   | 28205581       | rs7577342 | T            | C            | 0.7856 | -0.0157     | 0.0025         | 7.29E-10|
| 2   | 27786188       | rs10208529 | A            | T            | 0.7347 | 0.0336      | 0.0024         | 7.92E-43|
| 2   | 28191629       | rs1841068 | T            | C            | 0.7863 | -0.0145     | 0.0026         | 1.58E-08|
| 2   | 27928797       | rs13030973 | T            | C            | 0.7885 | 0.0284      | 0.0025         | 2.01E-29|
| 2   | 27967260       | rs13023194 | C            | G            | 0.1818 | -0.0281     | 0.0031         | 1.20E-19|
| 2   | 27556721       | rs3739095 | A            | G            | 0.4294 | 0.0295      | 0.0024         | 1.46E-35|

Note: In total, 233 SNPs significantly associated with mannose (\(P_{QTL} \leq 5 \times 10^{-8}\), LD-\(r^2 > 0.1\)) were identified as candidate genetic IVs. The remaining 12 IVs were further examined for potential pleiotropic effects by heterogeneity in dependent instruments (HEIDI) outlier detection. In the end, there are 12 SNPs that meet the requirements of the IVs, including rs2068834, rs10189899, rs4666052, rs2305929, rs7349418, rs1561535, rs11684134, rs13013484, rs11681351, rs6547735, rs2141372, rs13030973, which are...
marked in gray background.
### eTable 4. Association Between SNPs Selected as Genetic IV for Mannose and ARDS Risk in MEARDS GWAS

| Chr | Position (hg19) | SNP     | Major allele | Minor allele | MAF   | N   | OR     | Standard Error | P     |
|-----|----------------|---------|--------------|--------------|-------|-----|--------|----------------|-------|
| 2   | 27544285       | rs1122227 | T            | C            | 0.2147 | 1630 | 0.7972 | 0.1078         | 0.0355|
| 2   | 27873326       | rs8731   | G            | C            | 0.2101 | 1630 | 1.0640 | 0.1070         | 0.5619|
| 2   | 27504312       | rs1992291 | G            | A            | 0.2291 | 1630 | 0.8154 | 0.1048         | 0.0514|
| 2   | 27825715       | rs12467476 | C          | T            | 0.2819 | 1630 | 1.1150 | 0.0951         | 0.2518|
| 2   | 28418189       | rs13000936 | A          | G            | 0.3233 | 1630 | 1.0260 | 0.0938         | 0.7831|
| 2   | 28225861       | rs11692105 | T          | G            | 0.2098 | 1630 | 0.8616 | 0.1090         | 0.1717|
| 2   | 28199424       | rs12465000 | G          | A            | 0.2144 | 1630 | 1.0120 | 0.1066         | 0.9120|
| 2   | 28344285       | rs4401177   | A          | G            | 0.1184 | 1630 | 1.0790 | 0.1312         | 0.5602|
| 2   | 27853245       | rs13002853 | G          | C            | 0.2764 | 1630 | 1.1250 | 0.0951         | 0.2158|
| 2   | 27839539       | rs2068834   | C          | T            | 0.2966 | 1630 | 1.1000 | 0.0944         | 0.3114|
| 2   | 27688601       | rs1647276   | T          | C            | 0.3709 | 1630 | 0.8070 | 0.0897         | 0.0168|
| 2   | 27508710       | rs11686131 | T          | C            | 0.2135 | 1630 | 0.8091 | 0.1077         | 0.0492|
| 2   | 27579231       | rs6760828   | C          | T            | 0.3736 | 1630 | 0.7967 | 0.0892         | 0.0109|
| 2   | 27743154       | rs780092    | G          | A            | 0.1512 | 1630 | 1.0400 | 0.1210         | 0.7439|
| 2   | 27519153       | rs13404327  | T          | G            | 0.2672 | 1630 | 0.8340 | 0.1001         | 0.0698|
| 2   | 27961344       | rs1317580   | C          | G            | 0.2748 | 1630 | 1.1180 | 0.0944         | 0.2370|
| 2   | 28088580       | rs4666028   | A          | T            | 0.1709 | 1630 | 1.1340 | 0.1148         | 0.2739|
| 2   | 27811722       | rs12478841  | G          | A            | 0.2825 | 1630 | 1.1120 | 0.0951         | 0.2647|
| 2   | 27528692       | rs4665963   | C          | T            | 0.2678 | 1630 | 0.8386 | 0.1000         | 0.0784|
| 2   | 27767107       | rs1972669   | T          | G            | 0.4972 | 1630 | 0.8714 | 0.0860         | 0.1093|
| 2   | 28107692       | rs6708889   | C          | T            | 0.2064 | 1630 | 1.0240 | 0.1087         | 0.8264|
| 2   | 27644464       | rs1728922   | C          | A            | 0.3715 | 1630 | 0.8094 | 0.0895         | 0.0181|
| 2   | 27995931       | rs3792252   | G          | A            | 0.2488 | 1630 | 1.0850 | 0.1005         | 0.4154|
| 2   | 27722416       | rs1260320   | A          | G            | 0.3699 | 1630 | 0.7876 | 0.0899         | 0.0079|
| 2   | 27855397       | rs10173720  | T          | A            | 0.2107 | 1630 | 1.0620 | 0.1070         | 0.5746|
| 2   | 27550967       | rs1049817   | G          | A            | 0.3736 | 1630 | 0.7945 | 0.0890         | 0.0098|
| 2   | 27750546       | rs2911711   | T          | A            | 0.4822 | 1630 | 1.2340 | 0.0849         | 0.0134|
| 2   | 27933642       | rs4616435   | T          | C            | 0.2347 | 1630 | 1.1210 | 0.1011         | 0.2583|
| Chr | Position (hg19) | SNP    | Major allele | Minor allele | MAF    | N     | OR    | Standard Error | P     |
|-----|----------------|--------|--------------|--------------|--------|-------|-------|----------------|-------|
| 2   | 27715207       | rs8395 | A            | T            | 0.3675 | 1630  | 0.8150| 0.0898         | 0.0227|
| 2   | 28200152       | rs233737 | G          | A            | 0.2141 | 1630  | 1.0140| 0.1066         | 0.8973|
| 2   | 28367761       | rs6751559 | G          | T            | 0.1003 | 1630  | 1.2930| 0.1361         | 0.0589|
| 2   | 28301540       | rs937813 | C          | T            | 0.1215 | 1630  | 1.1540| 0.1297         | 0.2702|
| 2   | 27801418       | rs1919126 | C          | A            | 0.4975 | 1630  | 0.8754| 0.0860         | 0.1218|
| 2   | 28281545       | rs6547820 | G          | A            | 0.2061 | 1630  | 1.0260| 0.1087         | 0.8146|
| 2   | 28523834       | rs12617913 | C          | T            | 0.3699 | 1630  | 0.9063| 0.0899         | 0.2737|
| 2   | 28232279       | rs2839791 | A          | C            | 0.2135 | 1630  | 1.0190| 0.1066         | 0.8616|
| 2   | 27839832       | rs7571558 | G          | C            | 0.2064 | 1630  | 1.0790| 0.1064         | 0.4768|
| 2   | 27798611       | rs965813 | A          | T            | 0.2043 | 1630  | 1.0940| 0.1067         | 0.3999|
| 2   | 28396483       | rs7586645 | A          | G            | 0.3196 | 1630  | 1.0420| 0.0935         | 0.6585|
| 2   | 27910706       | rs13023094 | C          | A            | 0.2298 | 1630  | 1.1370| 0.1019         | 0.2071|
| 2   | 27995781       | rs3736594 | A          | C            | 0.2546 | 1630  | 1.0630| 0.0995         | 0.5375|
| 2   | 28090059       | rs10171517 | T          | C            | 0.2080 | 1630  | 1.0110| 0.1073         | 0.9153|
| 2   | 28079344       | rs4233719 | A          | C            | 0.2150 | 1630  | 1.0070| 0.1065         | 0.9457|
| 2   | 27802805       | rs3811644 | G          | A            | 0.2043 | 1630  | 1.0760| 0.1069         | 0.4959|
| 2   | 27741237       | rs780094 | T          | C            | 0.4239 | 1630  | 1.2400| 0.0861         | 0.0125|
| 2   | 27952406       | rs12994085 | C          | T            | 0.2273 | 1630  | 1.1090| 0.1025         | 0.3126|
| 2   | 27840640       | rs4666002 | C          | G            | 0.2825 | 1630  | 1.1110| 0.0951         | 0.2668|
| 2   | 27801759       | rs1919128 | G          | A            | 0.2822 | 1630  | 1.1140| 0.0951         | 0.2563|
| 2   | 27574953       | rs4665969 | C          | T            | 0.3718 | 1630  | 0.7821| 0.0894         | 0.0060|
| 2   | 27706640       | rs2272417 | C          | T            | 0.3883 | 1630  | 0.7955| 0.0888         | 0.0100|
| 2   | 27663416       | rs1260342 | T          | G            | 0.3709 | 1630  | 0.8071| 0.0895         | 0.0166|
| 2   | 27488432       | rs6547521 | C          | G            | 0.3052 | 1630  | 0.8675| 0.0949         | 0.1342|
| 2   | 27846645       | rs1528403 | G          | C            | 0.4865 | 1630  | 1.1290| 0.0861         | 0.1580|
| 2   | 27895073       | rs2178198 | T          | C            | 0.1374 | 1630  | 1.1420| 0.1235         | 0.2810|
| 2   | 28082494       | rs4578809 | A          | G            | 0.1712 | 1630  | 1.1400| 0.1147         | 0.2545|
| 2   | 27426878       | rs1275522 | C          | T            | 0.3028 | 1630  | 0.8708| 0.0948         | 0.1446|
| 2   | 27721971       | rs813592 | C          | T            | 0.3702 | 1630  | 0.7910| 0.0899         | 0.0091|
| 2   | 28256831       | rs9309658 | A          | G            | 0.2135 | 1630  | 1.0190| 0.1066         | 0.8616|
| 2   | 27637235       | rs2010087 | T          | C            | 0.3681 | 1630  | 0.8144| 0.0896         | 0.0220|
| Chr | Position (hg19) | SNP      | Major allele | Minor allele | MAF     | N      | OR      | Standard Error | P      |
|-----|----------------|----------|--------------|--------------|---------|--------|---------|----------------|--------|
| 2   | 27613617       | rs11891554 | A            | G            | 0.0454  | 1630   | 1.0270  | 0.2049         | 0.8977 |
| 2   | 27424636       | rs1395    | G            | A            | 0.3172  | 1630   | 0.8615  | 0.0937         | 0.1115 |
| 2   | 27455726       | rs13399758 | C            | T            | 0.0629  | 1630   | 0.9127  | 0.1813         | 0.6144 |
| 2   | 27449293       | rs7593448 | G            | C            | 0.3043  | 1630   | 0.8708  | 0.0947         | 0.1440 |
| 2   | 27731212       | rs3817588 | C            | T            | 0.1748  | 1630   | 0.9346  | 0.1170         | 0.5633 |
| 2   | 28418031       | rs6712705 | C            | T            | 0.3252  | 1630   | 1.0120  | 0.0940         | 0.8949 |
| 2   | 27783801       | rs4665382 | C            | T            | 0.2822  | 1630   | 1.1140  | 0.0951         | 0.2563 |
| 2   | 27393030       | rs1659689 | A            | G            | 0.3064  | 1630   | 0.8807  | 0.0938         | 0.1758 |
| 2   | 27958855       | rs6753736 | C            | G            | 0.2279  | 1630   | 1.1070  | 0.1025         | 0.3221 |
| 2   | 27975394       | rs6547796 | T            | C            | 0.2503  | 1630   | 1.1180  | 0.0991         | 0.2591 |
| 2   | 28520083       | rs10189899| A            | G            | 0.3613  | 1630   | 0.8875  | 0.0904         | 0.1866 |
| 2   | 27659491       | rs780102  | C            | T            | 0.3709  | 1630   | 0.8071  | 0.0895         | 0.0166 |
| 2   | 28162861       | rs4390729 | T            | C            | 0.2138  | 1630   | 1.0170  | 0.1066         | 0.8762 |
| 2   | 27746832       | rs8179252 | C            | A            | 0.3733  | 1630   | 0.7942  | 0.0898         | 0.0103 |
| 2   | 27604279       | rs4582    | G            | A            | 0.3709  | 1630   | 0.8053  | 0.0894         | 0.0154 |
| 2   | 28162274       | rs13416434| T            | C            | 0.2135  | 1630   | 1.0190  | 0.1066         | 0.8798 |
| 2   | 27742603       | rs780093  | T            | C            | 0.4236  | 1630   | 1.2270  | 0.0859         | 0.0172 |
| 2   | 27703495       | rs1260345 | G            | A            | 0.3926  | 1630   | 0.7854  | 0.0889         | 0.0066 |
| 2   | 27611469       | rs7594812 | G            | A            | 0.3712  | 1630   | 0.8045  | 0.0894         | 0.0149 |
| 2   | 27452784       | rs6717980 | C            | T            | 0.3037  | 1630   | 0.8744  | 0.0949         | 0.1571 |
| 2   | 27519254       | rs13404446| A            | G            | 0.2672  | 1630   | 0.8340  | 0.1001         | 0.0698 |
| 2   | 27841305       | rs6756238 | G            | A            | 0.4969  | 1630   | 0.8797  | 0.0863         | 0.1372 |
| 2   | 27852637       | rs6547738 | G            | A            | 0.4896  | 1630   | 1.1400  | 0.0860         | 0.1285 |
| 2   | 28530720       | rs4666052 | A            | G            | 0.3623  | 1630   | 0.8939  | 0.0906         | 0.2157 |
| 2   | 28113911       | rs2305929 | G            | A            | 0.2015  | 1630   | 1.1260  | 0.1066         | 0.2673 |
| 2   | 27443196       | rs4665958 | G            | A            | 0.3037  | 1630   | 0.8743  | 0.0946         | 0.1559 |
| 2   | 27987046       | rs12477908| A            | C            | 0.2552  | 1630   | 1.0700  | 0.0991         | 0.4932 |
| 2   | 28443050       | rs7349418 | C            | T            | 0.4745  | 1630   | 1.1210  | 0.0861         | 0.1843 |
| 2   | 27652153       | rs780100  | T            | G            | 0.3709  | 1630   | 0.8071  | 0.0895         | 0.0166 |
| 2   | 28144067       | rs1870325 | G            | A            | 0.2058  | 1630   | 1.0270  | 0.1087         | 0.8081 |
| 2   | 27471025       | rs1561535 | T            | C            | 0.3009  | 1630   | 0.8645  | 0.0952         | 0.1262 |
| Chr | Position (hg19) | SNP       | Major allele | Minor allele | MAF   | N    | OR     | Standard Error | P    |
|-----|----------------|-----------|--------------|--------------|-------|------|--------|----------------|------|
| 2   | 28255302       | rs937812  | C            | T            | 0.2135| 1630 | 1.0190 | 0.1066         | 0.8616|
| 2   | 27851918       | rs3749147 | A            | G            | 0.2767| 1630 | 1.1150 | 0.0951         | 0.2509|
| 2   | 27932587       | rs6727388 | G            | A            | 0.2347| 1630 | 1.1210 | 0.1011         | 0.2583|
| 2   | 27801493       | rs1919127 | C            | T            | 0.2825| 1630 | 1.1120 | 0.0951         | 0.2647|
| 2   | 28213424       | rs10175508| C            | T            | 0.2141| 1630 | 1.0140 | 0.1066         | 0.8973|
| 2   | 27748624       | rs1260333 | A            | G            | 0.4718| 1630 | 1.2240 | 0.0847         | 0.0170|
| 2   | 28018293       | rs4666012 | G            | A            | 0.1951| 1630 | 1.0550 | 0.1100         | 0.6276|
| 2   | 28258027       | rs7593127 | G            | A            | 0.2135| 1630 | 1.0190 | 0.1066         | 0.8616|
| 2   | 28517861       | rs4666051 | A            | G            | 0.3607| 1630 | 0.8916 | 0.0906         | 0.2052|
| 2   | 28140349       | rs2337372 | A            | G            | 0.1678| 1630 | 1.1540 | 0.1152         | 0.2147|
| 2   | 28219941       | rs1458398 | A            | G            | 0.2141| 1630 | 1.0140 | 0.1066         | 0.8973|
| 2   | 27968454       | rs9967838 | A            | C            | 0.2509| 1630 | 1.1410 | 0.0987         | 0.1823|
| 2   | 27818721       | rs1919129 | G            | C            | 0.2061| 1630 | 1.0860 | 0.1061         | 0.4346|
| 2   | 27536380       | rs4665965 | C            | T            | 0.2681| 1630 | 0.8251 | 0.1000         | 0.0547|
| 2   | 27693485       | rs1647266 | C            | T            | 0.3709| 1630 | 0.8070 | 0.0897         | 0.0168|
| 2   | 27450724       | rs3769143 | A            | G            | 0.3043| 1630 | 0.8708 | 0.0947         | 0.1440|
| 2   | 27648726       | rs4665978 | C            | T            | 0.4184| 1630 | 0.8159 | 0.0882         | 0.0211|
| 2   | 27432547       | rs1275530 | A            | G            | 0.3028| 1630 | 0.8708 | 0.0948         | 0.1446|
| 2   | 27755825       | rs4665987 | A            | G            | 0.2822| 1630 | 1.1430 | 0.0950         | 0.1600|
| 2   | 27441397       | rs1275538 | A            | G            | 0.3031| 1630 | 0.8697 | 0.0948         | 0.1409|
| 2   | 28094270       | rs13016573| G            | C            | 0.1709| 1630 | 1.1340 | 0.1148         | 0.2739|
| 2   | 27430781       | rs1275528 | A            | G            | 0.3028| 1630 | 0.8708 | 0.0948         | 0.1446|
| 2   | 27812252       | rs6760250 | A            | G            | 0.2825| 1630 | 1.1120 | 0.0951         | 0.2647|
| 2   | 27567407       | rs6743819 | T            | G            | 0.3733| 1630 | 0.7921 | 0.0892         | 0.0090|
| 2   | 27791555       | rs4665383 | G            | C            | 0.2822| 1630 | 1.1140 | 0.0951         | 0.2563|
| 2   | 27600239       | rs13472   | A            | G            | 0.3663| 1630 | 0.8106 | 0.0897         | 0.0192|
| 2   | 27972833       | rs12104449| G            | A            | 0.1279| 1630 | 1.0800 | 0.1268         | 0.5462|
| 2   | 27398196       | rs2580754 | T            | A            | 0.3083| 1630 | 0.8585 | 0.0938         | 0.1040|
| 2   | 27566502       | rs11689803| A            | T            | 0.2436| 1630 | 0.8032 | 0.1039         | 0.0349|
| 2   | 27860258       | rs2141371 | G            | A            | 0.2721| 1630 | 0.8677 | 0.0983         | 0.1486|
| 2   | 28202936       | rs898032  | C            | G            | 0.2144| 1630 | 1.0120 | 0.1066         | 0.9120|
| Chr | Position (hg19) | SNP   | Major allele | Minor allele | MAF  | N    | OR   | Standard Error | P     |
|-----|----------------|-------|--------------|--------------|------|------|------|----------------|-------|
| 2   | 26124171       | rs10177845 | G             | A            | 0.2144 | 1630| 1.0130 | 0.1065          | 0.9037 |
| 2   | 27416702       | rs1275504  | A             | T            | 0.3393 | 1630| 0.8779 | 0.0919          | 0.1564 |
| 2   | 28101938       | rs6706209  | C             | T            | 0.2163 | 1630| 1.0240 | 0.1054          | 0.8202 |
| 2   | 27589810       | rs2280737  | C             | T            | 0.3681 | 1630| 0.8121 | 0.0895          | 0.0201 |
| 2   | 27728777       | rs2293572  | G             | C            | 0.3681 | 1630| 0.8150 | 0.0898          | 0.0227 |
| 2   | 27635582       | rs1060525  | G             | A            | 0.3715 | 1630| 0.8094 | 0.0895          | 0.0181 |
| 2   | 280529165      | rs10165668 | G             | A            | 0.3623 | 1630| 0.8939 | 0.0906          | 0.2157 |
| 2   | 28127811       | rs6706209  | C             | T            | 0.2163 | 1630| 1.0240 | 0.1054          | 0.8202 |
| 2   | 27728777       | rs2293572  | G             | C            | 0.3681 | 1630| 0.8150 | 0.0898          | 0.0227 |
| 2   | 27635582       | rs1060525  | G             | A            | 0.3715 | 1630| 0.8094 | 0.0895          | 0.0181 |
| 2   | 280529165      | rs10165668 | G             | A            | 0.3623 | 1630| 0.8939 | 0.0906          | 0.2157 |
| 2   | 28127811       | rs6706209  | C             | T            | 0.2163 | 1630| 1.0240 | 0.1054          | 0.8202 |
| 2   | 27728777       | rs2293572  | G             | C            | 0.3681 | 1630| 0.8150 | 0.0898          | 0.0227 |
| 2   | 27635582       | rs1060525  | G             | A            | 0.3715 | 1630| 0.8094 | 0.0895          | 0.0181 |
| 2   | 280529165      | rs10165668 | G             | A            | 0.3623 | 1630| 0.8939 | 0.0906          | 0.2157 |
| Chr | Position (hg19) | SNP    | Major allele | Minor allele | MAF   | N    | OR   | Standard Error | P    |
|-----|----------------|--------|--------------|--------------|-------|------|------|----------------|------|
| 2   | 27677691       | rs780104 | A            | G            | 0.3702 | 1630 | 0.8085 | 0.0896          | 0.0177 |
| 2   | 27830990       | rs6547734 | G            | T            | 0.4975 | 1630 | 0.8754 | 0.0860          | 0.1218 |
| 2   | 27718474       | rs780090 | T            | C            | 0.0844 | 1630 | 1.4760 | 0.1457          | 0.0076 |
| 2   | 28209283       | rs10209126 | C            | T            | 0.2141 | 1630 | 1.0140 | 0.1066          | 0.8973 |
| 2   | 28023120       | rs11127125 | C            | T            | 0.2028 | 1630 | 1.0080 | 0.1085          | 0.9410 |
| 2   | 28098724       | rs13411592 | G            | A            | 0.2150 | 1630 | 1.0070 | 0.1065          | 0.9457 |
| 2   | 28118662       | rs7607546 | G            | A            | 0.1712 | 1630 | 1.1280 | 0.1145          | 0.2936 |
| 2   | 27934731       | rs6727215 | A            | G            | 0.2347 | 1630 | 1.1210 | 0.1011          | 0.2583 |
| 2   | 28090820       | rs898034 | T            | C            | 0.2080 | 1630 | 1.0110 | 0.1073          | 0.9153 |
| 2   | 27980944       | rs10209020 | C            | T            | 0.2497 | 1630 | 1.1020 | 0.0992          | 0.3294 |
| 2   | 27774702       | rs2384628 | G            | T            | 0.4905 | 1630 | 1.1670 | 0.0861          | 0.0724 |
| 2   | 27684734       | rs780107 | G            | A            | 0.3709 | 1630 | 0.8070 | 0.0897          | 0.0168 |
| 2   | 27558252       | rs11684134 | G            | A            | 0.4153 | 1630 | 0.8430 | 0.0860          | 0.0470 |
| 2   | 27568565       | rs10205219 | C            | T            | 0.3736 | 1630 | 0.7913 | 0.0892          | 0.0087 |
| 2   | 28020966       | rs3935148 | A            | T            | 0.1939 | 1630 | 1.0330 | 0.1108          | 0.7686 |
| 2   | 27796526       | rs10165098 | C            | T            | 0.4988 | 1630 | 0.8688 | 0.0862          | 0.1027 |
| 2   | 28136351       | rs1458396 | A            | G            | 0.2144 | 1630 | 1.0130 | 0.1065          | 0.9066 |
| 2   | 27460968       | rs1141313 | G            | A            | 0.3037 | 1630 | 0.8744 | 0.0949          | 0.1571 |
| 2   | 27730817       | rs8179219 | A            | G            | 0.0472 | 1630 | 0.9546 | 0.2046          | 0.8202 |
| 2   | 27712408       | rs7583698 | T            | C            | 0.0485 | 1630 | 1.0200 | 0.2000          | 0.9192 |
| 2   | 27613031       | rs12476704 | A            | C            | 0.3669 | 1630 | 0.8095 | 0.0896          | 0.0183 |
| 2   | 27951658       | rs867282 | T            | C            | 0.2202 | 1630 | 1.1070 | 0.1046          | 0.3307 |
| 2   | 27715416       | rs2303369 | T            | C            | 0.3669 | 1630 | 0.8186 | 0.0897          | 0.0256 |
| 2   | 28189280       | rs1902966 | G            | A            | 0.2138 | 1630 | 1.0150 | 0.1066          | 0.8868 |
| 2   | 27892023       | rs2272406 | T            | A            | 0.2294 | 1630 | 1.1410 | 0.1019          | 0.1957 |
| 2   | 28155195       | rs6547815 | T            | A            | 0.2058 | 1630 | 1.0270 | 0.1087          | 0.8081 |
| 2   | 27698343       | rs780117 | G            | C            | 0.3702 | 1630 | 0.8085 | 0.0896          | 0.0177 |
| 2   | 27988821       | rs13013484 | G            | A            | 0.2663 | 1630 | 1.0780 | 0.0978          | 0.4442 |
| 2   | 27772879       | rs6749052 | A            | T            | 0.4979 | 1630 | 0.8735 | 0.0861          | 0.1160 |
| 2   | 28268467       | rs6738887 | C            | T            | 0.2135 | 1630 | 1.0190 | 0.1066          | 0.8616 |
| 2   | 27631191       | rs7563162 | T            | C            | 0.3718 | 1630 | 0.8088 | 0.0895          | 0.0177 |
| Chr | Position (hg19) | SNP   | Major allele | Minor allele | MAF   | N   | OR   | Standard Error | P     |
|-----|----------------|-------|--------------|--------------|-------|-----|------|----------------|-------|
| 2   | 27681598       | rs780106 | C            | A            | 0.3709| 1630| 0.8070 | 0.0897         | 0.0168|
| 2   | 27646770       | rs6547626 | T            | C            | 0.3715| 1630| 0.8094 | 0.0895         | 0.0181|
| 2   | 28394293       | rs17759746 | C            | T            | 0.0997| 1630| 1.2800 | 0.1364         | 0.0699|
| 2   | 28235184       | rs7602328 | G            | A            | 0.2135| 1630| 1.0190 | 0.1066         | 0.8616|
| 2   | 27663215       | rs1260341 | A            | T            | 0.3709| 1630| 0.8071 | 0.0895         | 0.0166|
| 2   | 27441302       | rs1275537 | C            | G            | 0.3031| 1630| 0.8697 | 0.0948         | 0.1409|
| 2   | 27743423       | rs11681351 | A            | G            | 0.3733| 1630| 0.7942 | 0.0898         | 0.0103|
| 2   | 28261163       | rs6731650 | C            | A            | 0.2135| 1630| 1.0190 | 0.1066         | 0.8616|
| 2   | 27608115       | rs1647284 | T            | C            | 0.3712| 1630| 0.8045 | 0.0894         | 0.0149|
| 2   | 27808154       | rs6734059 | C            | T            | 0.2052| 1630| 1.0850 | 0.1062         | 0.4442|
| 2   | 27595756       | rs1528533 | C            | G            | 0.3709| 1630| 0.8011 | 0.0895         | 0.0132|
| 2   | 28143017       | rs10173848 | G            | T            | 0.2003| 1630| 1.0020 | 0.1099         | 0.9823|
| 2   | 28003174       | rs13030345 | T            | G            | 0.1985| 1630| 1.1030 | 0.1062         | 0.3556|
| 2   | 28029649       | rs4665392 | G            | A            | 0.2040| 1630| 1.0060 | 0.1084         | 0.9533|
| 2   | 27640325       | rs4665976 | G            | A            | 0.3715| 1630| 0.8094 | 0.0895         | 0.0181|
| 2   | 27844601       | rs1881396 | G            | T            | 0.2046| 1630| 1.0640 | 0.1069         | 0.5632|
| 2   | 27725761       | rs715326 | T            | C            | 0.3666| 1630| 0.8041 | 0.0899         | 0.0153|
| 2   | 27667297       | rs4803  | G            | A            | 0.3709| 1630| 0.8070 | 0.0897         | 0.0168|
| 2   | 27462405       | rs2014252 | A            | T            | 0.3040| 1630| 0.8739 | 0.0948         | 0.1552|
| 2   | 28079775       | rs4233720 | G            | A            | 0.1712| 1630| 1.1400 | 0.1147         | 0.2545|
| 2   | 27851120       | rs12615690 | C            | T            | 0.4902| 1630| 1.1400 | 0.0862         | 0.1294|
| 2   | 27642734       | rs11675428 | C            | A            | 0.1433| 1630| 0.8326 | 0.1283         | 0.1534|
| 2   | 27584666       | rs7586601 | G            | A            | 0.4144| 1630| 0.8177 | 0.0876         | 0.0216|
| 2   | 27796927       | rs6704596 | G            | A            | 0.2037| 1630| 1.0800 | 0.1072         | 0.4725|
| 2   | 27847364       | rs2384654 | C            | T            | 0.4957| 1630| 0.8836 | 0.0862         | 0.1511|
| 2   | 27592423       | rs7602534 | T            | C            | 0.3672| 1630| 0.8082 | 0.0898         | 0.0177|
| 2   | 28164553       | rs10170872 | C            | T            | 0.2135| 1630| 1.0190 | 0.1066         | 0.8616|
| 2   | 27716494       | rs704795  | A            | G            | 0.3712| 1630| 0.8095 | 0.0897         | 0.0184|
| 2   | 27878686       | rs4666010 | C            | T            | 0.2098| 1630| 1.0570 | 0.1073         | 0.6033|
| 2   | 27832055       | rs2384656 | G            | A            | 0.2822| 1630| 1.1130 | 0.0951         | 0.2601|
| 2   | 27733452       | rs4425043 | A            | G            | 0.3675| 1630| 0.8118 | 0.0899         | 0.0205|
| Chr | Position (hg19) | SNP       | Major allele | Minor allele | MAF    | N     | OR       | Standard Error | P       |
|-----|----------------|-----------|--------------|--------------|--------|-------|----------|----------------|---------|
| 2   | 27766284       | rs4665991 | A            | G            | 0.2804 | 1630  | 1.1290   | 0.0954         | 0.2049  |
| 2   | 28078994       | rs7426295 | A            | G            | 0.2150 | 1630  | 1.0070   | 0.1065         | 0.9457  |
| 2   | 28151354       | rs10185472| G            | A            | 0.2058 | 1630  | 1.0270   | 0.1087         | 0.8081  |
| 2   | 27815510       | rs13022873| C            | A            | 0.2825 | 1630  | 1.1100   | 0.0950         | 0.2715  |
| 2   | 27831607       | rs6547735 | C            | T            | 0.2061 | 1630  | 1.0860   | 0.1061         | 0.4346  |
| 2   | 28121190       | rs7592580 | T            | C            | 0.1681 | 1630  | 1.1520   | 0.1152         | 0.2181  |
| 2   | 27794150       | rs4260197 | G            | C            | 0.4868 | 1630  | 1.1550   | 0.0862         | 0.0947  |
| 2   | 27827196       | rs2141372 | T            | G            | 0.2061 | 1630  | 1.0860   | 0.1061         | 0.4346  |
| 2   | 27419282       | rs1275501 | T            | G            | 0.3028 | 1630  | 0.8708   | 0.0948         | 0.1446  |
| 2   | 27729480       | rs2293571 | A            | G            | 0.3681 | 1630  | 0.8150   | 0.0898         | 0.0227  |
| 2   | 27807624       | rs13026621| G            | A            | 0.4979 | 1630  | 0.8735   | 0.0861         | 0.1160  |
| 2   | 27626945       | rs2911712 | T            | A            | 0.3718 | 1630  | 0.8129   | 0.0893         | 0.0203  |
| 2   | 27730940       | rs1260326 | T            | C            | 0.4310 | 1630  | 1.2070   | 0.0861         | 0.0290  |
| 2   | 28205581       | rs7577342 | C            | T            | 0.2150 | 1630  | 1.0080   | 0.1067         | 0.9422  |
| 2   | 27786188       | rs10208529| T            | A            | 0.2825 | 1630  | 1.1120   | 0.0951         | 0.2647  |
| 2   | 28191629       | rs1841066 | C            | T            | 0.2132 | 1630  | 1.0020   | 0.1072         | 0.9862  |
| 2   | 27928797       | rs13030973| C            | T            | 0.2347 | 1630  | 1.1210   | 0.1011         | 0.2583  |
| 2   | 27967260       | rs13023194| C            | G            | 0.1933 | 1630  | 1.0940   | 0.1069         | 0.4025  |
| 2   | 27556721       | rs3739095 | A            | G            | 0.4120 | 1630  | 0.8015   | 0.0878         | 0.0117  |

Note: The remaining 12 IVs were further examined for potential pleiotropic effects by heterogeneity in dependent instruments (HEIDI) outlier detection. In the end, there are 12 SNPs that meet the requirements of the IVs, including rs2068834, rs10189899, rs4666052, rs2305929, rs7349418, rs1561535, rs11684134, rs13013484, rs11681351, rs6547735, rs2141372, rs13030973, which are marked in gray background.
### Table 5. Pearson's Correlation Coefficient *r* Between Pairs of Metabolites (X-11440 and X-12850) Measured in Metabolome-wide Association Study

| Metabolite                                      | Pathway                                      | Super pathway | X-11440 | X-12850 |
|------------------------------------------------|----------------------------------------------|---------------|---------|---------|
| 4-androsten-3beta,17beta-diol disulfate 1*     | Sterol, Steroid                              | Lipid         | 0.77    | 0.26    |
| 4-androsten-3beta,17beta-diol disulfate 2*     | Sterol, Steroid                              | Lipid         | 0.76    | 0.19    |
| dehydroisoandrosterone sulfate (DHEA-S)         | Sterol, Steroid                              | Lipid         | 0.66    | 0.11    |
| 5alpha-androstan-3beta,17beta-diol disulfate   | Sterol, Steroid                              | Lipid         | 0.61    | 0.22    |
| androsterone sulfate                           | Sterol, Steroid                              | Lipid         | 0.47    | 0.08    |
| epiandrosterone sulfate                        | Sterol, Steroid                              | Lipid         | 0.46    | 0.06    |
| 5alpha-pregnan-3beta,20alpha-diol disulfate    | Sterol, Steroid                              | Lipid         | 0.35    | 0.08    |
| 3-(4-hydroxyphenyl)lactate                     | Phenylalanine & tyrosine metabolism          | Amino acid    | 0.23    | 0.13    |
| alpha-hydroxyisovalerate                        | Valine, leucine and isoleucine metabolism    | Amino acid    | 0.23    | 0.20    |
| urate                                          | Purine metabolism, urate metabolism          | Nucleotide    | 0.21    | 0.07    |
| X-12244--N-acetylcarnosine                     | Dipeptide                                    | Peptide       | 0.20    | 0.03    |
| 3-methyl-2-oxovalerate                         | Valine, leucine and isoleucine metabolism    | Amino acid    | 0.20    | 0.13    |
| 4-methyl-2-oxopentanoate                       | Valine, leucine and isoleucine metabolism    | Amino acid    | 0.18    | 0.08    |
| 1,5-anhydroglucitol (1,5-AG)                    | Glycolysis, gluconeogenesis, pyruvate metabolism | Carbohydrate | 0.14    | 0.06    |
| creatinine                                     | Creatine metabolism                          | Amino acid    | 0.14    | 0.07    |
| creatinine                                     | Sterol, Steroid                              | Lipid         | 0.14    | 0.10    |
| leucine                                        | Valine, leucine and isoleucine metabolism    | Amino acid    | 0.13    | 0.07    |
| isoleucine                                     | Valine, leucine and isoleucine metabolism    | Amino acid    | 0.12    | 0.11    |
| 3-methyl-2-oxobutyrate                         | Valine, leucine and isoleucine metabolism    | Amino acid    | 0.12    | 0.05    |
| cortisol                                       | Sterol, Steroid                              | Lipid         | 0.12    | 0.13    |
| lactate                                        | Glycolysis, gluconeogenesis, pyruvate metabolism | Carbohydrate | 0.12    | 0.08    |
| phenyllactate (PLA)                            | Phenylalanine & tyrosine metabolism          | Amino acid    | 0.11    | 0.16    |
| 2-hydroxybutyrate (AHB)                        | Cysteine, methionine, SAM, taurine metabolism | Amino acid    | 0.11    | 0.02    |
| Substance                                    | Metabolism                                      | Type                      | Score | P-value |
|----------------------------------------------|-------------------------------------------------|---------------------------|-------|---------|
| 10-undecenoate (11:1n1)                      | Medium chain fatty acid                         | Lipid                     | 0.11  | 0.00    |
| aspartate                                    | Alanine and aspartate metabolism                | Amino acid                | 0.10  | 0.11    |
| proline                                      | Urea cycle; arginine-, proline-, metabolism    | Amino acid                | 0.10  | 0.11    |
| 2-aminovalerate                              | Butanoate metabolism                            | Amino acid                | 0.10  | 0.00    |
| carbamazepine*                               | Drug                                            | Xenobiotics               | 0.10  | 0.12    |
| bilirubin (E,E)*                             | Hemoglobin and porphyrin metabolism             | Cofactors and vitamins    | 0.10  | 0.04    |
| biliverdin                                   | Hemoglobin and porphyrin metabolism             | Cofactors and vitamins    | 0.09  | 0.04    |
| metoprolol acid metabolite*                  | Drug                                            | Xenobiotics               | 0.09  | 0.03    |
| gamma-glutamylglutamate                      | gamma-glutamyl                                  | Peptide                   | 0.09  | 0.21    |
| X-12510--2-aminoocanoic acid                 | Amino fatty acid                                | Amino acid                | 0.09  | 0.10    |
| 1-arachidonoylglycerophosphoinositol*        | Lysolipid                                       | Lipid                     | 0.09  | 0.13    |
| hexadecanediol                                | Fatty acid, dicarboxylate                       | Lipid                     | 0.09  | 0.16    |
| valine                                       | Valine, leucine and isoleucine metabolism       | Amino acid                | 0.09  | 0.03    |
| bilirubin (E,Z or Z,E)*                      | Hemoglobin and porphyrin metabolism             | Cofactors and vitamins    | 0.08  | 0.06    |
| pipecolate                                   | Lysine metabolism                               | Amino acid                | 0.08  | 0.11    |
| oleoylcarnitine                              | Carnitine metabolism                            | Lipid                     | 0.08  | 0.06    |
| adrenate (22:4n6)                            | Long chain fatty acid                           | Lipid                     | 0.08  | 0.07    |
| taurochenodeoxycholate                        | Bile acid metabolism                            | Lipid                     | 0.08  | 0.33    |
| pyroglutamine*                               | Glutamate metabolism                            | Amino acid                | 0.08  | 0.09    |
| gamma-glutamylvaline                         | gamma-glutamyl                                  | Peptide                   | 0.08  | 0.03    |
| beta-hydroxyisovalerate                      | Valine, leucine and isoleucine metabolism       | Amino acid                | 0.08  | 0.04    |
| piperine                                     | Food component, Plant                           | Xenobiotics               | 0.08  | 0.05    |
| X-12441--12-hydroxyicosatetraenoate (12-HETE)| Eicosanoid                                      | Lipid                     | 0.08  | 0.05    |
| gamma-glutamylleucine                        | gamma-glutamyl                                  | Peptide                   | 0.08  | 0.04    |
| X-12990--docosapentaenoic acid (n6-DPA)       | Essential fatty acid                            | Lipid                     | 0.08  | 0.05    |
| dihomo-linoleate (20:2n6)                    | Long chain fatty acid                           | Lipid                     | 0.08  | 0.04    |
| threonine                                    | Glycine, serine and threonine metabolism        | Amino acid                | 0.08  | 0.09    |
| indolelactate                                | Tryptophan metabolism                           | Amino acid                | 0.08  | 0.08    |
| 2-tetradecenoyl carnitine                    | Carnitine metabolism                            | Lipid                     | 0.07  | 0.07    |
| palmitoylcarnitine                           | Carnitine metabolism                            | Lipid                     | 0.07  | 0.05    |
| 2-methylbutyroylcarnitine                    | Valine, leucine and isoleucine metabolism       | Amino acid                | 0.07  | 0.07    |
| Compound                                    | Metabolism                           | Location       | Energy | Cofactors and vitamins |
|---------------------------------------------|--------------------------------------|----------------|--------|------------------------|
| malate                                      | Krebs cycle                          | Energy         | 0.07   | 0.12                   |
| gamma-glutamylmethionine*                   | gamma-glutamyl                       | Peptide        | 0.07   | 0.03                   |
| 1,3,7-trimethylurate                        | Xanthine metabolism                  | Xenobiotics    | 0.07   | 0.10                   |
| palmitate (16:0)                            | Long chain fatty acid                | Lipid          | 0.07   | 0.03                   |
| 3-hydroxybutyrate (BHBA)                    | Ketone bodies                        | Lipid          | 0.07   | 0.07                   |
| methionine                                  | Cysteine, methionine, SAM, taurine   | Amino acid     | 0.07   | 0.09                   |
| phenylalanine                               | Phenylalanine & tyrosine metabolism  | Amino acid     | 0.07   | 0.08                   |
| gamma-glutamylisoleucine*                   | gamma-glutamyl                       | Peptide        | 0.07   | 0.09                   |
| tetradecanedioate                           | Fatty acid, dicarboxylate            | Lipid          | 0.07   | 0.12                   |
| isovaleryl carnitine                        | Valine, leucine and isoleucine       | Amino acid     | 0.07   | 0.02                   |
| X-12100--hydroxytryptophan*                 | Tryptophan metabolism                | Amino acid     | 0.07   | 0.05                   |
| 4-vinylphenol sulfate                       | Benzoate metabolism                  | Xenobiotics    | 0.07   | 0.09                   |
| tryptophan betaine                          | Tryptophan metabolism                | Amino acid     | 0.06   | 0.06                   |
| aspartylphenylalanine                       | Dipeptide                            | Peptide        | 0.06   | 0.13                   |
| taurolithocholate 3-sulfate                 | Bile acid metabolism                 | Lipid          | 0.06   | 0.35                   |
| isovalerate                                 | Fatty acid metabolism                | Lipid          | 0.06   | 0.03                   |
| N2,N2-dimethylguanosine                     | Purine metabolism, guanine containing| Nucleotide     | 0.06   | 0.09                   |
| tryptophan                                  | Tryptophan metabolism                | Amino acid     | 0.06   | 0.04                   |
| 1-palmitoleoylglycerophosphocholine*        | Lysolipid                            | Lipid          | 0.06   | 0.08                   |
| gamma-tocopherol                            | Tocopherol metabolism                | Cofactors and vitamins | 0.06 | 0.00                   |
| gamma-glutamylthreonine*                    | gamma-glutamyl                       | Peptide        | 0.06   | 0.06                   |
| laurycarnitine                              | Carnitine metabolism                 | Lipid          | 0.06   | 0.08                   |
| 2-linoleoylglycerophosphocholine*           | Lysolipid                            | Lipid          | 0.06   | 0.08                   |
| octadecanedioate                            | Fatty acid, dicarboxylate            | Lipid          | 0.06   | 0.12                   |
| glycocholate                                | Bile acid metabolism                 | Lipid          | 0.06   | 0.39                   |
| 5-oxoproline                               | Glutathione metabolism               | Amino acid     | 0.06   | 0.04                   |
| hyodeoxycholate                             | Bile acid metabolism                 | Lipid          | 0.06   | 0.05                   |
| glycoursoxydeoxycholate                     | Bile acid metabolism                 | Lipid          | 0.06   | 0.32                   |
| mannose                                     | Fructose, mannose, galactose, starch, and sucrose metabolism | Carbohydrate | 0.06 | 0.00 |
| X-11593--O-methylascorbate*                 | Ascorbate and aldarate metabolism    | Cofactors and vitamins | 0.06 | 0.03 |
| acetylcarnitine                             | Carnitine metabolism                 | Lipid          | 0.06   | 0.04                   |

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| Compound                                    | Category                | Class                              | Value1 | Value2 |
|--------------------------------------------|-------------------------|------------------------------------|--------|--------|
| gamma-glutamylphenylalanine                | Peptide                 | Amino acid                         | 0.06   | 0.08   |
| glutaroyl carnitine                        | Lysine metabolism       | Amino acid                         | 0.06   | 0.02   |
| glutamate                                  | Glutamate metabolism    | Amino acid                         | 0.05   | 0.03   |
| arachidonate (20:4n6)                      | Long chain fatty acid   | Lipid                              | 0.05   | 0.00   |
| 1-arachidonoylglycerophosphoethanolamin e* | Lysolipid               | Lipid                              | 0.05   | 0.11   |
| 2-palmitoylglycerophosphocholine*          | Lysolipid               | Lipid                              | 0.05   | 0.05   |
| glycylvaline                               | Dipeptide               | Peptide                            | 0.05   | 0.07   |
| N-acetyltreonine                           | Glycine, serine and threonine metabolism | Amino acid | 0.05 | 0.06 |
| oleate (18:1n9)                            | Long chain fatty acid   | Lipid                              | 0.05   | 0.02   |
| N-acetyllalanine                           | Alanine and aspartate metabolism | Amino acid | 0.05 | 0.05 |
| N-(2-furoyl)glycine                        | Food component, Plant   | Xenobiotics                        | 0.05   | -0.02  |
| carnitine                                  | Carnitine metabolism    | Lipid                              | 0.04   | -0.01  |
| 1-linoleoylglycerophosphoethanolamine*     | Lysolipid               | Lipid                              | 0.04   | 0.14   |
| d homo-linolenate (20:3n3 or n6)           | Essential fatty acid    | Lipid                              | 0.04   | 0.00   |
| 2-hydroxypalmitate                         | Fatty acid, monohydroxy | Lipid                              | 0.04   | 0.07   |
| cotinine                                   | Tobacco metabolite      | Xenobiotics                        | 0.04   | 0.09   |
| decanoylcarnitine                          | Carnitine metabolism    | Lipid                              | 0.04   | 0.01   |
| stearate (18:0)                            | Long chain fatty acid   | Lipid                              | 0.04   | 0.02   |
| 7-methylguanine                            | Purine metabolism, guanine containing | Nucleotide | 0.04 | 0.03 |
| 1-linoleoylglycerophosphocholine            | Lysolipid               | Lipid                              | 0.04   | 0.07   |
| phenylalanylphenylalanine                  | Dipeptide               | Peptide                            | 0.04   | 0.04   |
| glycochenodeoxycholate                      | Bile acid metabolism    | Lipid                              | 0.04   | 0.39   |
| 1-palmitoylglycerophosphoinositol*          | Lysolipid               | Lipid                              | 0.04   | 0.12   |
| 1-arachidonoylglycerophosphocholine*       | Lysolipid               | Lipid                              | 0.04   | 0.02   |
| histidine                                  | Histidine metabolism    | Amino acid                         | 0.04   | 0.02   |
| eicosenoate (20:1n9 or 11)                 | Long chain fatty acid   | Lipid                              | 0.04   | 0.02   |
| serotonin (5HT)                            | Tryptophan metabolism   | Amino acid                         | 0.04   | 0.04   |
| pseudouridine                              | Pyrimidine metabolism, uracil containing | Nucleotide | 0.04 | 0.05 |
| 2-oleoylglycerophosphocholine*             | Lysolipid               | Lipid                              | 0.04   | 0.08   |
| hexanoylcarnitine                          | Carnitine metabolism    | Lipid                              | 0.04   | 0.02   |
| 1-oleoylglycerophosphoethanolamine          | Lysolipid               | Lipid                              | 0.04   | 0.19   |
| lathosterol                                | Sterol, Steroid         | Lipid                              | 0.03   | -0.02  |
| Compound/Metabolite                        | Type/Pathway                                                                 | Category     | Score 1 | Score 2 |
|-------------------------------------------|------------------------------------------------------------------------------|--------------|---------|---------|
| alpha-ketoglutarate                       | Krebs cycle                                                                  | Energy       | 0.03    | 0.06    |
| cyclo(leu-pro)                            | Dipeptide                                                                    | Peptide      | 0.03    | 0.12    |
| 1-oleoylglycerol (1-monoolein)            | Monoacylglycerol                                                             | Lipid        | 0.03    | 0.01    |
| hydroxyisovaleryl carnitine               | Valine, leucine and isoleucine metabolism                                    | Amino acid   | 0.03    | 0.02    |
| guanosine                                 | Purine metabolism, guanine containing                                        | Nucleotide   | 0.03    | -0.05   |
| thymol sulfate                            | Food component, Plant                                                       | Xenobiotics  | 0.03    | 0.03    |
| 2-hydroxyglutarate                        | Fatty acid, dicarboxylate                                                   | Lipid        | 0.03    | 0.09    |
| xanthine                                  | Purine metabolism, (hypo)xanthine, inosine containing                        | Nucleotide   | 0.03    | -0.01   |
| theophylline                              | Xanthine metabolism                                                         | Xenobiotics  | 0.03    | -0.01   |
| 1-eicosatrienoylglycerolphosphocholine*    | Lysolipid                                                                    | Lipid        | 0.03    | 0.04    |
| linoleate (18:2n6)                        | Essential fatty acid                                                        | Lipid        | 0.03    | 0.02    |
| butyrylcarnitine                          | Fatty acid metabolism (also BCAA metabolism)                                | Lipid        | 0.03    | 0.04    |
| taurocholate                              | Bile acid metabolism                                                        | Lipid        | 0.03    | 0.26    |
| hypoxanthine                              | Purine metabolism, (hypo)xanthine, inosine containing                       | Nucleotide   | 0.03    | 0.03    |
| 1-oleoylglycerolphosphocholine*            | Lysolipid                                                                    | Lipid        | 0.03    | 0.06    |
| stearoylcarnitine                         | Carnitine metabolism                                                        | Lipid        | 0.03    | 0.01    |
| atenolol                                  | Drug                                                                         | Xenobiotics  | 0.03    | 0.02    |
| 1-palmitoylglycerolphosphocholine          | Lysolipid                                                                    | Lipid        | 0.03    | 0.02    |
| choline                                   | Glycerolipid metabolism                                                      | Lipid        | 0.03    | 0.07    |
| palmitoleate (16:1n7)                     | Long chain fatty acid                                                       | Lipid        | 0.02    | 0.02    |
| glucose                                   | Glycolysis, gluconeogenesis, pyruvate metabolism                             | Carbohydrate | 0.02    | -0.01   |
| theobromine                               | Xanthine metabolism                                                         | Xenobiotics  | 0.02    | 0.00    |
| cis-4-decenoyl carnitine                  | Carnitine metabolism                                                        | Lipid        | 0.02    | 0.02    |
| cholate                                   | Bile acid metabolism                                                        | Lipid        | 0.02    | 0.08    |
| 1-palmitoylplasmenylethanolamine*         | Lysolipid                                                                    | Lipid        | 0.02    | 0.01    |
| HWESASXX*                                 | Polypeptide                                                                  | Peptide      | 0.02    | 0.01    |
| cysteine-glutathione disulfide            | Glutathione metabolism                                                      | Amino acid   | 0.02    | -0.05   |
| asparagin                                 | Alanine and aspartate metabolism                                             | Amino acid   | 0.02    | 0.04    |
| 1-eicosadienoylglycerolphosphocholine*     | Lysolipid                                                                    | Lipid        | 0.02    | 0.05    |
| pyruvate                                  | Glycolysis, gluconeogenesis, pyruvate metabolism                             | Carbohydrate | 0.02    | 0.00    |
| ornithine                                 | Urea cycle; arginine-, proline-, metabolism                                 | Amino acid   | 0.02    | 0.03    |
| Metabolite                                    | Pathway                                | Category        | Score1 | Score2 |
|----------------------------------------------|----------------------------------------|-----------------|--------|--------|
| 3-methylhistidine                            | Histidine metabolism                   | Amino acid      | 0.02   | -0.01  |
| 7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca) | Sterol, Steroid                         | Lipid           | 0.02   | 0.08   |
| X-12442--5,8-tetradecadienoate               | Long chain fatty acid                   | Lipid           | 0.02   | 0.02   |
| betaine                                      | Glycine, serine and threonine metabolism | Amino acid      | 0.02   | 0.04   |
| N1-methyladenosine                           | Purine metabolism, adenine containing   | Nucleotide      | 0.02   | 0.05   |
| trans-4-hydroxyproline                       | Urea cycle; arginine-, proline-, metabolism | Amino acid      | 0.02   | 0.06   |
| 1-linoleoylglycerol (1-monolinolein)         | Monoacylglycerol                        | Lipid           | 0.02   | 0.08   |
| bradykinin, des-arg(9)                       | Polypeptide                             | Peptide         | 0.02   | -0.02  |
| octanoylcarnitine                            | Carnitine metabolism                    | Lipid           | 0.02   | -0.01  |
| 10-nonadecenoate (19:1n9)                    | Long chain fatty acid                   | Lipid           | 0.02   | 0.00   |
| heme*                                        | Hemoglobin and porphyrin metabolism    | Cofactors and vitamins | 0.02 | 0.03  |
| gamma-glutamyltyrosine                       | gamma-glutamyl                         | Peptide         | 0.02   | 0.05   |
| glycerophosphorylcholine (GPC)               | Glycerolipid metabolism                 | Lipid           | 0.01   | -0.03  |
| ADSGEGDFXAEAGGGVR*                           | Fibrinogen cleavage peptide            | Peptide         | 0.01   | 0.00   |
| caffeine                                      | Xanthine metabolism                    | Xenobiotics     | 0.01   | 0.03   |
| 1-stearoylglycerophosphocholine              | Lysolipid                              | Lipid           | 0.01   | 0.00   |
| allantoin                                     | Purine metabolism, urate metabolism    | Nucleotide      | 0.01   | 0.07   |
| leucylleucine                                 | Dipeptide                              | Peptide         | 0.01   | 0.01   |
| 1-myristoylglycerophosphocholine              | Lysolipid                              | Lipid           | 0.01   | 0.01   |
| X-14450--phenylalanylleucine                 | Dipeptide                              | Peptide         | 0.01   | 0.11   |
| bilirubin (Z,Z)                               | Hemoglobin and porphyrin metabolism    | Cofactors and vitamins | 0.01 | 0.00  |
| 1-stearoylglycerophosphinositol              | Lysolipid                              | Lipid           | 0.01   | 0.04   |
| glycodedoxycholate                           | Bile acid metabolism                   | Lipid           | 0.01   | 0.20   |
| alanine                                       | Alanine and aspartate metabolism       | Amino acid      | 0.01   | -0.03  |
| X-14205--alpha-glutamyltyrosine              | Dipeptide                              | Peptide         | 0.01   | 0.07   |
| erythrose                                     | Fructose, mannose, galactose, starch, and sucrose metabolism | Carbohydrate     | 0.01   | 0.03   |
| erythritol                                    | Sugar, sugar substitute, starch        | Xenobiotics     | 0.01   | 0.06   |
| tyrosine                                      | Phenylalanine & tyrosine metabolism    | Amino acid      | 0.01   | 0.04   |
| X-04499--3,4-dihydroxybutyrate linolenate [alpha or gamma; (18:3n3 or 6)] | Butanoate metabolism                    | Amino acid      | 0.01   | 0.10   |
| 7-methylxanthine                             | Xanthine metabolism                    | Xenobiotics     | 0.00   | -0.03  |
| Compound                          | Metabolic Pathway                                      | Cofactors and Vitamins | 
|----------------------------------|-------------------------------------------------------|------------------------|
| pantothenate                     | Pantothenate and CoA metabolism                       | 0.00 -0.04             |
| indoleacetate                    | Tryptophan metabolism                                 | 0.00 0.00              |
| DSGEGDFXAECCGVR*                 | Fibrinogen cleavage peptide                           | 0.00 0.00              |
| 3-methoxytyrosine                | Phenylalanine & tyrosine metabolism                   | 0.00 0.02              |
| dimethylarginine (SDMA + ADMA)   | Urea cycle; arginine-, proline-, metabolism           | 0.00 0.02              |
| 2-stearylglycerophosphocholine*  | Lysolipid                                             | 0.00 0.01              |
| 2-hydroxystearate                | Fatty acid, monohydroxy                               | 0.00 0.03              |
| pyroglutamylglycine              | Dipeptide                                             | 0.00 0.07              |
| lysine                           | Lysine metabolism                                     | 0.00 -0.03             |
| paraxanthine                     | Xanthine metabolism                                   | 0.00 -0.02             |
| X-13431--nonanoylcarnitine*      | Carnitine metabolism                                  | 0.00 0.02              |
| 5-dodecenoyl (12:1n7)            | Medium chain fatty acid                               | 0.00 0.05              |
| cysteine                         | Cysteine, methionine, SAM, taurine metabolism         | 0.00 0.01              |
| n-Butyl Oleate                   | Fatty acid, ester                                     | 0.00 0.01              |
| uridine                          | Pyrimidine metabolism, uracil containing              | 0.00 -0.15             |
| 15-methylpalmitate (isobar with 2-methylpalmitate) | Fatty acid, branched                               | 0.00 -0.02             |
| pro-hydroxy-pro                  | Dipeptide                                             | -0.01 0.01             |
| ursodeoxycholate                 | Bile acid metabolism                                  | -0.01 0.07             |
| 10-heptadecenoate (17:1n7)       | Long chain fatty acid                                 | -0.01 0.02             |
| myristate (14:0)                 | Long chain fatty acid                                 | -0.01 0.00             |
| indolepropionate                 | Tryptophan metabolism                                 | -0.01 0.01             |
| glycerol 2-phosphate             | Chemical                                              | -0.01 0.00             |
| inosine                          | Purine metabolism, (hypo)xanthine, inosine containing | -0.01 -0.04            |
| erythrone*                       | Aminosugars metabolism                               | -0.01 0.02             |
| kynurenine                       | Tryptophan metabolism                                 | -0.01 0.03             |
| N-acetylornithine                | Urea cycle; arginine-, proline-, metabolism           | -0.01 0.06             |
| X-11786--methylcysteine          | Cysteine, methionine, SAM, taurine metabolism         | -0.02 0.05             |
| 4-hydroxyhippururate             | Benzoate metabolism                                  | -0.02 0.06             |
| taurodeoxycholate                | Bile acid metabolism                                 | -0.02 0.09             |
| margarate (17:0)                 | Long chain fatty acid                                 | -0.02 0.04             |
| arginine                         | Urea cycle; arginine-, proline-, metabolism           | -0.02 0.01             |

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| Compound                          | Pathway                      | Category       | p-value 1 | p-value 2 |
|----------------------------------|------------------------------|----------------|-----------|-----------|
| valerate                         | Short chain fatty acid       | Lipid          | -0.02     | 0.01      |
| C-glycosyltryptophan*            | Tryptophan metabolism       | Amino acid     | -0.02     | 0.01      |
| succinylcarnitine                | Krebs cycle                  | Energy         | -0.02     | 0.01      |
| scylo-inositol                   | Inositol metabolism         | Lipid          | -0.02     | 0.05      |
| myo-inositol                     | Inositol metabolism         | Lipid          | -0.02     | 0.02      |
| 1-palmitoylgllycerol (1-monopalmitin) | Monoacylglycerol          | Lipid          | -0.02     | -0.01     |
| nonadecanoate (19:0)             | Long chain fatty acid       | Lipid          | -0.02     | 0.00      |
| glycerol                         | Glycerolipid metabolism     | Lipid          | -0.02     | 0.04      |
| glycerol 3-phosphate (G3P)       | Glycerolipid metabolism     | Lipid          | -0.02     | -0.03     |
| ADpSGEGDFXAEWGVR*                | Fibrinogen cleavage peptide | Peptide        | -0.02     | 0.00      |
| 4-acetamidobutanoate             | Guanidino and acetamido metabolism | Amino acid  | -0.02     | 0.05      |
| arabinose                        | Nucleotide sugars, pentose metabolism | Carbohydrate | -0.02     | 0.06      |
| docosapentaenoate (n3 DPA; 22:5n3) | Essential fatty acid       | Lipid          | -0.03     | -0.06     |
| 3-indoxyl sulfate                | Tryptophan metabolism       | Amino acid     | -0.03     | -0.05     |
| X-13183--stearamide              | Fatty acid amide            | Lipid          | -0.03     | -0.02     |
| propionylcarnitine               | Fatty acid metabolism (also BCAA metabolism) | Lipid     | -0.03     | -0.03     |
| dodecanedioate                   | Fatty acid, dicarboxylate   | Lipid          | -0.03     | 0.06      |
| 1,7-dimethylurate                | Xanthine metabolism         | Xenobiotics    | -0.03     | -0.03     |
| ibuprofen                        | Drug                         | Xenobiotics    | -0.03     | 0.00      |
| serine                           | Glycine, serine and threonine metabolism | Amino acid | -0.03     | -0.02     |
| myristoleate (14:1n5)            | Long chain fatty acid       | Lipid          | -0.03     | 0.00      |
| chiro-inositol                   | Inositol metabolism         | Lipid          | -0.03     | 0.03      |
| creatine                         | Creatine metabolism         | Amino acid     | -0.04     | -0.07     |
| gamma-glutamyl/glutamine         | gamma-glutamyl              | Peptide        | -0.04     | -0.04     |
| 1-stearoylglycerol (1-monostearin) | Monoacylglycerol          | Lipid          | -0.04     | -0.02     |
| fructose                         | Fructose, mannose, galactose, starch, and sucrose metabolism | Carbohydrate  | -0.04     | 0.00      |
| glutamine                        | Glutamate metabolism        | Amino acid     | -0.04     | -0.03     |
| X-14304--leucylalanine           | Dipeptide                    | Peptide        | -0.04     | -0.02     |
| phenol sulfate                   | Phenylalanine & tyrosine metabolism | Amino acid | -0.04     | 0.00      |
| homocitrulline                   | Urea cycle; arginine-, proline-, metabolism | Amino acid | -0.04     | 0.06      |
| pentadecanoate (15:0)            | Long chain fatty acid       | Lipid          | -0.04     | -0.06     |
| 3-methylxanthine                 | Xanthine metabolism         | Xenobiotics    | -0.04     | -0.02     |
| stachydrine                      | Food component, Plant       | Xenobiotics    | -0.04     | 0.02      |

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| Compound                               | Class                        | Category                               | Value 1 | Value 2 |
|----------------------------------------|------------------------------|----------------------------------------|---------|---------|
| caproate (6:0)                         | Medium chain fatty acid      | Lipid                                  | -0.04   | 0.00    |
| 1-methylxanthine                       | Xanthine metabolism         | Xenobiotics                            | -0.04   | -0.02   |
| mannitol                               | Fructose, mannose, galactose, starch, and sucrose metabolism | Carbohydrate | -0.04 | 0.04    |
| saccharin                              | Food component, Plant       | Xenobiotics                            | -0.04   | 0.05    |
| 1-stearoylglycerophosphoethanolamine   | Lysolipid                   | Lipid                                  | -0.04   | 0.02    |
| undecanoate (11:0)                     | Medium chain fatty acid      | Lipid                                  | -0.05   | -0.03   |
| X-14977--vanillin                      | Food component/Plant        | Xenobiotics                            | -0.05   | 0.04    |
| 1-heptadecanoylglycerophosphocholine   | Lysolipid                   | Lipid                                  | -0.05   | -0.05   |
| 1,6-anhydroglucose                     | Glycolysis, gluconeogenesis, pyruvate metabolism | Carbohydrate | -0.05 | 0.08    |
| X-12095--N1-methyl-3-pyridone-4-carboxamide | NAD metabolism              | Nucleotide                             | -0.05   | -0.08   |
| 2-hydroxyisobutyrate                   | Valine, leucine and isoleucine metabolism | Amino acid | -0.05 | -0.04   |
| deoxycholate                           | Bile acid metabolism        | Lipid                                  | -0.05   | -0.03   |
| alpha-tocopherol                       | Tocopherol metabolism       | Cofactors and vitamins                 | -0.05   | -0.05   |
| levulinate (4-oxovalerate)             | Valine, leucine and isoleucine metabolism | Amino acid | -0.05 | -0.01   |
| threonate                              | Ascorbate and aldarate metabolism | Cofactors and vitamins | -0.06 | -0.06   |
| N-acetylglucine                        | Glycine, serine and threonine metabolism | Amino acid | -0.06 | -0.02   |
| 1-palmitoylglycerophosphoethanolamine  | Lysolipid                   | Lipid                                  | -0.06   | 0.05    |
| glycerate                              | Glycolysis, gluconeogenesis, pyruvate metabolism | Carbohydrate | -0.06 | -0.04   |
| 4-ethylphenylsulfate                   | Benzoate metabolism         | Xenobiotics                            | -0.06   | 0.00    |
| X-14189--leucylalanine                 | Dipeptide                   | Peptide                                | -0.06   | -0.04   |
| heptanoate (7:0)                       | Medium chain fatty acid      | Lipid                                  | -0.06   | -0.03   |
| 1-methylurate                          | Xanthine metabolism         | Xenobiotics                            | -0.06   | -0.01   |
| citrate                                | Krebs cycle                 | Energy                                 | -0.07   | -0.02   |
| caprate (10:0)                         | Medium chain fatty acid      | Lipid                                  | -0.07   | 0.03    |
| caprylate (8:0)                        | Medium chain fatty acid      | Lipid                                  | -0.07   | 0.02    |
| 3-(3-hydroxyphenyl)propionate          | Phenylalanine & tyrosine metabolism | Amino acid | -0.07 | 0.00    |
| salicylate                             | Drug                        | Xenobiotics                            | -0.07   | -0.01   |
| cholesterol                            | Sterol, Steroid             | Lipid                                  | -0.07   | -0.08   |
| pyridoxate                             | Vitamin B6 metabolism       | Cofactors and vitamins                 | -0.07   | -0.07   |
| Compound                  | Pathway                          | Class               | ΔR   | ΔM   |
|---------------------------|----------------------------------|---------------------|------|------|
| benzoate                  | Benzoate metabolism              | Xenobiotics         | -0.07| -0.01|
| ergothioneine             | Food component, Plant             | Xenobiotics         | -0.07| -0.07|
| 3-dehydrocarnitine*       | Carnitine metabolism             | Lipid               | -0.07| 0.02 |
| 2-hydroxyhippurate (salicylurate) | Benzoate metabolism          | Xenobiotics         | -0.07| 0.02 |
| estrone 3-sulfate         | Sterol, Steroid                  | Lipid               | -0.08| -0.06|
| laurate (12:0)            | Medium chain fatty acid          | Lipid               | -0.08| -0.01|
| X-14208--phenylalanylserine | Dipeptide                       | Peptide             | -0.08| 0.07 |
| acetylphosphate           | Oxidative phosphorylation        | Energy              | -0.08| -0.06|
| palmitoyl sphingomyelin   | Sphingolipid                     | Lipid               | -0.08| -0.06|
| pelargonate (9:0)         | Medium chain fatty acid          | Lipid               | -0.09| -0.06|
| docosahexaenoate (DHA; 22:6n3) | Essential fatty acid          | Lipid               | -0.10| -0.07|
| stearidonate (18:4n3)     | Long chain fatty acid            | Lipid               | -0.10| -0.05|
| 1-docosahexaenoylglycerophosphocholine* | Lysolipid                | Lipid               | -0.10| -0.10|
| salicyluric glucuronide*  | Drug                             | Xenobiotics         | -0.10| -0.05|
| urea                      | Urea cycle; arginine-, proline-, metabolism | Amino acid | -0.11| -0.06|
| phosphate                 | Oxidative phosphorylation        | Energy              | -0.11| -0.05|
| 3-phenylpropionate (hydrocinnamate) | Phenylalanine & tyrosine metabolism | Amino acid | -0.11| -0.05|
| quinate                   | Food component, Plant            | Xenobiotics         | -0.11| -0.04|
| catechol sulfate          | Benzoate metabolism             | Xenobiotics         | -0.12| -0.01|
| citrulline                | Urea cycle; arginine-, proline-, metabolism | Amino acid | -0.12| 0.01 |
| eicosapentaenoate (EPA; 20:5n3) | Essential fatty acid          | Lipid               | -0.12| -0.09|
| threitol                  | Nucleotide sugars, pentose metabolism | Carbohydrate       | -0.13| 0.01 |
| glycine                   | Glycine, serine and threonine metabolism | Amino acid | -0.13| -0.10|
| p-cresol sulfate          | Phenylalanine & tyrosine metabolism | Amino acid | -0.14| -0.13|
| phenylacetate             | Phenylalanine & tyrosine metabolism | Amino acid | -0.14| -0.07|
| 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF) | Fatty acid, dicarboxylate | Lipid               | -0.14| -0.14|
| naproxen                  | Drug                             | Xenobiotics         | -0.14| -0.18|
| isobutyrylcarnitine       | Valine, leucine and isoleucine metabolism | Amino acid | -0.15| -0.06|
| ascorbate (Vitamin C)     | Ascorbate and aldarate metabolism | Cofactors and vitamins | -0.15| -0.10|
| hippurate                 | Benzoate metabolism             | Xenobiotics         | -0.16| -0.06|
| homostachydrine*          | Food component, Plant            | Xenobiotics         | -0.17| 0.01 |
| hydroquinone sulfate      | Drug                             | Xenobiotics         | -0.17| -0.16|
| Metabolite                                               | Category                     | Subcategory       | Pearson's r | p-value |
|---------------------------------------------------------|------------------------------|-------------------|-------------|---------|
| phenylacetylglutamine                                   | Amino acid                   | Phenylalanine & tyrosine metabolism | -0.18       | 0.10    |
| 4-acetamidophenol                                       | Drug                         | Drug              | -0.20       | 0.03    |
| 3-(cystein-S-yl)acetaminophen*                          | Drug                         | Drug              | -0.28       | 0.00    |
| 2-methoxyacetaminophen sulfate*                         | Drug                         | Drug              | -0.29       | 0.02    |
| p-acetamidophenylglucuronide                            | Drug                         | Drug              | -0.35       | 0.02    |
| 2-hydroxyacetaminophen sulfate*                         | Drug                         | Drug              | -0.35       | 0.01    |
| 4-acetaminophen sulfate                                 | Drug                         | Drug              | -0.35       | 0.06    |

Note: Pearson’s correlation coefficient r between pairs of metabolites measured in TwinsUK and KORA F4 cohort study.
eTable 6. Sensitivity Analyses for Association Between Mannose and ARDS Risk Using Different Mendelian Randomization Methods and Different Sources of Association Results Between Genetic Instrumental Variables (SNPs) and ARDS Risk

| Method                              | Source of association results between genetic instrumental variables (SNPs) and ARDS risk | OR (95%CI) | P      | OR (95%CI) | P      | OR (95%CI) | P      | OR (95%CI) | P      |
|-------------------------------------|------------------------------------------------------------------------------------------|------------|--------|------------|--------|------------|--------|------------|--------|
|                                     | All participants in MEARDS (N\text{case}=403, N\text{control}=1227)                     |            |        |            |        |            |        |            |        |
| GSMR                                | 0.64 (0.53, 0.78)                                                                        | 7.46×10⁻⁶  | 0.80 (0.68, 0.94) | 7.49×10⁻³ | 0.85 (0.71, 0.92) | 8.33×10⁻³ | 0.81 (0.69, 0.96) | 1.66×10⁻² |
| Sensitivity analysis                 |                                                                                         |            |        |            |        |            |        |            |        |
| IVW                                 | 0.70 (0.62, 0.78)                                                                        | 2.79×10⁻⁹  | 0.82 (0.74, 0.91) | 1.57×10⁻⁴ | 0.82 (0.73, 0.92) | 6.35×10⁻⁴ | 0.84 (0.76, 0.93) | 1.20×10⁻³ |
| MR-PRESSO                           | 0.70 (0.63, 0.79)                                                                        | 8.77×10⁻⁵  | 0.82 (0.76, 0.88) | 3.44×10⁻⁴ | 0.81 (0.74, 0.88) | 3.41×10⁻⁴ | 0.84 (0.77, 0.91) | 1.90×10⁻³ |
| MR-Median                           | 0.63 (0.51, 0.79)                                                                        | 4.87×10⁻⁵  | 0.79 (0.66, 0.95) | 0.01      | 0.81 (0.67, 0.99) | 0.04      | 0.84 (0.70, 0.93) | 0.04 |
| MR-Maxlik                           | 0.70 (0.62, 0.79)                                                                        | 9.20×10⁻⁹  | 0.82 (0.74, 0.91) | 1.67×10⁻⁴ | 0.82 (0.73, 0.92) | 6.34×10⁻⁴ | 0.84 (0.76, 0.94) | 1.40×10⁻³ |
| MR-ModeBase                         | 0.61 (0.44, 0.83)                                                                        | 1.96×10⁻³  | 0.74 (0.57, 0.96) | 0.02      | 0.82 (0.64, 1.05) | 0.01      | 0.78 (0.60, 0.98) | 0.05 |
| MR-RAPS (MLE)                       | 0.70 (0.59, 0.83)                                                                        | 4.58×10⁻⁵  | 0.82 (0.71, 0.94) | 5.84×10⁻³ | 0.81 (0.69, 0.95) | 8.68×10⁻³ | 0.84 (0.72, 0.97) | 0.02 |
| MR-RAPS (Shrinkage)                 | 0.70 (0.59, 0.83)                                                                        | 3.43×10⁻⁵  | 0.82 (0.71, 0.94) | 4.91×10⁻³ | 0.81 (0.69, 0.94) | 7.38×10⁻³ | 0.84 (0.72, 0.97) | 0.02 |

* A series of comparable MR methods to verify the robustness of results including inverse-variance weighted (IVW), MR-PRESSO, weighted median (MR-Median), maximum likelihood (MR-Maxlik), mode-based estimation (MR-ModeBase), and Robust Adjusted Profile Score (MR-RAPS). Causal
association between mannose and ARDS risk was inferred using different MR analytical methods for association between genetic variants and metabolites, including GSMR, IVW MR-PRESSO, MR-Median, MR-Maxlik, MR-ModeBase, MR-RAPS(MLE), and MR-RAPS (Shrinkage).
eFigure 1. Standard Quality Control Procedure for GWAS Data

Sample QC

QC before imputation

2,233 individuals

3 individuals removed due to missing genotype data (0.13%)

2,230 individuals

3 individuals removed due to High heterozygosity (0.13%)

2,227 individuals

0 individuals removed with pi_hat greater than 25% in IBD analysis (0.00%)

2,227 individuals

17 individuals removed due to outlier (0.76%)

Final: 2,210 individuals

QC after imputation

iSPAAR with 2,233 individuals (1,312 males, 921 females), 518,259 SNPs (chr 1-22)

SNP QC

Sample QC

QC before imputation

2,233 individuals

3 individuals removed due to missing genotype data (0.13%)

2,230 individuals

3 individuals removed due to High heterozygosity (0.13%)

2,227 individuals

0 individuals removed with pi_hat greater than 25% in IBD analysis (0.00%)

2,227 individuals

17 individuals removed due to outlier (0.76%)

Final: 2,210 individuals

QC after imputation

Sample QC

4 SNPs removed due to missing genotype data (0.000772%)

518,259 SNPs

47,073,209 SNPs

919,171 SNPs removed due to missing genotype data (1.95%)

46,154,038 SNPs

1,372 SNPs removed due to duplicate IDs (0.00029%

46,152,666 SNPs

483,157 SNPs removed due to imputation quality r<0.8 (1.03%)

45,669,509 SNPs

36,621,736 SNPs removed due to minor allele frequency (77.80%)

Final: 9,047,773 (19.22%)

Sample QC

4 SNPs removed due to missing genotype data (0.000772%)

518,259 SNPs

47,073,209 SNPs

919,171 SNPs removed due to missing genotype data (1.95%)

46,154,038 SNPs

1,372 SNPs removed due to duplicate IDs (0.00029%)

46,152,666 SNPs

483,157 SNPs removed due to imputation quality r<0.8 (1.03%)

45,669,509 SNPs

36,621,736 SNPs removed due to minor allele frequency (77.80%)

Final: 9,047,773 (19.22%)
**eFigure 2.** GSMR Analysis Workflow

**ARDS GWAS**

- **m genotypes, G**
- **ARDS status, Y**

| ID | rs1 | rs2 | ... | rs_m |
|----|-----|-----|-----|------|
| id1 | 1   | 2   | ... | 1    |
| id2 | 0   | 1   | ... | 0    |
| id3 | 2   | 2   | ... | 1    |
| ... | ... | ... | ... | ...  |
| idn | 1   | 2   | ... | 1    |

**mQTL Analysis**

- **m genotypes, G**
- **Metabolite level, M**

| ID | rs1 | rs2 | ... | rs_m |
|----|-----|-----|-----|------|
| id1 | 1   | 2   | ... | 1    |
| id2 | 0   | 1   | ... | 0    |
| id3 | 2   | 2   | ... | 1    |
| ... | ... | ... | ... | ...  |
| idn | 1   | 2   | ... | 1    |

**Summarized results for genome-wide SNPs**

| SNP | b   | se  | P   |
|-----|-----|-----|-----|
| rs1 | 0.1 | 0.01| 1e-5|
| rs2 | 1.1 | 0.04| 0.09|
| ... | ... | ... | ... |
| rs_m| 0.8 | 0.23| 1e-8|

**Summarized results for significant SNPs**

| Metabolite 1 | Metabolite 2 | Metabolite 3 |
|--------------|--------------|--------------|
| rs1 | 0.3 | 0.1 | 1e-8 |
| rs2 | 1.3 | 0.4 | 9e-5 |
| ... | ... | ... | ... |
| rs_m| 1.8 | 0.2 | 8e-7 |

**Intersection set**

**Causal association**

| Metabolite | b    | se   | P   |
|------------|------|------|-----|
| Metabolite | 0.1  | 0.01 | 1e-5|
| Metabolite | 1.1  | 0.04 | 0.09|
| Metabolite | -0.2 | 0.09 | 0.89|

**GSMR estimation**

**logit(Y)=b·G+e**

**M=b·G+e**
eFigure 3. Framework Diagram of Mendelian Randomization

\[ b_{zx(i)} \]

MEARDS GWAS analysis

\[ b_{zy(i)} \]
mQTL analysis

SNP1 (IV1)

SNP2 (IV2)

...

SNPp (IVp)

Metabolite (M)

ARDS risk (Y)

Confounders (C)

GSMR analysis

\[ b_{xy(i)} = \frac{b_{zy(i)}}{b_{zx(i)}} \]

MEARDS GWAS summary-level data

\[ b_{xy} = \left(1'V^{-1}1\right)^{-1}1'V^{-1}\beta_{xy} \]

V: variance-covariance matrix in GWAS

\[ \text{var}(b_{xy}) = \left(1'V^{-1}1\right)^{-1} \]

mQTL summary-level data

\[ \text{var}(b_{zy}) = \left(1'V^{-1}1\right)^{-1} \]
eFigure 4. Sensitivity Analysis for Candidate Metabolites Associated With ARDS Risk

Causal associations between X-11440, X-12850, tryptophan betaine, and alpha-hydroxyisovalerate and ARDS risk were inferred after a series of comparable MR analytical methods, including a generalized summary data-based Mendelian randomization analysis (GSMR), inverse-variance weighting (IVW), MR-PRESSO, MR-Median, MR-Maxlik, MR-ModeBase, MR-RAPS (MLE), and MR-RAPS (Shrinkage).

The horizontal axis represents the effect size of the selected instrumental variable on metabolites (X-11440, X-12850, tryptophan betaine, and alpha-hydroxyisovalerate), and the vertical axis represents the effect size of the instrumental variable on ARDS risk. Each cross represents an instrumental variable and confidence intervals regarding x- and y-axis. The lines with different colors were estimated by different Mendelian Randomization methods; the slope of each line represents the estimated association effect between metabolites and ARDS risk of different Mendelian Randomization methods.
### Method OR(95%CI) P

#### GSMR

| Method                      | OR 95% CI | P       |
|-----------------------------|-----------|---------|
| IVW                         | 0.64 (0.54, 0.77) | 5.19×10⁻⁴ |
| MR-PRESSO                   | 0.64 (0.53, 0.78) | 4.17×10⁻⁴ |
| MR-Median                   | 0.63 (0.53, 0.78) | 4.17×10⁻⁴ |
| MR-Maxlik                   | 0.65 (0.44, 0.86) | 2.17×10⁻⁴ |
| MR-ModeBase                 | 0.95 (0.89, 1.01) | 7.16×10⁻⁴ |
| MR-RAPS (MLE)               | 0.95 (0.89, 1.01) | 2.73×10⁻⁴ |
| MR-RAPS (Shrinkage)         | 0.95 (0.89, 1.01) | 5.16×10⁻⁴ |

#### IVW

| Method                      | OR 95% CI | P       |
|-----------------------------|-----------|---------|
| IVW                         | 1.76 (1.28, 2.42) | 1.93×10⁻⁴ |
| MR-PRESSO                   | 1.68 (1.21, 2.34) | 1.23×10⁻⁴ |
| MR-Median                   | 0.63 (0.48, 0.83) | 1.31×10⁻⁴ |
| MR-Maxlik                   | 0.64 (0.53, 0.78) | 4.17×10⁻⁴ |
| MR-ModeBase                 | 0.62 (0.44, 0.86) | 1.09×10⁻³ |
| MR-RAPS (MLE)               | 0.95 (0.89, 1.01) | 0.09    |
| MR-RAPS (Shrinkage)         | 0.95 (0.89, 1.01) | 0.08    |

#### MR-Median

| Method                      | OR 95% CI | P       |
|-----------------------------|-----------|---------|
| MR-Median                   | 1.92 (1.37, 2.68) | 9.62×10⁻⁵ |
| MR-Maxlik                   | 1.79 (1.30, 2.48) | 2.17×10⁻⁴ |
| MR-ModeBase                 | 2.20 (1.37, 3.53) | 3.37×10⁻⁴ |
| MR-RAPS (MLE)               | 1.23 (1.19, 1.27) | 2.73×10⁻³ |
| MR-RAPS (Shrinkage)         | 1.23 (1.19, 1.27) | 5.16×10⁻⁴ |

#### MR-Maxlik

| Method                      | OR 95% CI | P       |
|-----------------------------|-----------|---------|
| MR-Maxlik                   | 1.70 (1.37, 2.11) | 1.36×10⁻⁶ |
| MR-ModeBase                 | 2.20 (1.37, 3.53) | 3.37×10⁻⁴ |
| MR-RAPS (MLE)               | 0.95 (0.89, 1.01) | 7.16×10⁻⁴ |
| MR-RAPS (Shrinkage)         | 0.95 (0.89, 1.01) | 7.16×10⁻⁴ |

**Sensitivity Analysis**

- **IVW**
  - 0.64 (0.53, 0.78)
  - 1.46×10⁻⁶
- **MR-PRESSO**
  - 0.64 (0.54, 0.77)
  - 5.19×10⁻⁴
- **MR-Median**
  - 0.64 (0.53, 0.78)
  - 4.17×10⁻⁴
- **MR-Maxlik**
  - 0.65 (0.44, 0.86)
  - 2.17×10⁻⁴
- **MR-ModeBase**
  - 0.62 (0.44, 0.86)
  - 2.17×10⁻³
- **MR-RAPS (MLE)**
  - 0.95 (0.89, 1.01)
  - 0.09
- **MR-RAPS (Shrinkage)**
  - 0.95 (0.89, 1.01)
  - 0.08
**eFigure 5.** Association Between Serum Mannose and Acute physiology severity using GSMR

\[ \beta = -0.28 (-0.37, -0.19) \]

\[ P = 5.38 \times 10^{-10} \]
eAppendix. Supplementary Methods
1. GSMR Algorithm

$Y$ is the outcome (risk of ARDS), $x$ is the exposure (metabolite), and $z$ is an instrumental variable. Four steps were performed in GSMR and presented in Supplementary Figure S5 and Supplementary Figure S3 (Nat Commun. Jan 15 2018;9(1):224):

i. The effect of each metabolite on ARDS ($\hat{b}_{xy}$) through: $\hat{b}_{xy(i)} = \hat{b}_{zy(i)}/\hat{b}_{zx(i)}$, $\hat{\beta}_{xy} = \{\hat{b}_{xy(1)}, \hat{b}_{xy(2)}, \ldots, \hat{b}_{xy(m)}\}$, where $\hat{b}_{zy(i)}$ is the estimate of effect of SNP on ARDS from MEARDS GWAS (Genome-Wide Association Study Of Acute Lung Injury Risk Loci In The Ispaar Consortium. 2011:A5536-A5536) and $\hat{b}_{zx(i)}$ is the estimate of a SNP effect on the abundance of a metabolite from mQTL (Nat Genet. Jun 2014;46(6):543-550).

ii. The sample variance of the effect of a metabolite on ARDS $\hat{b}_{xy}$ was estimated by $\text{var}\left(\hat{b}_{xy(i)}\right) = b_{xy(i)}^2\left[\frac{\text{var}\left(\hat{b}_{zx(i)}\right)}{b_{zx(i)}^2} + \frac{\text{var}\left(\hat{b}_{zy(i)}\right)}{b_{zy(i)}^2} - \frac{\text{var}^2\left(\hat{b}_{zx(i)}\right)}{b_{zx(i)}^4}\right]$, and the covariance of the effect calculated according to linkage disequilibrium (LD) correlation between the two SNPs (provided by MEARDS GWAS dataset).

iii. The estimated effect value of $\hat{b}_{xy}$ was calculated by the generalized least square method $\hat{b}_{xy} = (1'V^{-1}1)^{-1}1'V^{-1}\hat{\beta}_{xy}$.

iv. The approximate $\chi^2$ test statistic was used to test the statistical significance of $\hat{b}_{xy}$: $T_{GSMR} = \hat{b}_{xy}^2/\text{var}\left(\hat{b}_{xy}\right)$. 
2. Metabolomics Testing Procedures and Platform in Metabolon Inc.

**Sample Accessioning:** Following receipt, samples were inventoried and immediately stored at -80°C. Each sample was accessioned into the Metabolon LIMS system and assigned a unique identifier associated with the original source identifier. This identifier was used to track all sample handling, tasks, results, etc. The samples (and all derived aliquots) were tracked by the LIMS system. All portions of any sample were automatically assigned their own unique identifiers by LIMS when a new task was created; the relationship of these samples was also tracked. All samples were maintained at -80°C until processing.

**Sample Preparation:** Samples were prepared using the automated MicroLab STAR® system from Hamilton Company. Several recovery standards were added before the first step in the extraction process for QC purposes. To remove protein and dissociate small molecules bound to protein or trapped in a precipitated protein matrix, proteins were precipitated with methanol under vigorous shaking for 2 min (Glen Mills GenoGrinder 2000) followed by centrifugation to recover chemically diverse metabolites. The resulting extract was divided into five fractions: two for analysis by two separate reverse-phase (RP)/UPLC-MS/MS methods with positive ion mode electrospray ionization (ESI), one for analysis by RP/UPLC-MS/MS with negative ion mode ESI, one for analysis by HILIC/UPLC-MS/MS with negative ion mode ESI, and one reserved for backup. Samples were placed briefly on a TurboVap® (Zymark) to remove organic solvent. Sample extracts were stored overnight under nitrogen before analysis.

**QA/QC:** Controls were analyzed in concert with experimental samples: a pooled matrix sample generated by a small volume of each experimental sample (or alternatively, a pool of well-characterized human plasma) served as a technical replicate throughout the data set; extracted water samples served as process blanks; and a cocktail of QC standards that were carefully chosen not to interfere with measurement of endogenous compounds was added to every analyzed sample, allowing instrument performance monitoring and chromatographic alignment. Instrument variability was determined by the median relative standard deviation (RSD) for standards added to each sample before injection into mass spectrometers. Overall process variability was determined by calculating median RSD for all endogenous metabolites (i.e., non-instrument
standards) present in 100% of pooled matrix samples.

**Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (UPLC-MS/MS):** All methods used a Waters ACQUITY ultra-performance liquid chromatography (UPLC) and Thermo Scientific Q-Exactive high resolution/accurate mass spectrometer interfaced with a heated electrospray ionization (HESI-II) source and Orbitrap mass analyzer operated at 35,000 mass resolution. Sample extract was dried and reconstituted in solvents compatible with each of the four methods. Each reconstitution solvent contained a series of standards at fixed concentrations to ensure injection and chromatographic consistency. One aliquot was analyzed using acidic positive ion conditions and chromatographically optimized for more hydrophilic compounds. Extracts were gradient-eluted from a C18 column (Waters UPLC BEH C18-2.1x100 mm, 1.7 µm) using water and methanol containing 0.05% perfluoropentanoic acid (PFPA) and 0.1% formic acid (FA). Another aliquot was analyzed using acidic positive ion conditions; however, it was chromatographically optimized for more hydrophobic compounds. Extracts were gradient eluted from the C18 column using methanol, acetonitrile, water, 0.05% PFPA, and 0.01% FA and operated at an overall higher organic content. Another aliquot was analyzed using basic negative ion optimized conditions using a separate dedicated C18 column. Basic extracts were gradient eluted from the column using methanol and water with 6.5 mM ammonium bicarbonate at pH 8. The fourth aliquot was analyzed by negative ionization following elution from a HILIC column (Waters UPLC BEH Amide 2.1x150 mm, 1.7 µm) using a gradient consisting of water and acetonitrile with 10 mM ammonium formate, pH 10.8. The MS analysis alternated between MS and data-dependent MSn scans using dynamic exclusion. The scan range varied slightly between methods but covered 70–1000 m/z.

**Bioinformatics:** The informatics system consisted of four major components, the Laboratory Information Management System (LIMS), data extraction and peak-identification software, data processing tools for QC and compound identification, and a collection of information interpretation and visualization tools for use by data analysts. The hardware and software foundations for these informatics components were the LAN backbone and a database server running Oracle 10.2.0.1 Enterprise Edition.

**LIMS:** The purpose of the Metabolon LIMS system was to enable fully auditable
laboratory automation through a secure, easy to use, and highly specialized system. The scope of the Metabolon LIMS system encompasses sample accessioning, sample preparation and instrumental analysis, and reporting and advanced data analysis. All subsequent software systems are grounded in LIMS data structures. It has been modified to leverage and interface with in-house information extraction and data visualization systems as well as third-party instrumentation and data analysis software.

**Data Extraction and Compound Identification**: Raw data were extracted, peak-identified, and QC-processed using Metabolon’s hardware and software. These systems are built on a web-service platform using Microsoft’s NET technologies, which runs on high-performance application servers and fiber-channel storage arrays in clusters to provide active failover and load-balancing. Compounds were compared to library entries of purified standards or recurrent unknown entities. Metabolon maintains a library based on authenticated standards that contains the retention time/index (RI), mass to charge ratio (m/z), and chromatographic data (including MS/MS spectral data) on all molecules present in the library. Further, biochemical identifications are based on three criteria: retention index within a narrow RI window of the proposed identification, accurate mass match to the library ±10 ppm, and MS/MS forward and reverse scores between experimental data and authentic standards. MS/MS scores are based on comparison of ions present in the experimental spectrum and ions present in the library spectrum. While there may be similarities between these molecules based on one of these factors, use of all three data points can be utilized to distinguish and differentiate biochemicals. More than 3,300 commercially available purified standard compounds have been acquired and registered in LIMS for analyses on all platforms for determination of their analytical characteristics. Additional mass spectral entries have been created for structurally unnamed biochemicals, which have been identified by virtue of their recurrent nature (both chromatographic and mass spectral). These compounds have the potential to be identified by future acquisition of a matching purified standard or by classical structural analysis.

**Curation procedure**: A variety of curation procedures were carried out to ensure that a high-quality dataset was available for statistical analyses and data interpretation. QC and curation processes were designed to ensure accurate and consistent identification of true chemical entities and to remove those representing system artifacts, mis-
assignments, and background noise. Metabolon data analysts use proprietary visualization and interpretation software to confirm the consistency of peak identification among samples. Library matches for each compound were checked for each sample and corrected if necessary.

**Metabolite Quantification and Data Normalization:** Peaks were quantified using area-under-the-curve. For studies spanning multiple days, a data normalization step was performed to correct variation resulting from instrument inter-day tuning differences. Essentially, each compound was corrected in run-day blocks by registering the medians to equal one (1.00) and normalizing each data point proportionately (termed “block correction”). For studies that did not require more than one day of analysis, no normalization was necessary, other than for data visualization. In certain instances, biochemical data may have been normalized to an additional factor (e.g., cell counts, total protein as determined by Bradford assay, osmolality) to account for differences in metabolite levels due to differences in amount of material present in each sample.