**ONLINE SUPPLEMENTAL INFORMATION**

**DC19-2533-Revision 1**

**Microbiota-related metabolites and the risk of type 2 diabetes**

Jagadish Vangipurapu1, Lilian Fernandes Silva1, Teemu Kuulasmaa2, Ulf Smith3, Markku Laakso1,4

1Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland

2Institute of Biomedicine, Bioinformatics Center, University of Eastern Finland, Kuopio, Finland

3Lundberg Laboratory for Diabetes Research, Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

4Department of Medicine, Kuopio University Hospital, Kuopio, Finland

Supplemental Table 1. Metabolites included in statistical analyses

|  |
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| **Metabolites generated by microbiota** |
| **Bile acids** |  |
| Glycocholate | 2-hydroxyhippurate (salicylurate) |
| Taurochenodeoxycholate | 3-hydroxyhippurate |
| Ursodeoxycholate | 4-hydroxyhippurate |
| Glycodeoxycholate | **Energy metabolism** |
| Glycolithocholate sulfate\* | Lactate |
| Glycocholenate sulfate\* | Succinate |
| Taurocholenate sulfate | **Lipid metabolism** |
| Glycoursodeoxycholate | **Short chain fatty acid** |
| **Choline metabolism** | Isovalerate (i5:0) |
| Trimethylamine N-oxide (TMAO) | **Other metabolites** |
| **Aromatic amino acid metabolism** | 2-hydroxybutyrate/2-hydroxyisobutyrate |
| P-cresol sulfate | 3-hydroxyisobutyrate |
| Methyl indole-3-acetate | Benzoate |
| Indolepropionate | Homovanillate (HVA) |
| Phenyllactate | Serotonin |
| Xanthurenate in 1,2,3 | Spermidine |
| Phenylacetate | N-acetyl putrescine |
| 3-(4-hydroxyphenyl)lactate | 1-linoleoyl-GPA in 1,2 |
| 4-ethylphenylsulfate | **Lyso-phosphatidylcholines** |
| 4-hydroxyphenylacetate | 1-linolenoyl-GPC (18:3)\* |
| Phenylacetylglutamine | 1-linoleoyl-GPC (18:2) |
| 3-(3-hydroxyphenyl)propionate | 1-oleoyl-GPC (18:1) |
| 3-phenylpropionate (hydrocinnamate) | 1-palmitoleoyl-1)\* |
| Phenol sulfate | 1-palmitoyl-GPC (16:0) |
| Indolelactate | 1-lignoceroyl-GPC (24:0) |
| Indoleacetate | 1-stearoyl-GPC (18:0) |
| N-acetyltryptophan | 2-palmitoyl-GPC (16:0)\* |
| 3-indoxyl sulfate | **Lyso-phosphatidylethanolamines** |
| Indoleacetylglutamine | 1-arachidonoyl-GPE (20:4n6)\* |
| **Non-aromatic amino acid metabolism** | 1-linoleoyl-GPE (18:2)\* |
| 3-aminoisobutyrate | 1-oleoyl-GPE (18:1) |
| Imidazole propionate | 1-palmitoyl-GPE (16:0) |
| **Xenobiotic metabolism** | 1-stearoyl-GPE (18:0) |
| Hippurate | 2-stearoyl-GPE (18:0)\* |
| **Metabolites processed by microbiota** |
| **Bile Acids** | **Non-aromatic amino acid metabolism** |
| Cholate | N-acetylglycine |
| Chenodeoxycholate | **Energy metabolism** |
| Glycochenodeoxycholate | Urea |
| Taurolithocholate 3-sulfate | Creatine |
| Deoxycholate | Creatinine |
| Choline metabolism | **Other metabolites** |
| Choline | Urate |
| **Xenobiotic metabolism** | Uridine |
| Xylose | Xanthine |
| **Metabolite levels indirectly affected by microbiota**  |
| **(microbiota metabolizes its precursor, modulating its level)** |
| **Choline metabolism** | **Aromatic amino acid metabolism** |
| Betaine | Kynurenine |
| Dimethylglycine | Kynurenate |
| **Metabolites modulating the growth of microbiota** |
| **(due to antibacterial activity)** |
| **Monoacylglycerols** |   |
| 1-dihomo-linolenylglycerol (20:3) | 2-linoleoylglycerol (18:2) |
| 1-docosahexaenoylglycerol (22:6) | 2-oleoylglycerol (18:1) |
| 1-linoleoylglycerol (18:2) | 2-palmitoylglycerol (16:0) |
| 1-myristoylglycerol (14:0) | 1-palmitoleoylglycerol (16:1)\* |
| 1-oleoylglycerol (18:1) | 1-linolenoylglycerol (18:3) |
| 1-palmitoylglycerol (16:0) |   |

Supplemental Table 2. Association of various metabolites with incident type 2 diabetes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Metabolite | T2D N | Total N | HR (95% CI) | ***P*** | ***P*\*** |
| **Metabolites generated by microbiota** |
| **Bile acids** |  |  |  |  |  |
| glycocholate | 521 | 5178 | 1.21 (1.12 - 1.32) | **5.6E-06** | **0.001** |
| taurochenodeoxycholate | 521 | 5178 | 1.23 (1.13 - 1.33) | **1.6E-06** | **0.002** |
| ursodeoxycholate | 521 | 5178 | 1.14 (1.04 - 1.25) | **0.005** | 0.119 |
| glycodeoxycholate | 521 | 5178 | 1.13 (1.03 - 1.24) | **0.007** | **0.027** |
| glycolithocholate sulfate\* | 521 | 5178 | 1.02 (0.93 - 1.11) | 0.715 | 0.827 |
| glycocholenate sulfate\* | 521 | 5178 | 1.18 (1.08 - 1.28) | **2.4E-04** | **0.014** |
| taurocholenate sulfate | 521 | 5178 | 1.16 (1.06 - 1.26) | **9.6E-04** | 0.055 |
| glycoursodeoxycholate | 521 | 5178 | 1.12 (1.03 - 1.22) | **0.010** | 0.104 |
| **Choline metabolism** |  |  |  |  |  |
| trimethylamine N-oxide | 521 | 5178 | 1.05 (0.97 - 1.15) | 0.227 | 0.378 |
| **Aromatic amino acid metabolism** |  |  |  |  |
| p-cresol sulfate | 521 | 5178 | 0.97 (0.89 - 1.05) | 0.453 | 0.716 |
| methyl indole-3-acetate | 521 | 5178 | 1.11 (1.02 - 1.21) | **0.019** | 0.145 |
| indolepropionate | 521 | 5178 | 0.82 (0.76 - 0.88) | **1.1E-07** | **0.001** |
| phenyllactate (PLA) | 521 | 5178 | 1.14 (1.05 - 1.24) | **0.002** | **0.002** |
| Xanthurenate | 521 | 5178 | 1.31 (1.18 - 1.44) | **6.6E-08** | **3.0E-05** |
| 3-(4-hydroxyphenyl)lactate | 521 | 5178 | 1.30 (1.20 - 1.42) | **1.1E-09** | **4.8E-07** |
| 4-ethylphenylsulfate | 521 | 5178 | 0.99 (0.91 - 1.08) | 0.812 | 0.078 |
| 4-hydroxyphenylacetate | 430 | 4180 | 1.15 (1.05 - 1.27) | **0.003** | **0.029** |
| phenylacetylglutamine | 521 | 5178 | 1.00 (0.92 - 1.09) | 0.994 | 0.878 |
| 3-(3-hydroxyphenyl)propionate | 521 | 5178 | 0.97 (0.89 - 1.05) | 0.424 | 0.731 |
| 3-phenylpropionate (hydrocinnamate) | 521 | 5178 | 0.87 (0.80 - 0.94) | **3.6E-04** | **0.027** |
| phenylacetate | 521 | 5178 | 0.91 (0.83 - 0.99) | **0.024** | 0.071 |
| phenol sulfate | 521 | 5178 | 1.12 (1.03 - 1.21) | **0.010** | **0.023** |
| indolelactate | 521 | 5178 | 1.17 (1.07 - 1.27) | **3.4E-04** | **2.2E-04** |
| indoleacetate | 521 | 5178 | 1.02 (0.94 - 1.11) | 0.631 | 0.455 |
| N-acetyltryptophan | 521 | 5178 | 1.33 (1.21 - 1.45) | **5.4E-10** | **0.003** |
| 3-indoxyl sulfate | 521 | 5178 | 0.98 (0.90 - 1.07) | 0.719 | 0.554 |
| indoleacetylglutamine | 521 | 5178 | 1.14 (1.04 - 1.24) | **0.005** | 0.097 |
| **Non-aromatic amino acid metabolism** |  |  |  |  |
| 3-aminoisobutyrate | 521 | 5178 | 0.91 (0.84 - 0.99) | **0.030** | 0.054 |
| imidazole propionate | 521 | 5178 | 1.14 (1.04 - 1.23) | **0.003** | **0.040** |
| **Xenobiotic metabolism** |  |  |  |  |  |
| hippurate | 521 | 5178 | 0.87 (0.80 - 0.95) | **0.002** | **0.032** |
| 2-hydroxyhippurate (salicylurate) | 521 | 5178 | 1.19 (1.10 - 1.30) | **2.0E-05** | **2.9E-05** |
| 3-hydroxyhippurate | 521 | 5178 | 0.97 (0.89 - 1.06) | 0.552 | 0.558 |
| 4-hydroxyhippurate | 521 | 5178 | 1.01 (0.93 - 1.10) | 0.820 | 0.799 |
| **Energy metabolism** |  |  |  |  |  |
| lactate | 521 | 5178 | 1.19 (1.09 - 1.30) | **5.3E-05** | **0.004** |
| succinate | 521 | 5178 | 1.00 (0.92 - 1.09) | 0.995 | 0.924 |
| **Lipid metabolism** |  |  |  |  |  |
| **Short chain fatty acid** |  |  |  |  |  |
| isovalerate (i5:0) | 521 | 5178 | 1.18 (1.08 - 1.28) | **3.5E-04** | **0.005** |
| **Other metabolites** |  |  |  |  |  |
| 2-hydroxybutyrate/2-hydroxyisobutyrate | 521 | 5178 | 1.33 (1.21 - 1.46) | **2.2E-09** | **7.6E-06** |
| 3-hydroxyisobutyrate | 521 | 5178 | 1.17 (1.07 - 1.27) | **2.9E-04** | **0.007** |
| benzoate | 521 | 5178 | 1.00 (0.92 - 1.09) | 0.949 | 0.567 |
| homovanillate (HVA) | 423 | 3949 | 1.13 (1.02 - 1.24) | **0.014** | 0.086 |
| serotonin | 521 | 5178 | 0.89 (0.83 - 0.96) | **0.002** | 0.056 |
| spermidine | 521 | 5178 | 0.88 (0.81 - 0.96) | **0.004** | **0.038** |
| N-acetylputrescine | 521 | 5178 | 1.19 (1.10 - 1.30) | **4.0E-05** | **0.002** |
| **Lyso-phosphatidylcholines** |  |  |  |  |  |
| 1-linolenoyl-GPC (18:3)\* | 521 | 5178 | 0.82 (0.75 - 0.89) | **5.2E-06** | **0.042** |
| 1-linoleoyl-GPC (18:2) | 521 | 5178 | 0.67 (0.62 - 0.73) | **1.4E-20** | **1.6E-07** |
| 1-oleoyl-GPC (18:1) | 521 | 5178 | 0.77 (0.71 - 0.84) | **6.8E-09** | **0.004** |
| 1-palmitoleoyl-GPC (16:1)\* | 521 | 5178 | 1.06 (0.97 - 1.15) | 0.183 | 0.513 |
| 1-palmitoyl-GPC (16:0) | 521 | 5178 | 0.84 (0.77 - 0.91) | **6.6E-05** | **0.032** |
| 1-lignoceroyl-GPC (24:0) | 423 | 3949 | 0.78 (0.72 - 0.85) | **7.5E-09** | **7.9E-04** |
| 1-stearoyl-GPC (18:0) | 521 | 5178 | 0.82 (0.76 - 0.89) | **3.4E-06** | **0.021** |
| 2-palmitoyl-GPC (16:0)\* | 521 | 5178 | 0.93 (0.85 - 1.01) | 0.096 | 0.931 |
| **Lyso-phosphatidylethanolamines** |  |  |  |  |
| 1-arachidonoyl-GPE (20:4n6)\* | 521 | 5178 | 1.10 (1.01 - 1.20) | **0.029** | **0.016** |
| 1-linoleoyl-GPE (18:2)\* | 521 | 5178 | 0.88 (0.81 - 0.96) | **0.005** | 0.201 |
| 1-oleoyl-GPE (18:1) | 521 | 5178 | 1.04 (0.96 - 1.14) | 0.316 | 0.098 |
| 1-palmitoyl-GPE (16:0) | 521 | 5178 | 0.88 (0.81 - 0.96) | **0.003** | 0.102 |
| 1-stearoyl-GPE (18:0) | 521 | 5178 | 0.98 (0.90 - 1.06) | 0.580 | 0.618 |
| 2-stearoyl-GPE (18:0)\* | 521 | 5178 | 1.02 (0.93 - 1.11) | 0.733 | 0.219 |
| **Metabolites processed by microbiota** |
| **Bile acids** |  |  |  |  |  |
| cholate | 521 | 5178 | 1.10 (1.00 - 1.20) | **0.038** | 0.272 |
| chenodeoxycholate | 521 | 5178 | 1.13 (1.03 - 1.23) | **0.010** | 0.100 |
| glycochenodeoxycholate | 521 | 5178 | 1.20 (1.10 - 1.30) | **4.3E-05** | **0.006** |
| taurolithocholate 3-sulfate | 521 | 5178 | 1.00 (0.92 - 1.09) | 0.981 | 0.834 |
| deoxycholate | 521 | 5178 | 1.04 (0.95 - 1.14) | 0.433 | 0.642 |
| choline | 521 | 5178 | 1.03 (0.94 - 1.12) | 0.536 | 0.698 |
| **Xenobiotic metabolism** |  |  |  |  |  |
| xylose | 423 | 3949 | 1.02 (0.93 - 1.13) | 0.652 | 0.932 |
| **Non-aromatic amino acid metabolism** |  |  |  |  |
| N-acetylglycine | 521 | 5178 | 0.87 (0.79 - 0.96) | **0.004** | 0.377 |
| **Energy metabolism** |  |  |  |  |  |
| urea | 521 | 5178 | 1.08 (0.99 - 1.19) | 0.076 | 0.206 |
| creatine | 521 | 5178 | 1.43 (1.30 - 1.56) | **2.5E-14** | **1.2E-05** |
| creatinine | 521 | 5178 | 1.04 (0.95 - 1.13) | 0.440 | 0.034 |
| **Other metabolites** |  |  |  |  |  |
| Urate | 521 | 5178 | 1.39 (1.27 - 1.52) | **7.9E-13** | **2.0E-06** |
| Uridine | 521 | 5178 | 1.17 (1.07 - 1.28) | **5.0E-04** | **6.6E-04** |
| Xanthine | 521 | 5178 | 1.31 (1.21 - 1.42) | **4.3E-12** | **6.4E-07** |
| **Metabolite levels indirectly affected by microbiota**  |
| **Choline metabolism** |  |  |  |  |  |
| betaine | 521 | 5178 | 0.94 (0.86 - 1.02) | 0.138 | 0.773 |
| dimethylglycine | 521 | 5178 | 1.20 (1.12 - 1.28) | **5.4E-07** | **3.1E-05** |
| **Aromatic amino acid metabolism** |  |  |  |  |
| kynurenine | 521 | 5178 | 1.24 (1.14 - 1.35) | **8.6E-07** | **0.004** |
| kynurenate | 521 | 5178 | 1.31 (1.20 - 1.42) | **1.4E-09** | **1.9E-06** |
| **Metabolites modulating the growth of microbiota** |
| **Monoacylglycerols** |  |  |  |  |  |
| 1-dihomo-linolenylglycerol (20:3) | 521 | 5178 | 1.10 (1.01 - 1.20) | **0.029** | **0.028** |
| 1-docosahexaenoylglycerol (22:6) | 521 | 5178 | 1.01 (0.92 - 1.10) | 0.893 | 0.932 |
| 1-linoleoylglycerol (18:2) | 521 | 5178 | 1.04 (0.95 - 1.13) | 0.372 | 0.106 |
| 1-myristoylglycerol (14:0) | 521 | 5178 | 1.23 (1.13 - 1.34) | **1.8E-06** | **5.8E-05** |
| 1-oleoylglycerol (18:1) | 521 | 5178 | 1.29 (1.19 - 1.41) | **1.5E-09** | **1.9E-07** |
| 1-palmitoylglycerol (16:0) | 521 | 5178 | 1.12 (1.03 - 1.22) | **0.007** | **0.015** |
| 2-linoleoylglycerol (18:2) | 521 | 5178 | 0.94 (0.87 - 1.02) | 0.167 | 0.581 |
| 2-oleoylglycerol (18:1) | 521 | 5178 | 1.21 (1.10 - 1.34) | **1.2E-04** | **7.5E-04** |
| 2-palmitoylglycerol (16:0) | 521 | 5178 | 1.08 (0.99 - 1.19) | 0.079 | 0.095 |
| 1-palmitoleoylglycerol (16:1)\* | 430 | 4180 | 1.41 (1.28 - 1.55) | **4.9E-12** | **2.3E-07** |
| 1-linolenoylglycerol (18:3) | 423 | 3949 | 1.13 (1.02 - 1.24) | **0.015** | **0.040** |

Analyses based on Cox-regression analyses adjusted for batch only. P\* was additionally adjusted for age, body mass index, smoking and physical activity. T2D N, the number of participants diagnosed with incident type 2 diabetes, Total N, the number of all participants. *P*<5.8x10-5 marked as bold and underlined, *P*<0.05 marked as bold.

Supplemental Table 3. Association of various metabolites with fasting and 2-hour glucose levels at the follow-up visit

|  |  |  |
| --- | --- | --- |
|  | **Fasting glucose** | **2-hour glucose** |
| **Metabolite** | **Beta** | SE | *P* | Beta | SE | *P* |
| **Metabolites generated by microbiota** |  |  |  |  |  |  |
| **Bile acids** |  |  |  |  |  |  |
| glycocholate | 0.033 | 0.012 | **0.008** | 0.048 | 0.012 | **6.8E-05** |
| taurochenodeoxycholate | 0.039 | 0.012 | **0.002** | 0.068 | 0.012 | **2.4E-08** |
| ursodeoxycholate | 0.000 | 0.012 | 0.983 | 0.007 | 0.012 | 0.549 |
| glycodeoxycholate | 0.025 | 0.012 | **0.048** | 0.024 | 0.012 | **0.045** |
| glycolithocholate sulfate\* | 0.016 | 0.012 | 0.200 | 0.019 | 0.012 | 0.110 |
| glycocholenate sulfate\* | 0.035 | 0.012 | **0.005** | 0.019 | 0.012 | 0.124 |
| taurocholenate sulfate | 0.061 | 0.012 | **1.5E-06** | 0.039 | 0.012 | **0.002** |
| glycoursodeoxycholate | 0.017 | 0.012 | 0.170 | 0.022 | 0.012 | 0.066 |
| **Choline metabolism** |  |  |  |  |  |  |
| trimethylamine N-oxide | 0.006 | 0.012 | 0.624 | 0.019 | 0.012 | 0.128 |
| **Aromatic amino acid metabolism** |  |  |  |  |  |  |
| p-cresol sulfate | -0.023 | 0.012 | 0.067 | -0.013 | 0.012 | 0.285 |
| methyl indole-3-acetate | 0.025 | 0.012 | **0.045** | 0.031 | 0.012 | **0.011** |
| indolepropionate | -0.055 | 0.012 | **1.3E-05** | -0.036 | 0.012 | **0.003** |
| phenyllactate (PLA) | 0.011 | 0.012 | 0.383 | 0.025 | 0.012 | **0.038** |
| Xanthurenate | 0.072 | 0.012 | **1.5E-08** | 0.084 | 0.012 | **4.4E-12** |
| 3-(4-hydroxyphenyl)lactate | 0.050 | 0.012 | **8.7E-05** | 0.061 | 0.012 | **7.5E-07** |
| 4-ethylphenylsulfate | -0.014 | 0.012 | 0.272 | 0.010 | 0.012 | 0.404 |
| 4-hydroxyphenylacetate | 0.021 | 0.014 | 0.151 | 0.007 | 0.014 | 0.597 |
| phenylacetylglutamine | -0.038 | 0.012 | **0.003** | -0.016 | 0.012 | 0.192 |
| 3-(3-hydroxyphenyl)propionate | -0.019 | 0.012 | 0.139 | -0.039 | 0.012 | **0.001** |
| 3-phenylpropionate (hydrocinnamate) | -0.043 | 0.012 | **6.6E-04** | -0.043 | 0.012 | **3.6E-04** |
| phenylacetate | -0.035 | 0.012 | **0.006** | -0.033 | 0.012 | **0.006** |
| phenol sulfate | 0.015 | 0.012 | 0.244 | 0.021 | 0.012 | 0.090 |
| indolelactate | 0.043 | 0.012 | **6.8E-04** | 0.046 | 0.012 | **1.5E-04** |
| indoleacetate | 0.016 | 0.012 | 0.215 | 0.016 | 0.012 | 0.175 |
| N-acetyltryptophan | 0.055 | 0.012 | **1.6E-05** | 0.100 | 0.012 | **2.6E-16** |
| 3-indoxyl sulfate | -0.012 | 0.012 | 0.350 | -0.004 | 0.012 | 0.724 |
| indoleacetylglutamine | 0.023 | 0.012 | 0.069 | 0.041 | 0.012 | **6.6E-04** |
| **Non-aromatic amino acid metabolism** |  |  |  |  |  |  |
| 3-aminoisobutyrate | -0.007 | 0.012 | 0.557 | -0.008 | 0.012 | 0.513 |
| imidazole propionate | 0,001 | 0,012 | 0.958 | -0,005 | 0,012 | 0.663 |
| **Xenobiotic metabolism** |  |  |  |  |  |  |
| hippurate | -0.046 | 0.012 | **2.6E-04** | -0.029 | 0.012 | **0.019** |
| 2-hydroxyhippurate (salicylurate) | -0.012 | 0.012 | 0.333 | 0.013 | 0.012 | 0.303 |
| 3-hydroxyhippurate | -0.022 | 0.012 | 0.086 | -0.032 | 0.012 | **0.009** |
| 4-hydroxyhippurate | -0.014 | 0.012 | 0.270 | 0.000 | 0.012 | 0.996 |
| **Energy metabolism** |  |  |  |  |  |  |
| lactate | 0.034 | 0.012 | **0.007** | 0.034 | 0.012 | **0.007** |
| succinate | -0.009 | 0.012 | 0.498 | 0.012 | 0.012 | 0.339 |
| **Lipid metabolism** |  |  |  |  |  |  |
| **Short chain fatty acid** |  |  |  |  |  |  |
| isovalerate (i5:0) | 0.047 | 0.012 | **2.2E-04** | 0.020 | 0.012 | 0.098 |
| **Other metabolites** |  |  |  |  |  |  |
| 2-hydroxybutyrate/2-hydroxyisobutyrate | 0.093 | 0.012 | **2.0E-13** | 0.045 | 0.013 | **3.5E-04** |
| 3-hydroxyisobutyrate | 0.074 | 0.012 | **4.2E-09** | 0.035 | 0.012 | **0.004** |
| benzoate | -0.013 | 0.012 | 0.318 | -0.005 | 0.012 | 0.677 |
| homovanillate (HVA) | 0.012 | 0.013 | 0.415 | 0.051 | 0.014 | **2.3E-04** |
| serotonin | -0.030 | 0.012 | **0.019** | -0.026 | 0.012 | **0.032** |
| spermidine | 0.020 | 0.012 | 0.120 | -0.019 | 0.012 | 0.123 |
| N-acetylputrescine | 0.038 | 0.012 | **0.002** | 0.041 | 0.012 | **7.0E-04** |
| **Lyso-phosphatidylcholines** |  |  |  |  |  |  |
| 1-linolenoyl-GPC (18:3)\* | -0.048 | 0.012 | **1.6E-04** | -0.037 | 0.012 | **0.002** |
| 1-linoleoyl-GPC (18:2) | -0.089 | 0.012 | **2.8E-12** | -0.062 | 0.013 | **6.4E-07** |
| 1-oleoyl-GPC (18:1) | -0.053 | 0.012 | **2.8E-05** | -0.049 | 0.012 | **5.7E-05** |
| 1-palmitoleoyl-GPC (16:1)\* | 0.025 | 0.012 | **0.045** | 0.023 | 0.012 | 0.062 |
| 1-palmitoyl-GPC (16:0) | -0.007 | 0.012 | 0.595 | -0.019 | 0.012 | 0.114 |
| 1-lignoceroyl-GPC (24:0) | -0.039 | 0.013 | **0.006** | -0.075 | 0.014 | **4.6E-08** |
| 1-stearoyl-GPC (18:0) | -0.023 | 0.012 | 0.071 | -0.034 | 0.012 | **0.005** |
| 2-palmitoyl-GPC (16:0)\* | -0.002 | 0.012 | 0.877 | -0.016 | 0.012 | 0.200 |
| **Lyso-phosphatidylethanolamines** |  |  |  |  |
| 1-arachidonoyl-GPE (20:4n6)\* | 0.003 | 0.012 | 0.813 | 0.001 | 0.012 | 0.904 |
| 1-linoleoyl-GPE (18:2)\* | -0.049 | 0.012 | **9.8E-05** | -0.030 | 0.012 | **0.013** |
| 1-oleoyl-GPE (18:1) | -0.030 | 0.012 | **0.019** | 0.008 | 0.012 | 0.537 |
| 1-palmitoyl-GPE (16:0) | -0.022 | 0.012 | 0.089 | -0.017 | 0.012 | 0.167 |
| 1-stearoyl-GPE (18:0) | -0.006 | 0.012 | 0.649 | -0.016 | 0.012 | 0.202 |
| 2-stearoyl-GPE (18:0)\* | -0.005 | 0.012 | 0.688 | -0.008 | 0.012 | 0.490 |
| **Metabolites processed by microbiota** |
| **Bile acids** |  |  |  |  |  |  |
| cholate | -0.018 | 0.012 | 0.151 | -0.003 | 0.012 | 0.800 |
| chenodeoxycholate | 0.002 | 0.012 | 0.857 | 0.001 | 0.012 | 0.903 |
| glycochenodeoxycholate | 0.024 | 0.012 | 0.053 | 0.040 | 0.012 | **0.001** |
| taurolithocholate 3-sulfate | 0.022 | 0.012 | 0.081 | 0.029 | 0.012 | **0.019** |
| deoxycholate | 0.018 | 0.012 | 0.152 | 0.007 | 0.012 | 0.561 |
| choline | 0.014 | 0.012 | 0.286 | 0.034 | 0.012 | **0.005** |
| **Xenobiotic metabolism** |  |  |  |  |  |  |
| xylose | -0.006 | 0.013 | 0.692 | -0.002 | 0.014 | 0.908 |
| **Non-aromatic amino acid metabolism** |  |  |  |  |  |  |
| N-acetylglycine | 0.006 | 0.012 | 0.629 | -0.048 | 0.012 | **8.0E-05** |
| **Energy metabolism** |  |  |  |  |  |  |
| urea | 0.024 | 0.012 | 0.062 | 0.038 | 0.012 | **0.002** |
| creatine | 0.089 | 0.012 | **3.0E-12** | 0.054 | 0.012 | **8.0E-06** |
| creatinine | 0.011 | 0.012 | 0.364 | 0.007 | 0.012 | 0.563 |
| **Other metabolites** |  |  |  |  |  |  |
| Urate | 0.071 | 0.012 | **1.6E-08** | 0.068 | 0.012 | **3.3E-08** |
| Uridine | 0.090 | 0.012 | **9.4E-13** | 0.021 | 0.012 | 0.081 |
| Xanthine | 0.065 | 0.012 | **2.4E-07** | 0.050 | 0.013 | **4.4E-05** |
| **Metabolite levels indirectly affected by microbiota**  |  |  |
| **Choline metabolism** |  |  |  |  |  |  |
| betaine | -0.026 | 0.012 | **0.041** | -0.017 | 0.012 | 0.168 |
| dimethylglycine | -0.005 | 0.012 | 0.707 | 0.037 | 0.012 | **0.002** |
| **Aromatic amino acid metabolism** |  |  |  |  |  |  |
| kynurenine | 0.044 | 0.012 | **5.1E-04** | 0.061 | 0.012 | **5.9E-07** |
| kynurenate | 0.066 | 0.012 | **2.1E-07** | 0.083 | 0.012 | **8.9E-12** |
| **Metabolites modulating the growth of microbiota** |  |  |
| **Monoacylglycerols** |  |  |  |  |  |  |
| 1-dihomo-linolenylglycerol (20:3) | 0.024 | 0.012 | 0.063 | 0.001 | 0.012 | 0.911 |
| 1-docosahexaenoylglycerol (22:6) | 0.013 | 0.012 | 0.290 | 0.000 | 0.012 | 0.986 |
| 1-linoleoylglycerol (18:2) | -0.006 | 0.012 | 0.633 | -0.014 | 0.012 | 0.245 |
| 1-myristoylglycerol (14:0) | 0.028 | 0.012 | **0.028** | 0.037 | 0.012 | **0.002** |
| 1-oleoylglycerol (18:1) | 0.041 | 0.012 | **0.001** | 0.036 | 0.012 | **0.003** |
| 1-palmitoylglycerol (16:0) | 0.009 | 0.012 | 0.480 | 0.018 | 0.012 | 0.135 |
| 2-linoleoylglycerol (18:2) | -0.021 | 0.012 | 0.092 | -0.020 | 0.012 | 0.098 |
| 2-oleoylglycerol (18:1) | 0.018 | 0.012 | 0.146 | 0.015 | 0.012 | 0.224 |
| 2-palmitoylglycerol (16:0) | 0.012 | 0.012 | 0.323 | 0.010 | 0.012 | 0.431 |
| 1-palmitoleoylglycerol (16:1)\* | 0.066 | 0.014 | **5.2E-06** | 0.056 | 0.014 | **5.7E-05** |
| 1-linolenoylglycerol (18:3) | 0.004 | 0.013 | 0.774 | 0.001 | 0.014 | 0.958 |

Results based on linear regression analyses. Analyses at baseline was adjusted for batch alone and at follow-up, additionally for follow-up time and respective trait at baseline. *P*<5.8x10-5 marked as bold and underlined, *P*<0.05 marked as bold.

Supplemental Table 4. Association of various metabolites with Disposition index (DI) at baseline and the follow-up visit

|  |  |  |
| --- | --- | --- |
|  | **DI at baseline** | **DI at follow-up** |
| Metabolite | Beta | SE | ***P*** | Beta | SE | ***P*** |
| **Metabolites generated by microbiota** |  |  |  |  |  |  |
| **Bile acids** |  |  |  |  |  |  |
| glycocholate | -0.102 | 0.014 | **1.6E-13** | -0.023 | 0.011 | **0.044** |
| taurochenodeoxycholate | -0.101 | 0.014 | **3.9E-13** | -0.034 | 0.011 | **0.002** |
| ursodeoxycholate | -0.043 | 0.014 | **0.002** | -0.010 | 0.011 | 0.365 |
| glycodeoxycholate | -0.072 | 0.014 | **1.8E-07** | -0.013 | 0.011 | 0.269 |
| glycolithocholate sulfate\* | -0.017 | 0.014 | 0.216 | 0.003 | 0.011 | 0.825 |
| glycocholenate sulfate\* | -0.058 | 0.014 | **2.6E-05** | -0.024 | 0.011 | **0.034** |
| taurocholenate sulfate | -0.063 | 0.014 | **5.1E-06** | -0.044 | 0.011 | **9.3E-05** |
| glycoursodeoxycholate | -0.057 | 0.014 | **3.9E-05** | -0.017 | 0.011 | 0.127 |
| **Choline metabolism** |  |  |  |  |  |  |
| trimethylamine N-oxide | 0.042 | 0.014 | **0.003** | 0.001 | 0.011 | 0.908 |
| **Aromatic amino acid metabolism** |  |  |  |  |  |  |
| p-cresol sulfate | 0.032 | 0.014 | **0.020** | 0.017 | 0.011 | 0.138 |
| methyl indole-3-acetate | -0.038 | 0.014 | **0.006** | -0.016 | 0.011 | 0.147 |
| indolepropionate | 0.070 | 0.014 | **4.8E-07** | 0.031 | 0.011 | **0.006** |
| phenyllactate (PLA) | -0.058 | 0.014 | **3.3E-05** | -0.016 | 0.011 | 0.162 |
| Xanthurenate | -0.105 | 0.014 | **3.2E-14** | -0.063 | 0.011 | **3.2E-08** |
| 3-(4-hydroxyphenyl)lactate | -0.141 | 0.014 | **2.1E-24** | -0.051 | 0.011 | **7.1E-06** |
| 4-ethylphenylsulfate | 0.052 | 0.014 | **1.7E-04** | 0.001 | 0.011 | 0.963 |
| 4-hydroxyphenylacetate | -0.030 | 0.015 | 0.051 | -0.011 | 0.013 | 0.396 |
| phenylacetylglutamine | 0.021 | 0.014 | 0.131 | 0.038 | 0.011 | **7.8E-04** |
| 3-(3-hydroxyphenyl)propionate | 0.022 | 0.014 | 0.119 | 0.021 | 0.011 | 0.067 |
| 3-phenylpropionate (hydrocinnamate) | 0.076 | 0.014 | **5.2E-08** | 0.046 | 0.011 | **4.3E-05** |
| phenylacetate | 0.043 | 0.014 | **0.002** | 0.039 | 0.011 | **5.0E-04** |
| phenol sulfate | -0.017 | 0.014 | 0.229 | -0.018 | 0.011 | 0.120 |
| indolelactate | -0.024 | 0.014 | 0.086 | -0.034 | 0.011 | **0.002** |
| indoleacetate | 0.006 | 0.014 | 0.676 | -0.003 | 0.011 | 0.761 |
| N-acetyltryptophan | -0.106 | 0.014 | **1.6E-14** | -0.062 | 0.011 | **4.0E-08** |
| 3-indoxyl sulfate | 0.003 | 0.014 | 0.810 | 0.007 | 0.011 | 0.510 |
| indoleacetylglutamine | -0.034 | 0.014 | **0.015** | -0.023 | 0.011 | **0.042** |
| **Non-aromatic amino acid metabolism** |  |  |  |  |  |  |
| 3-aminoisobutyrate | 0.016 | 0.014 | 0.258 | 0.005 | 0.011 | 0.627 |
| imidazole propionate | -0.021 | 0.014 | 0.130 | -0.009 | 0.011 | 0.450 |
| **Xenobiotic metabolism** |  |  |  |  |  |  |
| hippurate | 0.088 | 0.014 | **1.9E-10** | 0.042 | 0.011 | **2.2E-04** |
| 2-hydroxyhippurate (salicylurate) | -0.032 | 0.014 | **0.020** | 0.013 | 0.011 | 0.251 |
| 3-hydroxyhippurate | 0.027 | 0.014 | 0.054 | 0.016 | 0.011 | 0.145 |
| 4-hydroxyhippurate | 0.011 | 0.014 | 0.412 | 0.001 | 0.011 | 0.946 |
| **Energy metabolism** |  |  |  |  |  |  |
| lactate | -0.176 | 0.014 | **2.5E-37** | -0.016 | 0.012 | 0.160 |
| succinate | 0.000 | 0.014 | 0.989 | 0.017 | 0.012 | 0.123 |
| **Lipid metabolism** |  |  |  |  |  |  |
| **Short chain fatty acid** |  |  |  |  |  |  |
| isovalerate (i5:0) | -0.059 | 0.014 | **2.4E-05** | -0.039 | 0.011 | **6.0E-04** |
| **Other metabolites** |  |  |  |  |  |  |
| 2-hydroxybutyrate/2-hydroxyisobutyrate | -0.219 | 0.013 | **1.9E-57** | -0.050 | 0.012 | **1.4E-05** |
| 3-hydroxyisobutyrate | -0.163 | 0.014 | **4.0E-32** | -0.033 | 0.011 | **0.004** |
| benzoate | 0.014 | 0.014 | 0.324 | 0.013 | 0.011 | 0.254 |
| homovanillate (HVA) | -0.071 | 0.016 | **8.4E-06** | -0.031 | 0.013 | **0.014** |
| serotonin | 0.023 | 0.014 | 0.105 | 0.026 | 0.011 | **0.023** |
| spermidine | 0.019 | 0.014 | 0.172 | -0.007 | 0.011 | 0.548 |
| N-acetylputrescine | -0.050 | 0.014 | **3.1E-04** | -0.035 | 0.011 | **0.002** |
| **Lyso-phosphatidylcholines** |  |  |  |  |  |  |
| 1-linolenoyl-GPC (18:3)\* | 0.058 | 0.014 | **2.7E-05** | 0.047 | 0.011 | **3.2E-05** |
| 1-linoleoyl-GPC (18:2) | 0.180 | 0.014 | **4.1E-39** | 0.068 | 0.012 | **2.2E-09** |
| 1-oleoyl-GPC (18:1) | 0.089 | 0.014 | **1.1E-10** | 0.054 | 0.011 | **1.9E-06** |
| 1-palmitoleoyl-GPC (16:1)\* | -0.091 | 0.014 | **5.7E-11** | -0.005 | 0.012 | 0.667 |
| 1-palmitoyl-GPC (16:0) | 0.032 | 0.014 | **0.023** | 0.014 | 0.011 | 0.209 |
| 1-lignoceroyl-GPC (24:0) | 0.078 | 0.015 | **8.4E-07** | 0.061 | 0.013 | **1.0E-06** |
| 1-stearoyl-GPC (18:0) | 0.057 | 0.014 | **4.5E-05** | 0.027 | 0.011 | **0.015** |
| 2-palmitoyl-GPC (16:0)\* | 0.026 | 0.014 | 0.066 | 0.008 | 0.011 | 0.472 |
| **Lyso-phosphatidylethanolamines** |  |  |  |  |
| 1-arachidonoyl-GPE (20:4n6)\* | -0.038 | 0.014 | **0.007** | -0.003 | 0.011 | 0.794 |
| 1-linoleoyl-GPE (18:2)\* | 0.073 | 0.014 | **1.5E-07** | 0.036 | 0.011 | **0.002** |
| 1-oleoyl-GPE (18:1) | 0.023 | 0.014 | 0.103 | 0.013 | 0.011 | 0.249 |
| 1-palmitoyl-GPE (16:0) | 0.051 | 0.014 | **2.3E-04** | 0.021 | 0.011 | 0.067 |
| 1-stearoyl-GPE (18:0) | 0.021 | 0.014 | 0.123 | 0.015 | 0.011 | 0.196 |
| 2-stearoyl-GPE (18:0)\* | 0.005 | 0.014 | 0.708 | 0.014 | 0.011 | 0.230 |
| **Metabolites processed by microbiota** |  |  |  |
| **Bile acids** |  |  |  |  |  |  |
| cholate | -0.053 | 0.014 | **1.4E-04** | 0.009 | 0.011 | 0.433 |
| chenodeoxycholate | -0.023 | 0.014 | 0.091 | -0.007 | 0.011 | 0.528 |
| glycochenodeoxycholate | -0.079 | 0.014 | **1.1E-08** | -0.013 | 0.011 | 0.238 |
| taurolithocholate 3-sulfate | -0.015 | 0.014 | 0.281 | -0.007 | 0.011 | 0.536 |
| deoxycholate | -0.019 | 0.014 | 0.180 | -0.009 | 0.011 | 0.421 |
| choline | 0.013 | 0.014 | 0.355 | -0.018 | 0.011 | 0.116 |
| **Xenobiotic metabolism** |  |  |  |  |  |  |
| xylose | -0.035 | 0.016 | **0.029** | 0.002 | 0.013 | 0.849 |
| **Non-aromatic amino acid metabolism** |  |  |  |  |  |  |
| N-acetylglycine | 0.071 | 0.014 | **3.5E-07** | 0.034 | 0.011 | **0.003** |
| **Energy metabolism** |  |  |  |  |  |  |
| urea | -0.036 | 0.014 | **0.010** | -0.021 | 0.011 | 0.059 |
| creatine | -0.107 | 0.014 | **1.2E-14** | -0.045 | 0.011 | **6.6E-05** |
| creatinine | 0.035 | 0.014 | **0.012** | -0.019 | 0.011 | 0.094 |
| **Other metabolites** |  |  |  |  |  |  |
| Urate | -0.123 | 0.014 | **4.6E-19** | -0.064 | 0.011 | **2.1E-08** |
| Uridine | -0.028 | 0.014 | **0.040** | -0.052 | 0.011 | **5.0E-06** |
| Xanthine | -0.123 | 0.014 | **7.9E-19** | -0.067 | 0.011 | **2.6E-09** |
| **Metabolite levels indirectly affected by microbiota**  |  |  |
| **Choline metabolism** |  |  |  |  |  |  |
| betaine | 0.044 | 0.014 | **0.001** | 0.018 | 0.011 | 0.103 |
| dimethylglycine | -0.003 | 0.014 | 0.831 | -0.022 | 0.011 | 0.052 |
| **Aromatic amino acid metabolism** |  |  |  |  |  |  |
| kynurenine | -0.060 | 0.014 | **1.7E-05** | -0.066 | 0.011 | **6.1E-09** |
| kynurenate | -0.138 | 0.014 | **1.4E-23** | -0.071 | 0.011 | **4.7E-10** |
| **Metabolites modulating the growth of microbiota** |
| **Monoacylglycerols** |  |  |  |  |  |  |
| 1-dihomo-linolenylglycerol (20:3) | -0.018 | 0.014 | 0.185 | -0.028 | 0.011 | **0.013** |
| 1-docosahexaenoylglycerol (22:6) | -0.021 | 0.014 | 0.122 | -0.011 | 0.011 | 0.321 |
| 1-linoleoylglycerol (18:2) | 0.030 | 0.014 | **0.030** | -0.011 | 0.011 | 0.339 |
| 1-myristoylglycerol (14:0) | -0.073 | 0.014 | **1.4E-07** | -0.046 | 0.011 | **4.1E-05** |
| 1-oleoylglycerol (18:1) | -0.070 | 0.014 | **3.9E-07** | -0.047 | 0.011 | **3.0E-05** |
| 1-palmitoylglycerol (16:0) | -0.011 | 0.014 | 0.429 | -0.025 | 0.011 | **0.026** |
| 2-linoleoylglycerol (18:2) | 0.054 | 0.014 | **1.0E-04** | 0.009 | 0.011 | 0.425 |
| 2-oleoylglycerol (18:1) | -0.041 | 0.014 | **0.003** | -0.038 | 0.011 | **8.8E-04** |
| 2-palmitoylglycerol (16:0) | -0.016 | 0.014 | 0.253 | -0.017 | 0.011 | 0.144 |
| 1-palmitoleoylglycerol (16:1)\* | -0.143 | 0.015 | **1.3E-20** | -0.064 | 0.013 | **7.2E-07** |
| 1-linolenoylglycerol (18:3) | -0.025 | 0.016 | 0.122 | -0.012 | 0.013 | 0.354 |

Results based on linear regression analyses. Analyses at baseline was adjusted for batch alone and at follow-up, additionally for follow-up time and respective trait at baseline. *P*<5.8x10-5 marked as bold and underlined, *P*<0.05 marked as bold.

Supplemental Table 5. Association of various metabolites with Matsuda ISI at baseline and follow-up

|  |  |  |
| --- | --- | --- |
|  | **Matsuda ISI at baseline** | **Matsuda ISI at follow-up** |
| **Metabolite** | **Beta** | **SE** | ***P*** | **Beta** | **SE** | ***P*** |
| **Metabolites generated by microbiota** |  |  |  |  |  |  |
| **Bile acids** |  |  |  |  |  |  |
| glycocholate | -0.207 | 0.014 | **2.5E-51** | 0.001 | 0.010 | 0.917 |
| taurochenodeoxycholate | -0.233 | 0.014 | **8.9E-65** | -0.025 | 0.010 | **0.011** |
| ursodeoxycholate | -0.105 | 0.014 | **3.5E-14** | 0.006 | 0.010 | 0.526 |
| glycodeoxycholate | -0.128 | 0.014 | **3.2E-20** | 0.008 | 0.010 | 0.400 |
| glycolithocholate sulfate\* | -0.024 | 0.014 | 0.085 | 0.004 | 0.010 | 0.675 |
| glycocholenate sulfate\* | -0.086 | 0.014 | **6.3E-10** | -0.009 | 0.010 | 0.351 |
| taurocholenate sulfate | -0.128 | 0.014 | **2.8E-20** | -0.057 | 0.010 | **3.5E-09** |
| glycoursodeoxycholate | -0.104 | 0.014 | **5.1E-14** | 0.006 | 0.010 | 0.504 |
| **Choline metabolism** |  |  |  |  |  |  |
| trimethylamine N-oxide | -0.006 | 0.014 | 0.689 | 0.004 | 0.010 | 0.711 |
| **Aromatic amino acid metabolism** |
| p-cresol sulfate | -0.017 | 0.014 | 0.218 | 0.009 | 0.010 | 0.363 |
| methyl indole-3-acetate | -0.086 | 0.014 | **5.4E-10** | 0.011 | 0.010 | 0.247 |
| indolepropionate | 0.092 | 0.014 | **4.0E-11** | 0.042 | 0.010 | **1.5E-05** |
| phenyllactate (PLA) | -0.164 | 0.014 | **2.4E-32** | 0.012 | 0.010 | 0.201 |
| Xanthurenate | -0.248 | 0.014 | **4.2E-73** | -0.030 | 0.010 | **0.002** |
| 3-(4-hydroxyphenyl)lactate | -0.317 | 0.013 | **8.4E-121** | -0.014 | 0.010 | 0.155 |
| 4-ethylphenylsulfate | -0.042 | 0.014 | **0.003** | 0.005 | 0.010 | 0.584 |
| 4-hydroxyphenylacetate | -0.069 | 0.015 | **8.3E-06** | -0.006 | 0.011 | 0.607 |
| phenylacetylglutamine | -0.007 | 0.014 | 0.615 | 0.014 | 0.010 | 0.159 |
| 3-(3-hydroxyphenyl)propionate | 0.022 | 0.014 | 0.114 | 0.014 | 0.010 | 0.141 |
| 3-phenylpropionate (hydrocinnamate) | 0.090 | 0.014 | **7.3E-11** | 0.025 | 0.010 | **0.010** |
| phenylacetate | 0.044 | 0.014 | **0.002** | 0.017 | 0.010 | 0.079 |
| phenol sulfate | -0.062 | 0.014 | **7.8E-06** | -0.014 | 0.010 | 0.137 |
| indolelactate | -0.159 | 0.014 | **1.6E-30** | 0.003 | 0.010 | 0.752 |
| indoleacetate | -0.029 | 0.014 | **0.037** | 0.015 | 0.010 | 0.126 |
| N-acetyltryptophan | -0.284 | 0.013 | **1.3E-96** | -0.023 | 0.010 | **0.021** |
| 3-indoxyl sulfate | -0.124 | 0.014 | **3.0E-19** | 0.003 | 0.010 | 0.779 |
| indoleacetylglutamine | -0.145 | 0.014 | **9.5E-26** | 0.023 | 0.010 | **0.017** |
| **Non-aromatic amino acid metabolism** |
| 3-aminoisobutyrate | 0.107 | 0.014 | **1.6E-14** | -0.035 | 0.010 | **2.7E-04** |
| imidazole propionate | -0.100 | 0.013 | **5.1E-13** | -0.005 | 0.010 | 0.582 |
| **Xenobiotic metabolism** |  |  |  |  |  |  |
| hippurate | 0.093 | 0.014 | **2.0E-11** | 0.042 | 0.010 | **1.4E-05** |
| 2-hydroxyhippurate (salicylurate) | -0.047 | 0.014 | **6.4E-04** | 0.034 | 0.010 | **4.8E-04** |
| 3-hydroxyhippurate | 0.005 | 0.014 | 0.704 | 0.018 | 0.010 | 0.065 |
| 4-hydroxyhippurate | -0.030 | 0.014 | **0.033** | 0.033 | 0.010 | **6.3E-04** |
| **Energy metabolism** |  |  |  |  |  |  |
| lactate | -0.331 | 0.013 | **4.7E-132** | 0.049 | 0.010 | **1.3E-06** |
| succinate | 0.009 | 0.014 | 0.510 | -0.004 | 0.010 | 0.681 |
| **Lipid metabolism** |  |  |  |  |  |  |
| **Short chain fatty acid** |  |  |  |  |  |  |
| isovalerate (i5:0) | -0.107 | 0.014 | **1.2E-14** | -0.021 | 0.010 | **0.026** |
| **Other metabolites** |  |  |  |  |  |  |
| 2-hydroxybutyrate/2-hydroxyisobutyrate | -0.187 | 0.014 | **6.2E-42** | -0.061 | 0.010 | **3.4E-10** |
| 3-hydroxyisobutyrate | -0.159 | 0.014 | **2.0E-30** | -0.037 | 0.010 | **1.2E-04** |
| benzoate | 0.015 | 0.014 | 0.277 | 0.017 | 0.010 | 0.085 |
| homovanillate (HVA) | -0.091 | 0.016 | **9.9E-09** | 0.011 | 0.011 | 0.294 |
| serotonin | -0.001 | 0.014 | 0.916 | 0.006 | 0.010 | 0.536 |
| spermidine | -0.040 | 0.014 | **0.004** | -0.008 | 0.010 | 0.384 |
| N-acetylputrescine | -0.092 | 0.014 | **3.9E-11** | -0.002 | 0.010 | 0.979 |
| **Lyso-phosphatidylcholines** |  |  |  |  |  |  |
| 1-linolenoyl-GPC (18:3)\* | 0.163 | 0.014 | **3.6E-32** | 0.090 | 0.010 | **1.7E-20** |
| 1-linoleoyl-GPC (18:2) | 0.362 | 0.013 | **5.1E-160** | 0.086 | 0.010 | **4.0E-17** |
| 1-oleoyl-GPC (18:1) | 0.303 | 0.013 | **1.9E-110** | 0.088 | 0.010 | **2.3E-18** |
| 1-palmitoleoyl-GPC (16:1)\* | -0.026 | 0.014 | 0.060 | 0.039 | 0.010 | **4.9E-05** |
| 1-palmitoyl-GPC (16:0) | 0.129 | 0.014 | **1.5E-20** | 0.073 | 0.010 | **2.8E-14** |
| 1-lignoceroyl-GPC (24:0) | 0.237 | 0.015 | **1.5E-51** | 0.080 | 0.011 | **2.8E-13** |
| 1-stearoyl-GPC (18:0) | 0.130 | 0.014 | **5.7E-21** | 0.077 | 0.010 | **1.1E-15** |
| 2-palmitoyl-GPC (16:0)\* | 0.081 | 0.014 | **6.4E-09** | 0.048 | 0.010 | **7.5E-07** |
| **Lyso-phosphatidylethanolamines** |  |  |  |  |  |
| 1-arachidonoyl-GPE (20:4n6)\* | 0.028 | 0.014 | **0.047** | 0.023 | 0.010 | **0.015** |
| 1-linoleoyl-GPE (18:2)\* | 0.109 | 0.014 | **4.6E-15** | 0.067 | 0.010 | **3.7E-12** |
| 1-oleoyl-GPE (18:1) | 0.051 | 0.014 | **2.4E-04** | 0.055 | 0.010 | **1.1E-08** |
| 1-palmitoyl-GPE (16:0) | 0.153 | 0.014 | **2.6E-28** | 0.071 | 0.010 | **3.3E-13** |
| 1-stearoyl-GPE (18:0) | 0.059 | 0.014 | **2.0E-05** | 0.054 | 0.010 | **2.0E-08** |
| 2-stearoyl-GPE (18:0)\* | 0.021 | 0.014 | 0.132 | 0.040 | 0.010 | **2.5E-05** |
| **Metabolites processed by microbiota** |  |  |  |
| **Bile acids** |  |  |  |  |  |  |
| cholate | -0.082 | 0.014 | **4.4E-09** | 0.036 | 0.010 | **1.7E-04** |
| chenodeoxycholate | -0.044 | 0.014 | **0.002** | 0.021 | 0.010 | **0.028** |
| glycochenodeoxycholate | -0.171 | 0.014 | **3.3E-35** | 0.011 | 0.010 | 0.239 |
| taurolithocholate 3-sulfate | -0.055 | 0.014 | **7.0E-05** | -0.011 | 0.010 | 0.252 |
| deoxycholate | -0.092 | 0.014 | **3.3E-11** | 0.009 | 0.010 | 0.329 |
| choline | 0.048 | 0.014 | **5.7E-04** | -0.004 | 0.010 | 0.693 |
| **Xenobiotic metabolism** |  |  |  |  |  |  |
| xylose | -0.015 | 0.016 | 0.347 | 0.007 | 0.011 | 0.490 |
| **Non-aromatic amino acid metabolism** |
| N-acetylglycine | 0.377 | 0.013 | **3.3E-174** | -0.013 | 0.010 | 0.198 |
| **Energy metabolism** |  |  |  |  |  |  |
| urea | 0.005 | 0.014 | 0.709 | -0.013 | 0.010 | 0.188 |
| creatine | -0.184 | 0.014 | **2.3E-40** | -0.057 | 0.010 | **5.9E-09** |
| creatinine | -0.042 | 0.014 | **0.002** | 0.024 | 0.010 | **0.012** |
| **Other metabolites** |  |  |  |  |  |  |
| Urate | -0.274 | 0.013 | **9.2E-90** | -0.030 | 0.010 | **0.003** |
| Uridine | -0.137 | 0.014 | **5.7E-23** | -0.030 | 0.010 | **0.002** |
| Xanthine | -0.294 | 0.013 | **1.4E-103** | -0.044 | 0.010 | **1.2E-05** |
| **Metabolite levels indirectly affected by microbiota**  |  |  |
| **Choline metabolism** |  |  |  |  |  |  |
| betaine | 0.167 | 0.014 | **1.8E-33** | 0.010 | 0.010 | 0.324 |
| dimethylglycine | -0.074 | 0.014 | **1.2E-07** | -0.038 | 0.010 | **9.2E-05** |
| **Aromatic amino acid metabolism** |  |  |  |  |  |
| kynurenine | -0.280 | 0.013 | **1.6E-93** | -0.045 | 0.010 | **6.9E-06** |
| kynurenate | -0.283 | 0.013 | **1.2E-95** | -0.023 | 0.010 | **0.021** |
|  **Metabolites modulating the growth of microbiota** |  |  |
| **Monoacylglycerols** |  |  |  |  |  |  |
| 1-dihomo-linolenylglycerol (20:3) | -0.050 | 0.014 | **2.9E-04** | 0.000 | 0.010 | 0.959 |
| 1-docosahexaenoylglycerol (22:6) | 0.014 | 0.014 | 0.300 | 0.010 | 0.010 | 0.298 |
| 1-linoleoylglycerol (18:2) | -0.005 | 0.014 | 0.707 | 0.022 | 0.010 | **0.024** |
| 1-myristoylglycerol (14:0) | -0.213 | 0.014 | **4.7E-54** | 0.013 | 0.010 | 0.182 |
| 1-oleoylglycerol (18:1) | -0.193 | 0.014 | **1.9E-44** | 0.001 | 0.010 | 0.925 |
| 1-palmitoylglycerol (16:0) | -0.038 | 0.014 | **0.007** | -0.012 | 0.010 | 0.209 |
| 2-linoleoylglycerol (18:2) | 0.052 | 0.014 | **2.1E-04** | 0.020 | 0.010 | **0.036** |
| 2-oleoylglycerol (18:1) | -0.129 | 0.014 | **1.2E-20** | 0.007 | 0.010 | 0.476 |
| 2-palmitoylglycerol (16:0) | -0.040 | 0.014 | **0.004** | -0.015 | 0.010 | 0.108 |
| 1-palmitoleoylglycerol (16:1)\* | -0.257 | 0.015 | **4.9E-64** | 0.002 | 0.011 | 0.863 |
| 1-linolenoylglycerol (18:3) | -0.113 | 0.016 | **1.2E-12** | 0.025 | 0.011 | **0.021** |

Results based on linear regression analyses. Analyses at baseline was adjusted for batch alone and at follow-up, additionally for follow-up time and respective trait at baseline. *P*<5.8x10-5 marked as bold and underlined, *P*<0.05 marked as bold.