

**Supplementary Table S1.** UVMR effect estimates from UK Biobank selected SNPs (main analysis) and Kettunen selected SNPs.

| Metabolite   | Effect estimate (95% CI),<br>UK Biobank selected SNPs | Pval., UK Bi-<br>obank se-<br>lected SNPs | Effect estimate (95% CI),<br>Kettunen selected SNPs | Pval.,<br>Kettunen se-<br>lected SNPs |
|--|---|---|---|---------------------------------------|
| 3-Hydroxybutyrate  | 0.025 (-0.086, 0.137)                                 | 0.654                                     | 0.273 (0.144, 0.403)                                | <0.001                                |
| Acetate  | 0.107 (-0.147, 0.36)                                  | 0.409                                     | --  | --                                    |
| Acetoacetate   | 0.008 (-0.142, 0.159)                                 | 0.915                                     | 0.052 (-0.186, 0.29)                                | 0.666                                 |
| Acetone  | -0.083 (-0.207, 0.041)                                | 0.188                                     | --  | --                                    |
| Alanine  | 0.137 (0.036, 0.239)                                  | 0.008                                     | 0.011 (-0.111, 0.132)                               | 0.862                                 |
| Albumin  | 0.041 (-0.018, 0.101)                                 | 0.175                                     | 0.035 (-0.032, 0.101)                               | 0.308                                 |
| Apolipoprotein A1  | -0.026 (-0.058, 0.006)                                | 0.116                                     | 0.01 (-0.016, 0.037)                                | 0.451                                 |
| Apolipoprotein B   | 0.016 (-0.008, 0.041)                                 | 0.194                                     | 0.006 (-0.017, 0.03)                                | 0.609                                 |
| Citrate  | -0.007 (-0.039, 0.024)                                | 0.641                                     | -0.029 (-0.079, 0.022)                              | 0.264                                 |
| Creatinine   | -0.013 (-0.067, 0.041)                                | 0.639                                     | -0.02 (-0.084, 0.045)                               | 0.549                                 |
| Docosahexaenoic acid                                     | 0.004 (-0.025, 0.033)                                 | 0.796                                     | 0.046 (-0.013, 0.105)                               | 0.124                                 |
| Glucose  | 0.328 (0.219, 0.436)                                  | 0.000                                     | 0.259 (0.104, 0.414)                                | 0.001                                 |
| Glutamine  | 0.089 (0.033, 0.144)                                  | 0.002                                     | 0.071 (-0.049, 0.192)                               | 0.247                                 |
| Glycine  | 0.016 (-0.011, 0.042)                                 | 0.242                                     | --  | --                                    |
| Glycoprotein acetyls                                     | 0.027 (-0.007, 0.06)                                  | 0.119                                     | 0 (-0.052, 0.053)                                   | 0.997                                 |
| Histidine  | 0.058 (-0.08, 0.195)                                  | 0.412                                     | 0 (-0.085, 0.084)                                   | 0.995                                 |
| Isoleucine   | -0.046 (-0.17, 0.078)                                 | 0.469                                     | -0.127 (-0.226, -0.029)                             | 0.011                                 |
| Lactate  | -0.146 (-0.365, 0.073)                                | 0.190                                     | -0.022 (-0.386, 0.342)                              | 0.906                                 |
| Leucine  | -0.012 (-0.156, 0.132)                                | 0.871                                     | -0.074 (-0.186, 0.038)                              | 0.197                                 |
| Linoleic acid  | 0.01 (-0.021, 0.04)                                   | 0.536                                     | 0.002 (-0.024, 0.028)                               | 0.874                                 |
| Monounsaturated fatty acids                              | 0.003 (-0.024, 0.031)                                 | 0.806                                     | 0.013 (-0.049, 0.075)                               | 0.687                                 |
| Omega-3 fatty acids                                      | 0.001 (-0.021, 0.023)                                 | 0.939                                     | 0.006 (-0.067, 0.079)                               | 0.873                                 |
| Omega-6 fatty acids                                      | 0.007 (-0.021, 0.035)                                 | 0.642                                     | 0.006 (-0.027, 0.039)                               | 0.718                                 |
| Phenylalanine  | -0.024 (-0.088, 0.04)                                 | 0.460                                     | -0.055 (-0.115, 0.006)                              | 0.076                                 |
| Phosphatidylcholines                                     | -0.001 (-0.034, 0.033)                                | 0.973                                     | -0.002 (-0.033, 0.029)                              | 0.898                                 |
| Pyruvate   | -0.015 (-0.072, 0.041)                                | 0.590                                     | -0.135 (-0.239, -0.031)                             | 0.011                                 |
| Saturated fatty acids                                    | 0.002 (-0.032, 0.036)                                 | 0.904                                     | 0.023 (-0.04, 0.086)                                | 0.470                                 |
| Sphingomyelins   | 0.011 (-0.023, 0.045)                                 | 0.527                                     | 0.003 (-0.033, 0.038)                               | 0.880                                 |
| Total esterified cholesterol                             | 0.008 (-0.021, 0.037)                                 | 0.592                                     | --  | --                                    |
| Total free cholesterol                                   | 0.004 (-0.024, 0.033)                                 | 0.761                                     | 0.014 (-0.008, 0.037)                               | 0.206                                 |
| Total lipids in chylomicrons and<br>extremely large VLDL | 0.029 (-0.001, 0.059)                                 | 0.058                                     | 0.001 (-0.077, 0.08)                                | 0.976                                 |
| Total lipids in IDL                                      | 0.019 (-0.011, 0.048)                                 | 0.220                                     | 0.007 (-0.012, 0.027)                               | 0.470                                 |
| Total lipids in large HDL                                | -0.009 (-0.033, 0.016)                                | 0.491                                     | 0.007 (-0.013, 0.027)                               | 0.516                                 |
| Total lipids in large LDL                                | 0.011 (-0.014, 0.035)                                 | 0.396                                     | 0.01 (-0.009, 0.029)                                | 0.307                                 |
| Total lipids in large VLDL                               | 0.026 (-0.003, 0.055)                                 | 0.083                                     | 0.005 (-0.049, 0.058)                               | 0.864                                 |
| Total lipids in medium HDL                               | -0.023 (-0.054, 0.008)                                | 0.150                                     | 0.047 (-0.006, 0.1)                                 | 0.082                                 |
| Total lipids in medium LDL                               | 0.016 (-0.011, 0.043)                                 | 0.249                                     | 0.013 (-0.007, 0.033)                               | 0.199                                 |
| Total lipids in medium VLDL                              | 0.017 (-0.012, 0.045)                                 | 0.253                                     | 0.008 (-0.039, 0.054)                               | 0.748                                 |
| Total lipids in small HDL                                | -0.013 (-0.054, 0.027)                                | 0.526                                     | 0.001 (-0.036, 0.038)                               | 0.951                                 |
| Total lipids in small VLDL                               | 0.013 (-0.014, 0.04)                                  | 0.337                                     | 0.002 (-0.037, 0.042)                               | 0.907                                 |
| Total lipids in very large HDL                           | 0 (-0.026, 0.025)                                     | 0.978                                     | -0.006 (-0.032, 0.02)                               | 0.645                                 |
| Total lipids in very small VLDL                          | 0.007 (-0.016, 0.03)                                  | 0.544                                     | 0.006 (-0.021, 0.033)                               | 0.645                                 |
| Total phospholipids in lipopro-<br>tein particles        | 0.006 (-0.03, 0.041)                                  | 0.748                                     | --  | --                                    |

|                     |                        |       |                        |       |
|---------------------|------------------------|-------|------------------------|-------|
| Total triglycerides | 0.013 (-0.014, 0.041)  | 0.351 | --                     | --    |
| Tyrosine            | 0.031 (-0.037, 0.098)  | 0.371 | 0.002 (-0.042, 0.047)  | 0.911 |
| Valine              | -0.043 (-0.108, 0.023) | 0.205 | -0.012 (-0.061, 0.037) | 0.642 |

CI: confidence interval; pval.: p-value. "--" indicating no SNPs were available for analyses.

**Supplementary Table S2.** The number of SNPs (K) representing each metabolite in UVMR analyses.

| (1) UKBB selected SNPs                                |          | (2) Kettunen selected SNPs                            |          | Number of overlapping SNPs (k) |
|---|----------|---|----------|--------------------------------|
| Metabolite  | SNPs (K) | Metabolite  | SNPs (K) |                                |
| 3-Hydroxybutyrate                                     | 17       | 3-Hydroxybutyrate                                     | 1        | 0                              |
| Acetate   | 9        | Acetate   | 0        | 0                              |
| Acetoacetate  | 7        | Acetoacetate  | 2        | 1                              |
| Acetone   | 11       | Acetone   | 0        | 0                              |
| Alanine   | 33       | Alanine   | 6        | 2                              |
| Albumin   | 33       | Albumin   | 4        | 0                              |
| Apolipoprotein A1                                     | 93       | Apolipoprotein A1                                     | 13       | 1                              |
| Apolipoprotein B                                      | 68       | Apolipoprotein B                                      | 25       | 3                              |
| Citrate   | 38       | Citrate   | 5        | 0                              |
| Creatinine  | 69       | Creatinine  | 6        | 1                              |
| Docosahexaenoic acid                                  | 61       | Docosahexaenoic acid                                  | 6        | 0                              |
| Glucose   | 23       | Glucose   | 4        | 1                              |
| Glutamine   | 47       | Glutamine   | 5        | 2                              |
| Glycine   | 65       | Glycine   | 0        | 0                              |
| Glycoprotein acetyls                                  | 71       | Glycoprotein acetyls                                  | 9        | 0                              |
| Histidine   | 20       | Histidine   | 5        | 1                              |
| Isoleucine  | 9        | Isoleucine  | 1        | 1                              |
| Lactate   | 10       | Lactate   | 2        | 0                              |
| Leucine   | 17       | Leucine   | 3        | 1                              |
| Linoleic acid   | 63       | Linoleic acid   | 17       | 2                              |
| Monounsaturated fatty acids                           | 84       | Monounsaturated fatty acids                           | 7        | 2                              |
| Omega-3 fatty acids                                   | 75       | Omega-3 fatty acids                                   | 6        | 2                              |
| Omega-6 fatty acids                                   | 67       | Omega-6 fatty acids                                   | 12       | 2                              |
| Phenylalanine   | 14       | Phenylalanine   | 4        | 0                              |
| Phosphatidylcholines                                  | 79       | Phosphatidylcholine                                   | 8        | 2                              |
| Pyruvate  | 20       | Pyruvate  | 1        | 1                              |
| Saturated fatty acids                                 | 69       | Saturated fatty acids                                 | 7        | 2                              |
| Sphingomyelins  | 70       | Sphingomyelins  | 8        | 1                              |
| Total esterified cholesterol                          | 74       | Total esterified cholesterol                          | 0        | 0                              |
| Total free cholesterol                                | 67       | Total free cholesterol                                | 19       | 1                              |
| Total lipids in chylomicrons and extremely large VLDL | 83       | Total lipids in chylomicrons and extremely large VLDL | 7        | 2                              |
| Total lipids in IDL                                   | 69       | Total lipids in IDL                                   | 28       | 2                              |
| Total lipids in large HDL                             | 144      | Total lipids in large HDL                             | 18       | 2                              |
| Total lipids in large LDL                             | 62       | Total lipids in large LDL                             | 31       | 2                              |
| Total lipids in large VLDL                            | 90       | Total lipids in large VLDL                            | 9        | 3                              |
| Total lipids in medium HDL                            | 83       | Total lipids in medium HDL                            | 6        | 1                              |
| Total lipids in medium LDL                            | 56       | Total lipids in medium LDL                            | 26       | 1                              |
| Total lipids in medium VLDL                           | 81       | Total lipids in medium VLDL                           | 11       | 3                              |
| Total lipids in small HDL                             | 60       | Total lipids in small HDL                             | 12       | 1                              |
| Total lipids in small VLDL                            | 97       | Total lipids in small VLDL                            | 15       | 3                              |

|  |     |  |    |   |
|--|-----|--|----|---|
| Total lipids in very large HDL               | 123 | Total lipids in very large HDL               | 17 | 2 |
| Total lipids in very small VLDL              | 89  | Total lipids in very small VLDL              | 23 | 2 |
| Total phospholipids in lipoprotein particles | 70  | Total phospholipids in lipoprotein particles | 0  | 0 |
| Total triglycerides                          | 90  | Total triglycerides                          | 12 | 2 |
| Tyrosine                                     | 37  | Tyrosine                                     | 6  | 1 |
| Valine                                       | 24  | Valine                                       | 5  | 0 |

**Supplementary Table S3.** Mean F-statistics calculated for UVMR models.

| (1) UKBB selected SNPs                                |             | (2) Kettunen selected SNPs                            |             |
|---|-------------|---|-------------|
| Metabolite  | F-statistic | Metabolite  | F-statistic |
| 3-Hydroxybutyrate                                     | 64.084      | 3-Hydroxybutyrate                                     | 53.058      |
| Acetate   | 58.695      | Acetate   | --          |
| Acetoacetate  | 67.801      | Acetoacetate  | 36.916      |
| Acetone   | 61.027      | Acetone   | --          |
| Alanine   | 71.857      | Alanine   | 56.976      |
| Albumin   | 80.183      | Albumin   | 69.368      |
| Apolipoprotein A1                                     | 107.162     | Apolipoprotein A1                                     | 77.232      |
| Apolipoprotein B                                      | 137.030     | Apolipoprotein B                                      | 68.099      |
| Citrate   | 121.023     | Citrate   | 59.670      |
| Creatinine  | 54.863      | Creatinine  | 44.599      |
| Docosahexaenoic acid                                  | 152.255     | Docosahexaenoic acid                                  | 50.966      |
| Glucose   | 68.441      | Glucose   | 70.268      |
| Glutamine   | 112.504     | Glutamine   | 81.723      |
| Glycine   | 296.942     | Glycine   | --          |
| Glycoprotein acetyls                                  | 89.138      | Glycoprotein acetyls                                  | 58.778      |
| Histidine   | 75.065      | Histidine   | 52.215      |
| Isoleucine  | 96.513      | Isoleucine  | 66.965      |
| Lactate   | 59.865      | Lactate   | 31.871      |
| Leucine   | 82.782      | Leucine   | 74.680      |
| Linoleic acid   | 104.567     | Linoleic acid   | 61.669      |
| Monounsaturated fatty acids                           | 106.689     | Monounsaturated fatty acids                           | 55.607      |
| Omega-3 fatty acids                                   | 175.109     | Omega-3 fatty acids                                   | 62.058      |
| Omega-6 fatty acids                                   | 104.670     | Omega-6 fatty acids                                   | 59.918      |
| Phenylalanine   | 107.049     | Phenylalanine   | 52.999      |
| Phosphatidylcholines                                  | 120.368     | Phosphatidylcholine                                   | 61.189      |
| Pyruvate  | 98.857      | Pyruvate  | 65.721      |
| Saturated fatty acids                                 | 99.724      | Saturated fatty acids                                 | 58.279      |
| Sphingomyelins  | 132.187     | Sphingomyelins  | 56.732      |
| Total esterified cholesterol                          | 115.212     | Total esterified cholesterol                          | --          |
| Total free cholesterol                                | 119.797     | Total free cholesterol                                | 68.503      |
| Total lipids in chylomicrons and extremely large VLDL | 127.063     | Total lipids in chylomicrons and extremely large VLDL | 51.760      |
| Total lipids in IDL                                   | 146.857     | Total lipids in IDL                                   | 76.197      |
| Total lipids in large HDL                             | 115.069     | Total lipids in large HDL                             | 99.755      |
| Total lipids in large LDL                             | 150.708     | Total lipids in large LDL                             | 81.236      |
| Total lipids in large VLDL                            | 112.514     | Total lipids in large VLDL                            | 65.241      |
| Total lipids in medium HDL                            | 111.625     | Total lipids in medium HDL                            | 54.489      |
| Total lipids in medium LDL                            | 147.602     | Total lipids in medium LDL                            | 86.031      |
| Total lipids in medium VLDL                           | 105.435     | Total lipids in medium VLDL                           | 72.931      |

|  |         |  |         |
|--|---------|--|---------|
| Total lipids in small HDL                    | 96.463  | Total lipids in small HDL                    | 62.835  |
| Total lipids in small VLDL                   | 104.649 | Total lipids in small VLDL                   | 74.749  |
| Total lipids in very large HDL               | 119.263 | Total lipids in very large HDL               | 100.951 |
| Total lipids in very small VLDL              | 135.738 | Total lipids in very small VLDL              | 69.348  |
| Total phospholipids in lipoprotein particles | 114.359 | Total phospholipids in lipoprotein particles | ---     |
| Total triglycerides                          | 117.926 | Total triglycerides                          | 82.273  |
| Tyrosine                                     | 100.275 | Tyrosine                                     | 51.474  |
| Valine                                       | 94.578  | Valine                                       | 70.021  |

“---” is used where it was not possible to estimate the F-statistic for this metabolite.

**Supplementary Table S4: MVMR effect estimates using UKBB selected SNPs.**

| Metabolite        | Effect estimate (95% CI) | Pval.  |
|-------------------|--------------------------|--------|
| Alanine           | 0.083 (-0.016, 0.181)    | 0.104  |
| 3-Hydroxybutyrate | -0.011 (-0.141, 0.119)   | 0.972  |
| Glutamine         | 0.074 (0.019, 0.13)      | 0.011  |
| Glucose           | 0.291 (0.193, 0.389)     | <0.001 |
| Isoleucine        | -0.018 (-0.158, 0.123)   | 0.805  |
| Pyruvate          | -0.081 (-0.176, 0.013)   | 0.096  |

CI: confidence interval; pval.: p-value.

**Supplementary Table S5. MVMR effect estimates using Kettunen selected SNPs**

| Metabolite        | Effect estimate (95% CI) | Pval. |
|-------------------|--------------------------|-------|
| Alanine           | 0.115 (-0.231, 0.462)    | 0.539 |
| 3-Hydroxybutyrate | 0.322 (-0.33, 0.974)     | 0.370 |
| Glutamine         | 0.076 (-0.106, 0.257)    | 0.445 |
| Glucose           | 0.377 (0.093, 0.661)     | 0.041 |
| Isoleucine        | 0.032 (-0.782, 0.846)    | 0.941 |
| Pyruvate          | -0.026 (-0.851, 0.8)     | 0.954 |

CI: confidence interval; ; pval.: p-value.

**Supplementary Table S6. List of GWAS's included in SNP selection.**

| Analysis      | Samples included in SNP selection | Independent sample from UKBB | Number of metabolic measures available | Sample size |
|---------------|-----------------------------------|------------------------------|--|-------------|
| UKBB GWAS     | UKBB                              | No                           | 46                                     | 115,078     |
| Kettunen GWAS | Kettunen                          | Yes                          | 42                                     | 24,925      |

**Supplementary Table S7. UKBB NMR Metabolites included in analysis.**

| Biomarker name                     | Group                      | Subgroup | Included | Reason for exclusion                                   |
|------------------------------------|----------------------------|----------|----------|--|
| 3-Hydroxybutyrate                  | Ketone bodies              |          | Yes      | --   |
| Acetate                            | Ketone bodies              |          | Yes      | --   |
| Acetoacetate                       | Ketone bodies              |          | Yes      | --   |
| Acetone                            | Ketone bodies              |          | Yes      | --   |
| Alanine                            | Amino acids                |          | Yes      | --   |
| Albumin                            | Fluid balance              |          | Yes      | --   |
| Apolipoprotein A1                  | Apolipoproteins            |          | Yes      | --   |
| Apolipoprotein B                   | Apolipoproteins            |          | Yes      | --   |
| Average diameter for HDL particles | Lipoprotein particle sizes |          | No       | Representative of lipid composition within lipoprotein |

|  |   |   |    |   |
|--|---|---|----|---|
| Average diameter for LDL particles   | Lipoprotein particle sizes                |   | No | Representative of lipid composition within lipoprotein          |
| Average diameter for VLDL particles  | Lipoprotein particle sizes                |   | No | Representative of lipid composition within lipoprotein          |
| Cholesterol in chylomicrons and extremely large VLDL                       | Lipoprotein subclasses                    | Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards) | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in IDL   | Lipoprotein subclasses                    | IDL (average diameter 28.6 nm)  | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in large HDL   | Lipoprotein subclasses                    | Large HDL (average diameter 12.1 nm)  | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in large LDL   | Lipoprotein subclasses                    | Large LDL (average diameter 25.5 nm)  | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in large VLDL  | Lipoprotein subclasses                    | Large VLDL (average diameter 53.6 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in medium HDL  | Lipoprotein subclasses                    | Medium HDL (average diameter 10.9 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in medium LDL  | Lipoprotein subclasses                    | Medium LDL (average diameter 23 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in medium VLDL   | Lipoprotein subclasses                    | Medium VLDL (average diameter 44.5 nm)  | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in small HDL   | Lipoprotein subclasses                    | Small HDL (average diameter 8.7 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in small LDL   | Lipoprotein subclasses                    | Small LDL (average diameter 18.7 nm)  | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in small VLDL  | Lipoprotein subclasses                    | Small VLDL (average diameter 36.8 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in very large HDL  | Lipoprotein subclasses                    | Very large HDL (average diameter 14.3 nm)                                     | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in very large VLDL   | Lipoprotein subclasses                    | Very large VLDL (average diameter 64 nm)                                      | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol in very small VLDL   | Lipoprotein subclasses                    | Very small VLDL (average diameter 31.3 nm)                                    | No | Representative of lipid composition within lipoprotein subclass |
| Cholesterol to total lipids ratio in chylomicrons and extremely large VLDL | Relative lipoprotein lipid concentrations | Chylomicrons and extremely large VLDL ratios                                  | No | Derived measure   |
| Cholesterol to total lipids ratio in IDL                                   | Relative lipoprotein lipid concentrations | IDL ratios  | No | Derived measure   |

|   |   |   |    |   |
|---|---|---|----|---|
| Cholesterol to total lipids ratio in large HDL              | Relative lipoprotein lipid concentrations | Large HDL ratios  | No | Derived measure   |
| Cholesterol to total lipids ratio in large LDL              | Relative lipoprotein lipid concentrations | Large LDL ratios  | No | Derived measure   |
| Cholesterol to total lipids ratio in large VLDL             | Relative lipoprotein lipid concentrations | Large VLDL ratios   | No | Derived measure   |
| Cholesterol to total lipids ratio in medium HDL             | Relative lipoprotein lipid concentrations | Medium HDL ratios   | No | Derived measure   |
| Cholesterol to total lipids ratio in medium LDL             | Relative lipoprotein lipid concentrations | Medium LDL ratios   | No | Derived measure   |
| Cholesterol to total lipids ratio in medium VLDL            | Relative lipoprotein lipid concentrations | Medium VLDL ratios  | No | Derived measure   |
| Cholesterol to total lipids ratio in small HDL              | Relative lipoprotein lipid concentrations | Small HDL ratios  | No | Derived measure   |
| Cholesterol to total lipids ratio in small LDL              | Relative lipoprotein lipid concentrations | Small LDL ratios  | No | Derived measure   |
| Cholesterol to total lipids ratio in small VLDL             | Relative lipoprotein lipid concentrations | Small VLDL ratios   | No | Derived measure   |
| Cholesterol to total lipids ratio in very large HDL         | Relative lipoprotein lipid concentrations | Very large HDL ratios   | No | Derived measure   |
| Cholesterol to total lipids ratio in very large VLDL        | Relative lipoprotein lipid concentrations | Very large VLDL ratios  | No | Derived measure   |
| Cholesterol to total lipids ratio in very small VLDL        | Relative lipoprotein lipid concentrations | Very small VLDL ratios  | No | Derived measure   |
| Cholesteryl esters in chylomicrons and extremely large VLDL | Lipoprotein subclasses                    | Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards) | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in HDL                                   | Cholesteryl esters                        |   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in IDL                                   | Lipoprotein subclasses                    | IDL (average diameter 28.6 nm)  | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in large HDL                             | Lipoprotein subclasses                    | Large HDL (average diameter 12.1 nm)  | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in large LDL                             | Lipoprotein subclasses                    | Large LDL (average diameter 25.5 nm)  | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in large VLDL                            | Lipoprotein subclasses                    | Large VLDL (average diameter 53.6 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in LDL                                   | Cholesteryl esters                        |   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in medium HDL                            | Lipoprotein subclasses                    | Medium HDL (average diameter 10.9 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in medium LDL                            | Lipoprotein subclasses                    | Medium LDL (average diameter 23 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in medium VLDL                           | Lipoprotein subclasses                    | Medium VLDL (average diameter 44.5 nm)  | No | Representative of lipid composition within lipoprotein subclass |

|   |   |  |    |   |
|---|---|--|----|---|
| Cholesteryl esters in small HDL   | Lipoprotein sub-classes                   | Small HDL (average diameter 8.7 nm)          | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in small LDL   | Lipoprotein sub-classes                   | Small LDL (average diameter 18.7 nm)         | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in small VLDL  | Lipoprotein sub-classes                   | Small VLDL (average diameter 36.8 nm)        | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in very large HDL  | Lipoprotein sub-classes                   | Very large HDL (average diameter 14.3 nm)    | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in very large VLDL   | Lipoprotein sub-classes                   | Very large VLDL (average diameter 64 nm)     | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in very small VLDL   | Lipoprotein sub-classes                   | Very small VLDL (average diameter 31.3 nm)   | No | Representative of lipid composition within lipoprotein subclass |
| Cholesteryl esters in VLDL  | Cholesteryl esters                        |  | No | Representative of lipid composition within lipoprotein          |
| Cholesteryl esters to total lipids ratio in chylomicrons and extremely large VLDL | Relative lipoprotein lipid concentrations | Chylomicrons and extremely large VLDL ratios | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in IDL                                   | Relative lipoprotein lipid concentrations | IDL ratios                                   | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in large HDL                             | Relative lipoprotein lipid concentrations | Large HDL ratios                             | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in large LDL                             | Relative lipoprotein lipid concentrations | Large LDL ratios                             | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in large VLDL                            | Relative lipoprotein lipid concentrations | Large VLDL ratios                            | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in medium HDL                            | Relative lipoprotein lipid concentrations | Medium HDL ratios                            | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in medium LDL                            | Relative lipoprotein lipid concentrations | Medium LDL ratios                            | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in medium VLDL                           | Relative lipoprotein lipid concentrations | Medium VLDL ratios                           | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in small HDL                             | Relative lipoprotein lipid concentrations | Small HDL ratios                             | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in small LDL                             | Relative lipoprotein lipid concentrations | Small LDL ratios                             | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in small VLDL                            | Relative lipoprotein lipid concentrations | Small VLDL ratios                            | No | Derived measure   |
| Cholesteryl esters to total lipids ratio in very large HDL                        | Relative lipoprotein lipid concentrations | Very large HDL ratios                        | No | Derived measure   |

|  |   |   |     |   |
|--|---|---|-----|---|
| Cholesteryl esters to total lipids ratio in very large VLDL      | Relative lipoprotein lipid concentrations | Very large VLDL ratios  | No  | Derived measure   |
| Cholesteryl esters to total lipids ratio in very small VLDL      | Relative lipoprotein lipid concentrations | Very small VLDL ratios  | No  | Derived measure   |
| Citrate  | Glycolysis related metabolites            |   | Yes | --  |
| Clinical LDL cholesterol   | Cholesterol                               |   | No  | Representative of lipid composition within lipoprotein            |
| Concentration of chylomicrons and extremely large VLDL particles | Lipoprotein subclasses                    | Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards) | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of HDL particles                                   | Lipoprotein particle concentrations       |   | No  | Representative of lipid concentration within lipoprotein subclass |
| Concentration of IDL particles                                   | Lipoprotein subclasses                    | IDL (average diameter 28.6 nm)  | No  | Representative of lipid concentration within lipoprotein subclass |
| Concentration of large HDL particles                             | Lipoprotein subclasses                    | Large HDL (average diameter 12.1 nm)  | No  | Representative of lipid concentration within lipoprotein subclass |
| Concentration of large LDL particles                             | Lipoprotein subclasses                    | Large LDL (average diameter 25.5 nm)  | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of large VLDL particles                            | Lipoprotein subclasses                    | Large VLDL (average diameter 53.6 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of LDL particles                                   | Lipoprotein particle concentrations       |   | No  | Representative of lipid concentration within lipoprotein subclass |
| Concentration of medium HDL particles                            | Lipoprotein subclasses                    | Medium HDL (average diameter 10.9 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of medium LDL particles                            | Lipoprotein subclasses                    | Medium LDL (average diameter 23 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of medium VLDL particles                           | Lipoprotein subclasses                    | Medium VLDL (average diameter 44.5 nm)  | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of small HDL particles                             | Lipoprotein subclasses                    | Small HDL (average diameter 8.7 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of small LDL particles                             | Lipoprotein subclasses                    | Small LDL (average diameter 18.7 nm)  | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of small VLDL particles                            | Lipoprotein subclasses                    | Small VLDL (average diameter 36.8 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of very large HDL particles                        | Lipoprotein subclasses                    | Very large HDL (average diameter 14.3 nm)                                     | No  | Representative of lipid composition within lipoprotein subclass   |



|   |                                     |   |     |   |
|---|-------------------------------------|---|-----|---|
| Concentration of very large VLDL particles                | Lipoprotein sub-classes             | Very large VLDL (average diameter 64 nm)                                      | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of very small VLDL particles                | Lipoprotein sub-classes             | Very small VLDL (average diameter 31.3 nm)                                    | No  | Representative of lipid composition within lipoprotein subclass   |
| Concentration of VLDL particles                           | Lipoprotein particle concentrations |   | No  | Representative of lipid concentration within lipoprotein subclass |
| Creatinine  | Fluid balance                       |   | Yes | --  |
| Degree of unsaturation                                    | Fatty acids                         |   | No  | Composite fatty acid measure                                      |
| Docosahexaenoic acid                                      | Fatty acids                         |   | Yes | --  |
| Free cholesterol in chylomicrons and extremely large VLDL | Lipoprotein sub-classes             | Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards) | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in HDL                                   | Free cholesterol                    |   | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in IDL                                   | Lipoprotein sub-classes             | IDL (average diameter 28.6 nm)  | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in large HDL                             | Lipoprotein sub-classes             | Large HDL (average diameter 12.1 nm)  | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in large LDL                             | Lipoprotein sub-classes             | Large LDL (average diameter 25.5 nm)  | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in large VLDL                            | Lipoprotein sub-classes             | Large VLDL (average diameter 53.6 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in LDL                                   | Free cholesterol                    |   | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in medium HDL                            | Lipoprotein sub-classes             | Medium HDL (average diameter 10.9 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in medium LDL                            | Lipoprotein sub-classes             | Medium LDL (average diameter 23 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in medium VLDL                           | Lipoprotein sub-classes             | Medium VLDL (average diameter 44.5 nm)  | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in small HDL                             | Lipoprotein sub-classes             | Small HDL (average diameter 8.7 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in small LDL                             | Lipoprotein sub-classes             | Small LDL (average diameter 18.7 nm)  | No  | Representative of lipid composition within lipoprotein subclass   |
| Free cholesterol in small VLDL                            | Lipoprotein sub-classes             | Small VLDL (average diameter 36.8 nm)   | No  | Representative of lipid composition within lipoprotein subclass   |

|   |   |  |     |   |
|---|---|--|-----|---|
| Free cholesterol in very large HDL  | Lipoprotein sub-classes                   | Very large HDL (average diameter 14.3 nm)    | No  | Representative of lipid composition within lipoprotein subclass |
| Free cholesterol in very large VLDL   | Lipoprotein sub-classes                   | Very large VLDL (average diameter 64 nm)     | No  | Representative of lipid composition within lipoprotein subclass |
| Free cholesterol in very small VLDL   | Lipoprotein sub-classes                   | Very small VLDL (average diameter 31.3 nm)   | No  | Representative of lipid composition within lipoprotein subclass |
| Free cholesterol in VLDL  | Free cholesterol                          |  | No  | Representative of lipid composition within lipoprotein          |
| Free cholesterol to total lipids ratio in chylomicrons and extremely large VLDL | Relative lipoprotein lipid concentrations | Chylomicrons and extremely large VLDL ratios | No  | Derived measure   |
| Free cholesterol to total lipids ratio in IDL                                   | Relative lipoprotein lipid concentrations | IDL ratios                                   | No  | Derived measure   |
| Free cholesterol to total lipids ratio in large HDL                             | Relative lipoprotein lipid concentrations | Large HDL ratios                             | No  | Derived measure   |
| Free cholesterol to total lipids ratio in large LDL                             | Relative lipoprotein lipid concentrations | Large LDL ratios                             | No  | Derived measure   |
| Free cholesterol to total lipids ratio in large VLDL                            | Relative lipoprotein lipid concentrations | Large VLDL ratios                            | No  | Derived measure   |
| Free cholesterol to total lipids ratio in medium HDL                            | Relative lipoprotein lipid concentrations | Medium HDL ratios                            | No  | Derived measure   |
| Free cholesterol to total lipids ratio in medium LDL                            | Relative lipoprotein lipid concentrations | Medium LDL ratios                            | No  | Derived measure   |
| Free cholesterol to total lipids ratio in medium VLDL                           | Relative lipoprotein lipid concentrations | Medium VLDL ratios                           | No  | Derived measure   |
| Free cholesterol to total lipids ratio in small HDL                             | Relative lipoprotein lipid concentrations | Small HDL ratios                             | No  | Derived measure   |
| Free cholesterol to total lipids ratio in small LDL                             | Relative lipoprotein lipid concentrations | Small LDL ratios                             | No  | Derived measure   |
| Free cholesterol to total lipids ratio in small VLDL                            | Relative lipoprotein lipid concentrations | Small VLDL ratios                            | No  | Derived measure   |
| Free cholesterol to total lipids ratio in very large HDL                        | Relative lipoprotein lipid concentrations | Very large HDL ratios                        | No  | Derived measure   |
| Free cholesterol to total lipids ratio in very large VLDL                       | Relative lipoprotein lipid concentrations | Very large VLDL ratios                       | No  | Derived measure   |
| Free cholesterol to total lipids ratio in very small VLDL                       | Relative lipoprotein lipid concentrations | Very small VLDL ratios                       | No  | Derived measure   |
| Glucose   | Glycolysis related metabolites            |  | Yes | --  |
| Glutamine   | Amino acids                               |  | Yes | --  |

|  |                                |   |     |   |
|--|--------------------------------|---|-----|---|
| Glycine  | Amino acids                    |   | Yes | --  |
| Glycoprotein acetyls                                   | Inflammation                   |   | Yes | --  |
| HDL cholesterol  | Cholesterol                    |   | No  | Representative of lipid composition within lipoprotein            |
| Histidine  | Amino acids                    |   | Yes | --  |
| Isoleucine   | Amino acids                    | Branched-chain amino acids  | Yes | --  |
| Lactate  | Glycolysis related metabolites |   | Yes | --  |
| LDL cholesterol  | Cholesterol                    |   | No  | Representative of lipid composition within lipoprotein            |
| Leucine  | Amino acids                    | Branched-chain amino acids  | Yes | --  |
| Linoleic acid  | Fatty acids                    |   | Yes | --  |
| Monounsaturated fatty acids                            | Fatty acids                    |   | Yes | --  |
| Omega-3 fatty acids                                    | Fatty acids                    |   | Yes | --  |
| Omega-6 fatty acids                                    | Fatty acids                    |   | Yes | --  |
| Phenylalanine  | Amino acids                    | Aromatic amino acids  | Yes | --  |
| Phosphatidylcholines                                   | Other lipids                   |   | Yes | --  |
| Phosphoglycerides                                      | Other lipids                   |   | No  | Representative of lipid composition within lipoprotein            |
| Phospholipids in chylomicrons and extremely large VLDL | Lipoprotein sub-classes        | Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards) | No  | Representative of lipid composition within lipoprotein subclass   |
| Phospholipids in HDL                                   | Phospholipids                  |   | No  | Representative of lipid composition within lipoprotein subclass   |
| Phospholipids in IDL                                   | Lipoprotein sub-classes        | IDL (average diameter 28.6 nm)  | No  | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in large HDL                             | Lipoprotein sub-classes        | Large HDL (average diameter 12.1 nm)  | No  | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in large LDL                             | Lipoprotein sub-classes        | Large LDL (average diameter 25.5 nm)  | No  | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in large VLDL                            | Lipoprotein sub-classes        | Large VLDL (average diameter 53.6 nm)   | No  | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in LDL                                   | Phospholipids                  |   | No  | Representative of lipid composition within lipoprotein subclass   |
| Phospholipids in medium HDL                            | Lipoprotein sub-classes        | Medium HDL (average diameter 10.9 nm)   | No  | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in medium LDL                            | Lipoprotein sub-classes        | Medium LDL (average diameter 23 nm)   | No  | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in medium VLDL                           | Lipoprotein sub-classes        | Medium VLDL (average diameter 44.5 nm)  | No  | Representative of lipid composition within lipoprotein subclasses |

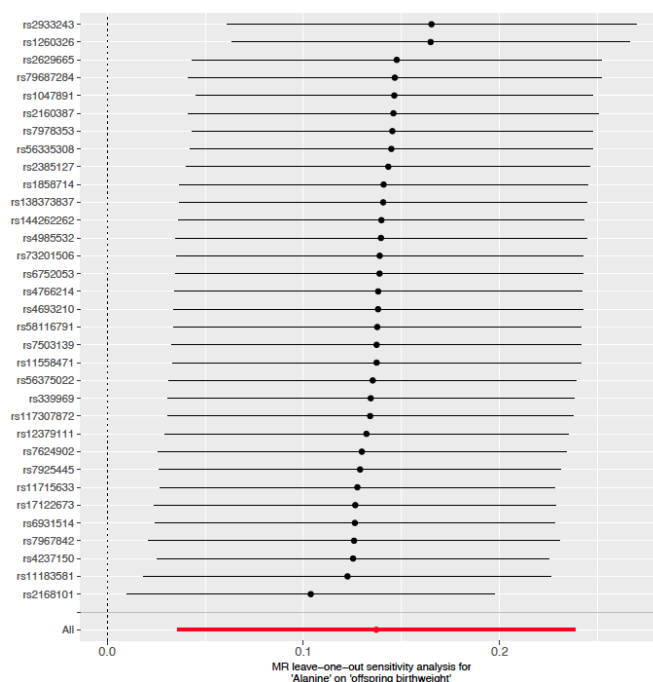
|  |   |  |    |   |
|--|---|--|----|---|
| Phospholipids in small HDL   | Lipoprotein sub-classes                   | Small HDL (average diameter 8.7 nm)          | No | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in small LDL   | Lipoprotein sub-classes                   | Small LDL (average diameter 18.7 nm)         | No | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in small VLDL  | Lipoprotein sub-classes                   | Small VLDL (average diameter 36.8 nm)        | No | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in very large HDL  | Lipoprotein sub-classes                   | Very large HDL (average diameter 14.3 nm)    | No | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in very large VLDL   | Lipoprotein sub-classes                   | Very large VLDL (average diameter 64 nm)     | No | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in very small VLDL   | Lipoprotein sub-classes                   | Very small VLDL (average diameter 31.3 nm)   | No | Representative of lipid composition within lipoprotein subclasses |
| Phospholipids in VLDL  | Phospholipids                             |  | No | Representative of lipid composition within lipoprotein subclass   |
| Phospholipids to total lipids ratio in chylomicrons and extremely large VLDL | Relative lipoprotein lipid concentrations | Chylomicrons and extremely large VLDL ratios | No | Derived measure   |
| Phospholipids to total lipids ratio in IDL                                   | Relative lipoprotein lipid concentrations | IDL ratios                                   | No | Derived measure   |
| Phospholipids to total lipids ratio in large HDL                             | Relative lipoprotein lipid concentrations | Large HDL ratios                             | No | Derived measure   |
| Phospholipids to total lipids ratio in large LDL                             | Relative lipoprotein lipid concentrations | Large LDL ratios                             | No | Derived measure   |
| Phospholipids to total lipids ratio in large VLDL                            | Relative lipoprotein lipid concentrations | Large VLDL ratios                            | No | Derived measure   |
| Phospholipids to total lipids ratio in medium HDL                            | Relative lipoprotein lipid concentrations | Medium HDL ratios                            | No | Derived measure   |
| Phospholipids to total lipids ratio in medium LDL                            | Relative lipoprotein lipid concentrations | Medium LDL ratios                            | No | Derived measure   |
| Phospholipids to total lipids ratio in medium VLDL                           | Relative lipoprotein lipid concentrations | Medium VLDL ratios                           | No | Derived measure   |
| Phospholipids to total lipids ratio in small HDL                             | Relative lipoprotein lipid concentrations | Small HDL ratios                             | No | Derived measure   |
| Phospholipids to total lipids ratio in small LDL                             | Relative lipoprotein lipid concentrations | Small LDL ratios                             | No | Derived measure   |
| Phospholipids to total lipids ratio in small VLDL                            | Relative lipoprotein lipid concentrations | Small VLDL ratios                            | No | Derived measure   |
| Phospholipids to total lipids ratio in very large HDL                        | Relative lipoprotein lipid concentrations | Very large HDL ratios                        | No | Derived measure   |

|   |   |                            |     |                              |
|---|---|----------------------------|-----|------------------------------|
| Phospholipids to total lipids ratio in very large VLDL                            | Relative lipoprotein lipid concentrations | Very large VLDL ratios     | No  | Derived measure              |
| Phospholipids to total lipids ratio in very small VLDL                            | Relative lipoprotein lipid concentrations | Very small VLDL ratios     | No  | Derived measure              |
| Polyunsaturated fatty acids   | Fatty acids                               |                            | No  | Composite fatty acid measure |
| Pyruvate  | Glycolysis related metabolites            |                            | Yes | --                           |
| Ratio of apolipoprotein B to apolipoprotein A1                                    | Apolipoproteins                           |                            | No  | Derived measure              |
| Ratio of docosahexaenoic acid to total fatty acids                                | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of linoleic acid to total fatty acids                                       | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of monounsaturated fatty acids to total fatty acids                         | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of omega-3 fatty acids to total fatty acids                                 | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of omega-6 fatty acids to omega-3 fatty acids                               | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of omega-6 fatty acids to total fatty acids                                 | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of polyunsaturated fatty acids to monounsaturated fatty acids               | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of polyunsaturated fatty acids to total fatty acids                         | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of saturated fatty acids to total fatty acids                               | Fatty acids                               | Fatty acid ratios          | No  | Derived measure              |
| Ratio of triglycerides to phosphoglycerides                                       | Other lipids                              |                            | No  | Derived measure              |
| Remnant cholesterol (non-HDL, non-LDL - cholesterol)                              | Cholesterol                               |                            | No  | Derived measure              |
| Saturated fatty acids   | Fatty acids                               |                            | Yes | ----                         |
| Sphingomyelins  | Other lipids                              |                            | Yes |                              |
| Total cholesterol   | Cholesterol                               |                            | No  |                              |
| Total cholesterol minus HDL-C   | Cholesterol                               |                            | No  | Derived measure              |
| Total cholines  | Other lipids                              |                            | No  |                              |
| Total concentration of branched-chain amino acids (leucine + isoleucine + valine) | Amino acids                               | Branched-chain amino acids | No  | Derived measure              |
| Total concentration of lipoprotein particles                                      | Lipoprotein particle concentrations       |                            | No  |                              |

|  |                         |   |     |                              |
|--|-------------------------|---|-----|------------------------------|
| Total esterified cholesterol                           | Cholesteryl esters      |   | Yes | --                           |
| Total fatty acids                                      | Fatty acids             |   | No  | Composite fatty acid measure |
| Total free cholesterol                                 | Free cholesterol        |   | Yes | --                           |
| Total lipids in chylomicrons and extremely large VLDL  | Lipoprotein sub-classes | Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards) | Yes | --                           |
| Total lipids in HDL                                    | Total lipids            |   | No  |                              |
| Total lipids in IDL                                    | Lipoprotein sub-classes | IDL (average diameter 28.6 nm)  | Yes | --                           |
| Total lipids in large HDL                              | Lipoprotein sub-classes | Large HDL (average diameter 12.1 nm)  | Yes | --                           |
| Total lipids in large LDL                              | Lipoprotein sub-classes | Large LDL (average diameter 25.5 nm)  | Yes | --                           |
| Total lipids in large VLDL                             | Lipoprotein sub-classes | Large VLDL (average diameter 53.6 nm)   | Yes | --                           |
| Total lipids in LDL                                    | Total lipids            |   | No  |                              |
| Total lipids in lipoprotein particles                  | Total lipids            |   | No  |                              |
| Total lipids in medium HDL                             | Lipoprotein sub-classes | Medium HDL (average diameter 10.9 nm)   | Yes | --                           |
| Total lipids in medium LDL                             | Lipoprotein sub-classes | Medium LDL (average diameter 23 nm)   | Yes | --                           |
| Total lipids in medium VLDL                            | Lipoprotein sub-classes | Medium VLDL (average diameter 44.5 nm)  | Yes | --                           |
| Total lipids in small HDL                              | Lipoprotein sub-classes | Small HDL (average diameter 8.7 nm)   | Yes | --                           |
| Total lipids in small LDL                              | Lipoprotein sub-classes | Small LDL (average diameter 18.7 nm)  | No  | High correlation             |
| Total lipids in small VLDL                             | Lipoprotein sub-classes | Small VLDL (average diameter 36.8 nm)   | Yes | --                           |
| Total lipids in very large HDL                         | Lipoprotein sub-classes | Very large HDL (average diameter 14.3 nm)                                     | Yes | --                           |
| Total lipids in very large VLDL                        | Lipoprotein sub-classes | Very large VLDL (average diameter 64 nm)                                      | No  | High correlation             |
| Total lipids in very small VLDL                        | Lipoprotein sub-classes | Very small VLDL (average diameter 31.3 nm)                                    | Yes | --                           |
| Total lipids in VLDL                                   | Total lipids            |   | No  |                              |
| Total phospholipids in lipoprotein particles           | Phospholipids           |   | Yes | --                           |
| Total triglycerides                                    | Triglycerides           |   | Yes | --                           |
| Triglycerides in chylomicrons and extremely large VLDL | Lipoprotein sub-classes | Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards) | No  |                              |
| Triglycerides in HDL                                   | Triglycerides           |   | No  |                              |
| Triglycerides in IDL                                   | Lipoprotein sub-classes | IDL (average diameter 28.6 nm)  | No  |                              |
| Triglycerides in large HDL                             | Lipoprotein sub-classes | Large HDL (average diameter 12.1 nm)  | No  |                              |

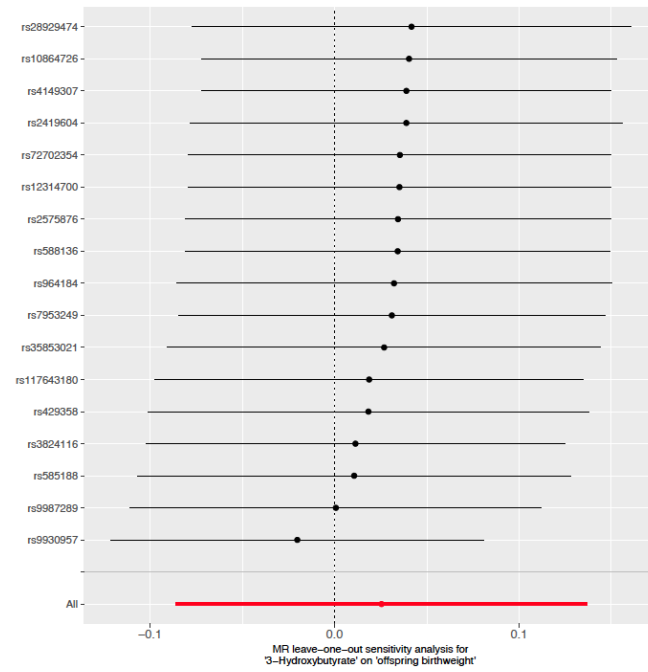
|  |   |  |    |                 |
|--|---|--|----|-----------------|
| Triglycerides in large LDL   | Lipoprotein sub-classes                   | Large LDL (average diameter 25.5 nm)         | No |                 |
| Triglycerides in large VLDL  | Lipoprotein sub-classes                   | Large VLDL (average diameter 53.6 nm)        | No |                 |
| Triglycerides in LDL   | Triglycerides                             |  | No |                 |
| Triglycerides in medium HDL  | Lipoprotein sub-classes                   | Medium HDL (average diameter 10.9 nm)        | No |                 |
| Triglycerides in medium LDL  | Lipoprotein sub-classes                   | Medium LDL (average diameter 23 nm)          | No |                 |
| Triglycerides in medium VLDL   | Lipoprotein sub-classes                   | Medium VLDL (average diameter 44.5 nm)       | No |                 |
| Triglycerides in small HDL   | Lipoprotein sub-classes                   | Small HDL (average diameter 8.7 nm)          | No |                 |
| Triglycerides in small LDL   | Lipoprotein sub-classes                   | Small LDL (average diameter 18.7 nm)         | No |                 |
| Triglycerides in small VLDL  | Lipoprotein sub-classes                   | Small VLDL (average diameter 36.8 nm)        | No |                 |
| Triglycerides in very large HDL  | Lipoprotein sub-classes                   | Very large HDL (average diameter 14.3 nm)    | No |                 |
| Triglycerides in very large VLDL   | Lipoprotein sub-classes                   | Very large VLDL (average diameter 64 nm)     | No |                 |
| Triglycerides in very small VLDL   | Lipoprotein sub-classes                   | Very small VLDL (average diameter 31.3 nm)   | No |                 |
| Triglycerides in VLDL  | Triglycerides                             |  | No |                 |
| Triglycerides to total lipids ratio in chylomicrons and extremely large VLDL | Relative lipoprotein lipid concentrations | Chylomicrons and extremely large VLDL ratios | No | Derived measure |
| Triglycerides to total lipids ratio in IDL                                   | Relative lipoprotein lipid concentrations | IDL ratios                                   | No | Derived measure |
| Triglycerides to total lipids ratio in large HDL                             | Relative lipoprotein lipid concentrations | Large HDL ratios                             | No | Derived measure |
| Triglycerides to total lipids ratio in large LDL                             | Relative lipoprotein lipid concentrations | Large LDL ratios                             | No | Derived measure |
| Triglycerides to total lipids ratio in large VLDL                            | Relative lipoprotein lipid concentrations | Large VLDL ratios                            | No | Derived measure |
| Triglycerides to total lipids ratio in medium HDL                            | Relative lipoprotein lipid concentrations | Medium HDL ratios                            | No | Derived measure |
| Triglycerides to total lipids ratio in medium LDL                            | Relative lipoprotein lipid concentrations | Medium LDL ratios                            | No | Derived measure |
| Triglycerides to total lipids ratio in medium VLDL                           | Relative lipoprotein lipid concentrations | Medium VLDL ratios                           | No | Derived measure |
| Triglycerides to total lipids ratio in small HDL                             | Relative lipoprotein lipid concentrations | Small HDL ratios                             | No | Derived measure |
| Triglycerides to total lipids ratio in small LDL                             | Relative lipoprotein lipid concentrations | Small LDL ratios                             | No | Derived measure |
| Triglycerides to total lipids ratio in small VLDL                            | Relative lipoprotein lipid concentrations | Small VLDL ratios                            | No | Derived measure |

|  |   |                            |     |   |
|--|---|----------------------------|-----|---|
| Triglycerides to total lipids ratio in very large HDL  | Relative lipoprotein lipid concentrations | Very large HDL ratios      | No  | Derived measure   |
| Triglycerides to total lipids ratio in very large VLDL | Relative lipoprotein lipid concentrations | Very large VLDL ratios     | No  | Derived measure   |
| Triglycerides to total lipids ratio in very small VLDL | Relative lipoprotein lipid concentrations | Very small VLDL ratios     | No  | Derived measure   |
| Tyrosine   | Amino acids                               | Aromatic amino acids       | Yes | --  |
| Valine   | Amino acids                               | Branched-chain amino acids | Yes | --  |
| VLDL cholesterol                                       | Cholesterol                               |                            | No  | Representative of lipid composition within lipoprotein subclass |

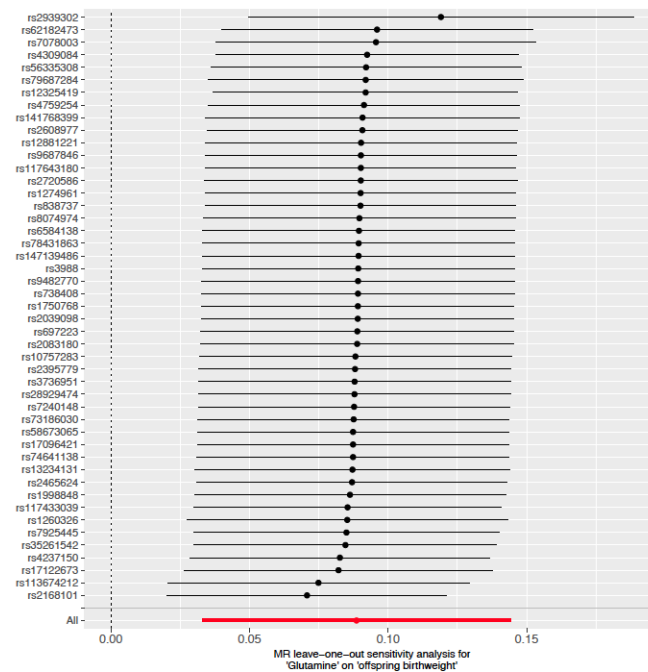


(A)

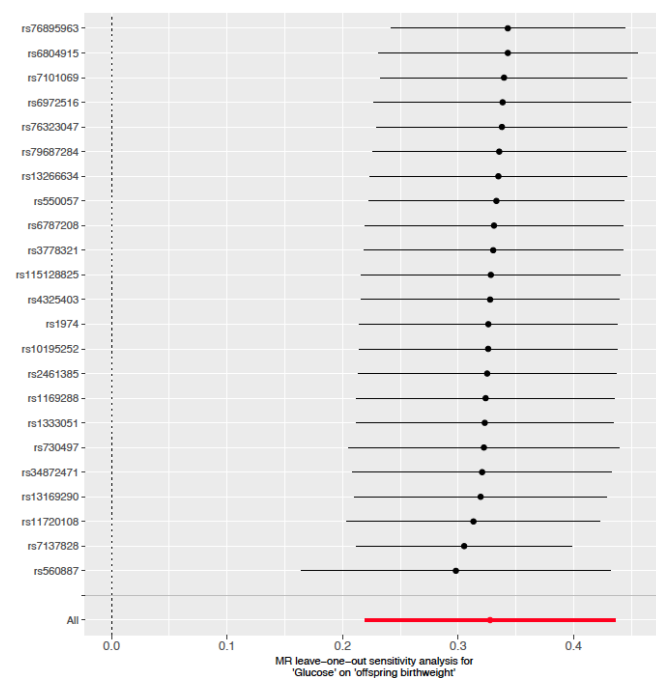




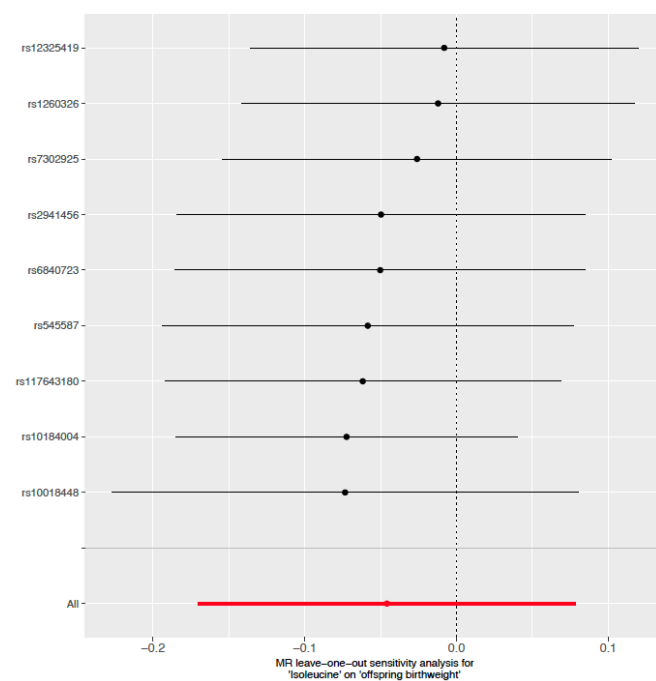
(B)



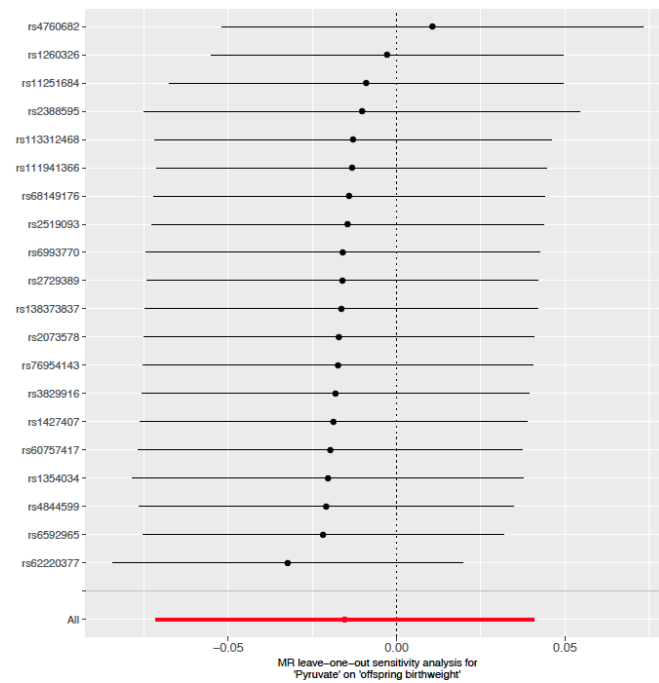
(C)



(D)

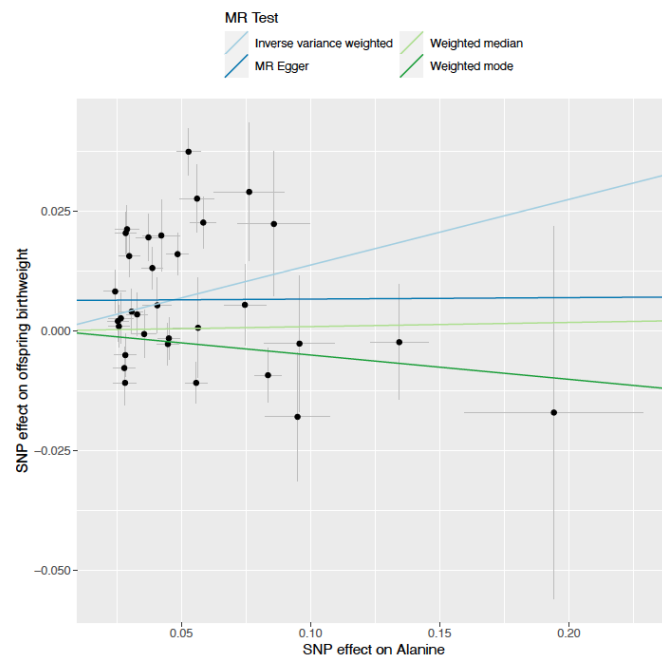


(E)

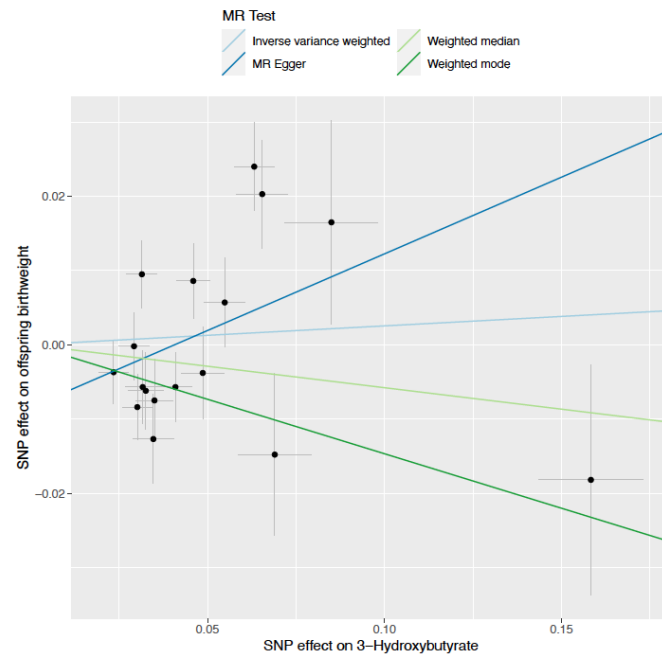


(F)

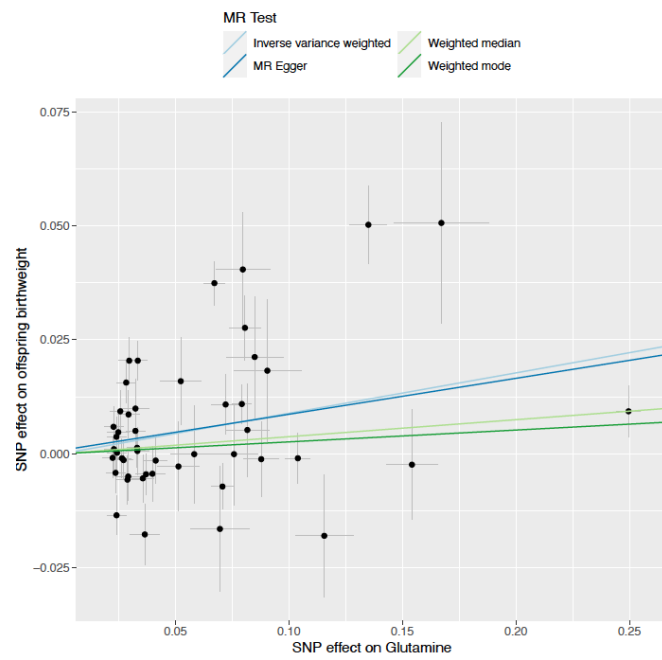
**Supplementary Figures S1 (A)-(F):** Plots of the leave-one-out sensitivity analysis of the IVW MR analysis excluding the specified SNP; a) alanine, b) 3-hydroxybutyrate, c) glutamine, d) glucose, e) isoleucine, f) pyruvate.



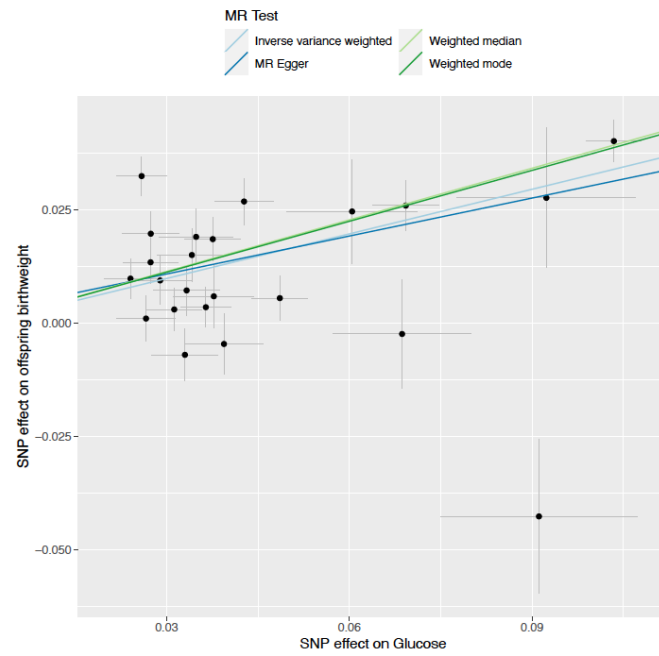
(A)



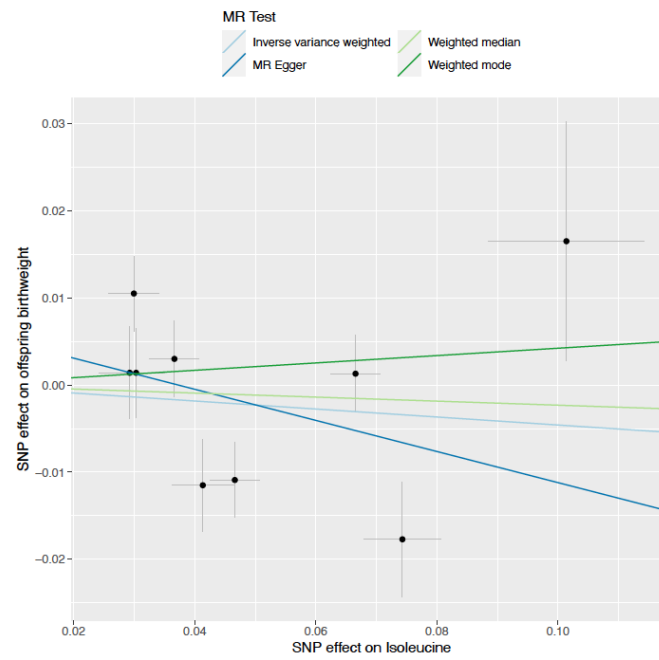
(B)



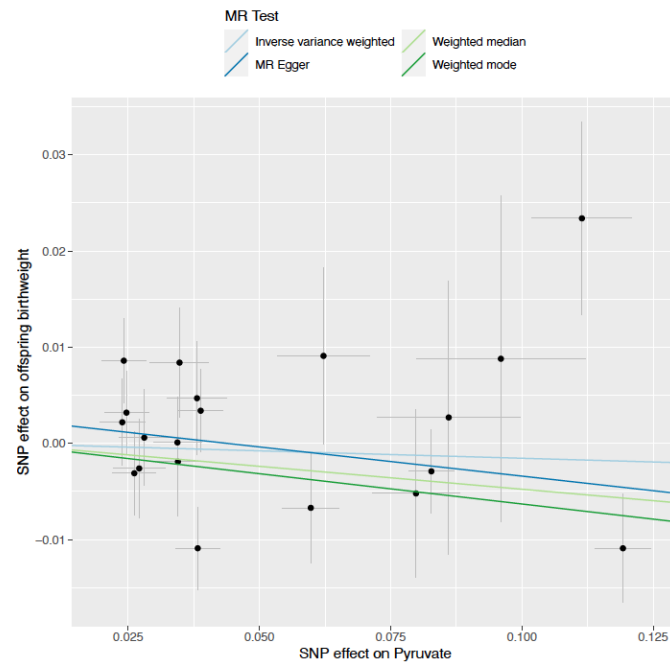
(C)



(D)

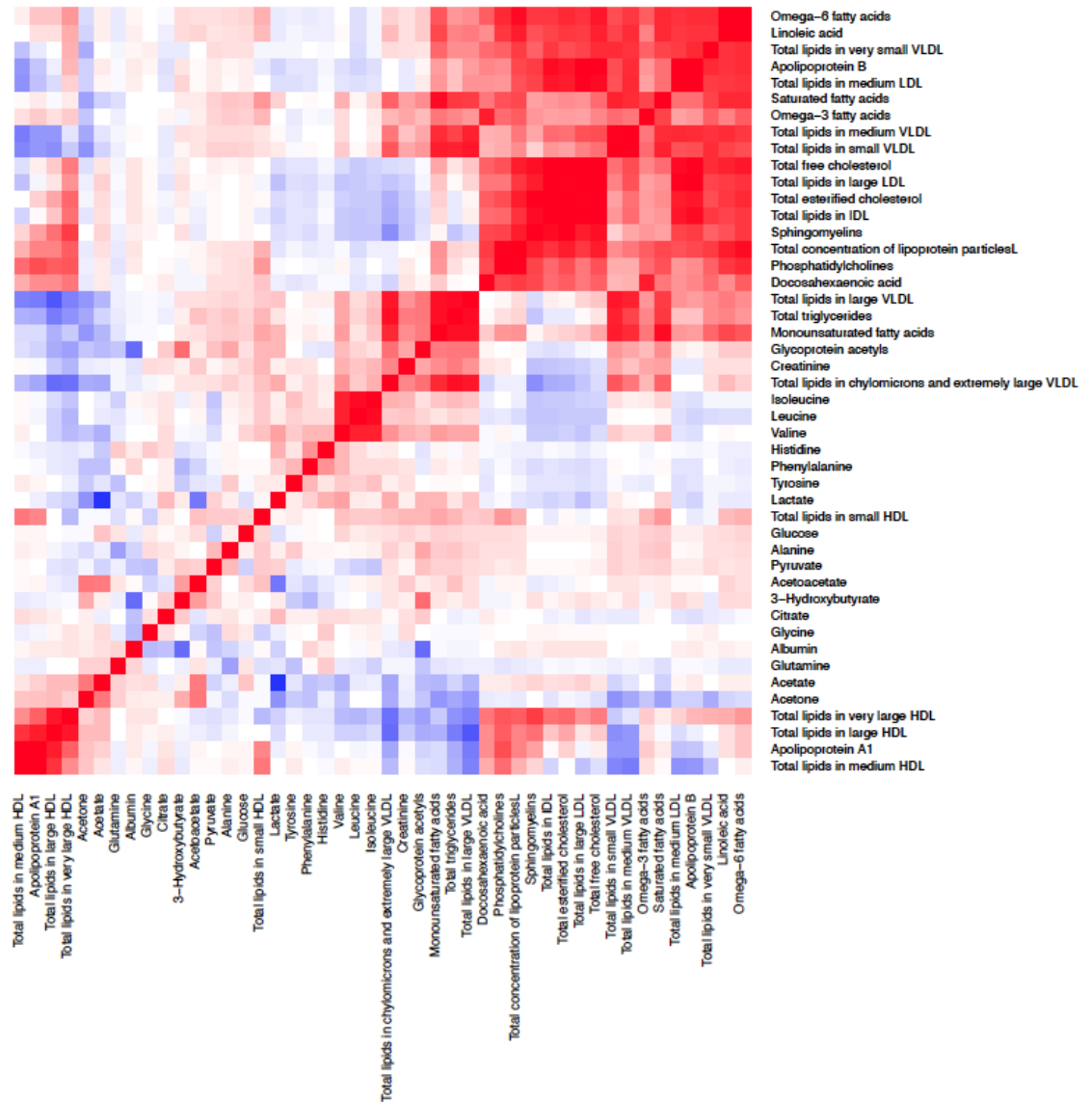
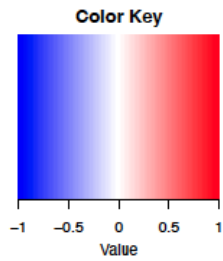


(E)

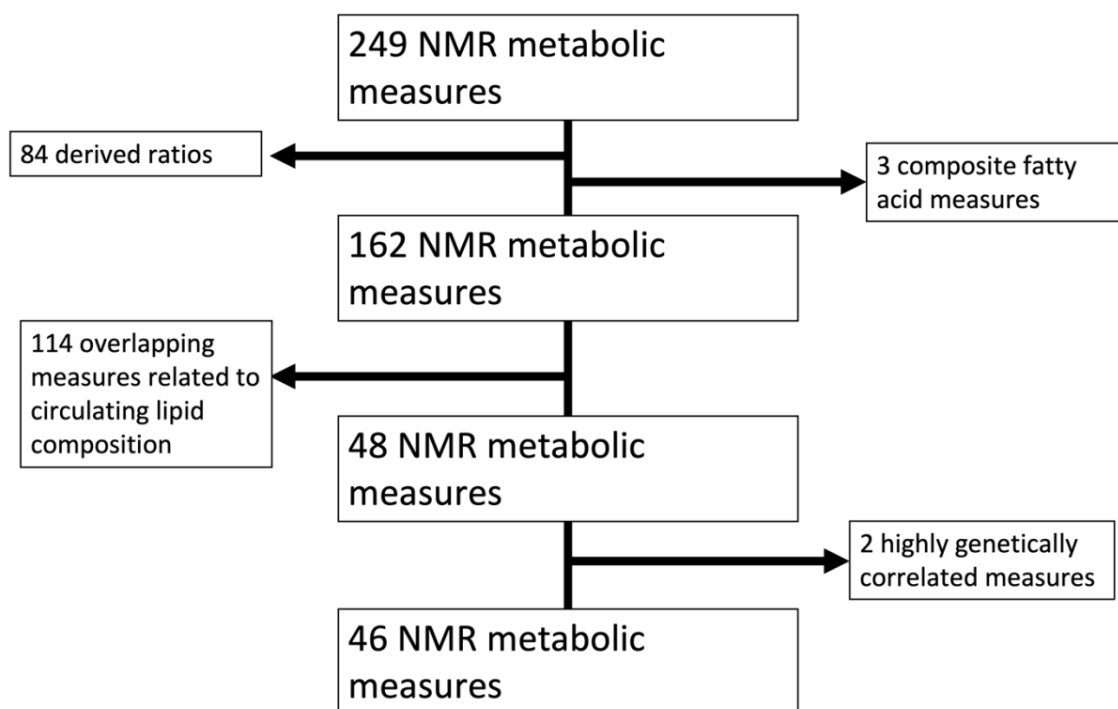


(F)

**Supplementary Figures S2 (A)-(F):** Scatter plots of UVMR analyses using IVW, MR-Egger, weighted median and weighted mode; a) alanine, b) 3-hydroxybutyrate, c) glutamine, d) glucose, e) isoleucine, f) pyruvate.



**Supplementary Figure S3.** Genetic correlation between metabolic measures based on n=114 harmonised SNPs within the Kettunen selected SNPs.



**Supplementary Figure S4.** Exclusions made to establish the list of metabolites.