**ONLINE SUPPLEMENTAL INFORMATION**

**DC19-2533-Revision 1**

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

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Supplemental Table 1. Metabolites included in statistical analyses

|  |  |
| --- | --- |
| **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.