**Supplementary Table 1. Completeness and exclusions of the different metabolites, with limits of detection (LOD) and limits of quantification (LOQ)**

| Metabolites[1] | Results outside the measurable range (N=599 samples) | | CV, % [3] |
|---|---|---|---|
| | Samples, % | Criteria for results considered out of the measurable range[2] | |
| **Acylcarnitines** | | | |
| C0 | 0.0 | <LOD | 3.5 |
| C2 | 0.0 | <LOD | 3.9 |
| C3 | 0.0 | <LOD | 4.3 |
| C3-DC (C4-OH) | 41.5 | <LOD | - |
| C4 | 0.0 | <LOD | 4.7 |
| C5 | 9.0 | <LOD | 6.2 |
| C10 | 62.7 | <LOD | - |
| C10:1 | 38.8 | <LOD | - |
| C12 | 37.8 | <LOD | - |
| C12:1 | 0.2 | <LOD | 8.5 |
| C14:1 | 0.0 | <LOD | 5.0 |
| C14:2 | 7.5 | <LOD | 5.1 |
| C16 | 0.0 | <LOD | 4.3 |
| C16:1 | 77.5 | <LOD | - |
| C18 | 0.0 | <LOD | 7.0 |
| C18:1 | 0.0 | <LOD | 4.8 |
| C18:2 | 0.0 | <LOD | 5.9 |
| **Amino acids** | | | |
| Alanine | 0.0 | <LLOQ (< 20 µmol/L) | 4.0 |
| Arginine | 1.8 | >ULOQ (> 400 µmol/L) | 4.4 |
| Asparagine | 0.0 | <LLOQ (< 5 µmol/L) | 4.9 |
| Aspartate | 0.0 | <LLOQ (< 5 µmol/L) | 11.5 |
| Citrulline | 0.0 | <LLOQ (< 5 µmol/L) | 5.2 |
| Glutamine | 0.0 | <LLOQ (< 20 µmol/L) | 5.3 |
| Glutamate | 0.0 | <LLOQ (< 10 µmol/L) | 6.0 |
| Glycine | 0.0 | <LLOQ (< 25 µmol/L) | 7.4 |
| Histidine | 0.0 | <LLOQ (< 5 µmol/L) | 3.9 |
| Isoleucine | 0.0 | <LLOQ (< 5 µmol/L) | 6.2 |
| Leucine | 0.0 | <LLOQ (< 50 µmol/L) | 4.9 |
| Lysine | 0.0 | <LLOQ (< 10 µmol/L) | 7.5 |
| Methionine | 0.0 | <LLOQ (< 5 µmol/L) | 9.6 |
| Ornithine | 0.0 | <LLOQ (< 5 µmol/L) | 7.5 |
| Phenylalanine | 0.0 | <LLOQ (< 5 µmol/L) | 4.1 |
| Proline | 0.0 | <LLOQ (< 10 µmol/L) | 4.7 |
| Serine | 0.0 | <LLOQ (< 5 µmol/L) | 4.0 |
| Threonine | 0.0 | <LLOQ (< 5 µmol/L) | 4.0 |
| Tryptophane | 0.0 | <LLOQ (< 5 µmol/L) | 4.3 |
| Tyrosine | 0.0 | <LLOQ (< 5 µmol/L) | 3.8 |
| Valine | 0.0 | <LLOQ (< 10 µmol/L) | 9.1 |
| **Biogenic amines** | | | |

| | | | |
|---|---|---|---|
| ADMA | 0.0 | <LLOQ (< 0.25 µmol/L) | 10.4 |
| Creatinine | 0.0 | <LLOQ (< 10 µmol/L) | 3.7 |
| Kynurenine | 0.5 | <LLOQ (< 1 µmol/L) | 7.5 |
| Putrescine | 73.8 | <LLOQ (< 0.1 µmol/L) | - |
| SDMA | 0.0 | <LLOQ (< 0.1 µmol/L) | 7.3 |
| Sarcosine | 48.5 | <LLOQ (< 1 µmol/L) | - |
| Serotonin[4] | 1.0 | <LLOQ (< 0.1 µmol/L) | - |
| Spermidine | 54.2 | <LLOQ (< 0.25 µmol/L | - |
| Spermine | 94.5 | <LLOQ (< 0.25 µmol/L | - |
| Taurine | 17.3 | >ULOQ (> 200 µmol/L) | 3.4 |
| alpha-AAA | 77.8 | <LLOQ (< 1 µmol/L) | - |
| t4-OH-Pro | 0.0 | | 5.8 |
| **Glycerophospholipids** | | | |
| PC aa C28:1 | 0.0 | <LOD | 6.1 |
| PC aa C30:0 | 0.0 | <LOD | 6.2 |
| PC aa C32:0 | 0.0 | <LOD | 6.1 |
| PC aa C32:1 | 0.0 | <LOD | 5.9 |
| PC aa C32:2 | 0.0 | <LOD | 5.5 |
| PC aa C32:3 | 0.0 | <LOD | 6.1 |
| PC aa C34:1 | 0.0 | <LOD | 4.6 |
| PC aa C34:2 | 0.0 | <LOD | 4.6 |
| PC aa C34:3 | 0.0 | <LOD | 5.3 |
| PC aa C34:4 | 0.0 | <LOD | 5.1 |
| PC aa C36:0 | 0.0 | <LOD | 6.3 |
| PC aa C36:1 | 0.0 | <LOD | 5.7 |
| PC aa C36:2 | 0.0 | <LOD | 4.6 |
| PC aa C36:3 | 0.0 | <LOD | 5.3 |
| PC aa C36:4 | 0.0 | <LOD | 4.7 |
| PC aa C36:5 | 0.0 | <LOD | 4.8 |
| PC aa C36:6 | 0.0 | <LOD | 5.6 |
| PC aa C38:0 | 0.0 | <LOD | 7.2 |
| PC aa C38:3 | 0.0 | <LOD | 5.3 |
| PC aa C38:4 | 0.0 | <LOD | 4.7 |
| PC aa C38:5 | 0.0 | <LOD | 4.9 |
| PC aa C38:6 | 0.0 | <LOD | 4.9 |
| PC aa C40:1 | 39.8 | <LOD | - |
| PC aa C40:2 | 0.0 | <LOD | 8.2 |
| PC aa C40:3 | 0.0 | <LOD | 8.7 |
| PC aa C40:4 | 0.0 | <LOD | 5.0 |
| PC aa C40:5 | 0.0 | <LOD | 5.3 |
| PC aa C40:6 | 0.0 | <LOD | 5.7 |
| PC aa C42:0 | 0.0 | <LOD | 7.4 |
| PC aa C42:1 | 0.0 | <LOD | 10.9 |
| PC aa C42:2 | 0.0 | <LOD | 9.5 |
| PC aa C42:4 | 0.0 | <LOD | 13.3 |
| PC aa C42:5 | 0.0 | <LOD | 9.0 |

| | | | |
|---|---|---|---|
| PC aa C42:6 | 0.0 | <LOD | 6.3 |
| PC ae C30:0 | 0.0 | <LOD | 8.5 |
| PC ae C30:2 | 0.0 | <LOD | 11.7 |
| PC ae C32:1 | 0.0 | <LOD | 6.2 |
| PC ae C32:2 | 0.0 | <LOD | 6.7 |
| PC ae C34:0 | 0.0 | <LOD | 6.8 |
| PC ae C34:1 | 0.0 | <LOD | 5.5 |
| PC ae C34:2 | 0.0 | <LOD | 6.2 |
| PC ae C34:3 | 0.0 | <LOD | 5.6 |
| PC ae C36:0 | 3.2 | <LOD | 7.6 |
| PC ae C36:1 | 0.0 | <LOD | 7.0 |
| PC ae C36:2 | 0.0 | <LOD | 5.2 |
| PC ae C36:3 | 0.0 | <LOD | 4.8 |
| PC ae C36:4 | 0.0 | <LOD | 5.5 |
| PC ae C36:5 | 0.0 | <LOD | 5.4 |
| PC ae C38:0 | 0.0 | <LOD | 7.6 |
| PC ae C38:2 | 0.0 | <LOD | 7.6 |
| PC ae C38:3 | 0.0 | <LOD | 7.1 |
| PC ae C38:4 | 0.0 | <LOD | 5.1 |
| PC ae C38:5 | 0.0 | <LOD | 5.5 |
| PC ae C38:6 | 0.0 | <LOD | 4.9 |
| PC ae C40:1 | 0.0 | <LOD | 8.3 |
| PC ae C40:2 | 0.0 | <LOD | 5.7 |
| PC ae C40:3 | 0.0 | <LOD | 5.6 |
| PC ae C40:4 | 0.0 | <LOD | 7.4 |
| PC ae C40:5 | 0.0 | <LOD | 6.7 |
| PC ae C40:6 | 0.0 | <LOD | 5.8 |
| PC ae C42:1 | 0.0 | <LOD | 10.1 |
| PC ae C42:2 | 0.0 | <LOD | 6.4 |
| PC ae C42:3 | 0.0 | <LOD | 7.4 |
| PC ae C42:4 | 0.5 | <LOD | 7.8 |
| PC ae C42:5 | 0.0 | <LOD | 5.2 |
| PC ae C44:3 | 0.0 | <LOD | 11.8 |
| PC ae C44:4 | 0.0 | <LOD | 7.1 |
| PC ae C44:5 | 0.0 | <LOD | 6.5 |
| PC ae C44:6 | 0.0 | <LOD | 5.9 |
| lysoPC a C16:0 | 0.0 | <LOD | 5.7 |
| lysoPC a C16:1 | 0.0 | <LOD | 6.4 |
| lysoPC a C17:0 | 0.0 | <LOD | 6.3 |
| lysoPC a C18:0 | 0.0 | <LOD | 5.8 |
| lysoPC a C18:1 | 0.0 | <LOD | 6.1 |
| lysoPC a C18:2 | 0.0 | <LOD | 6.8 |
| lysoPC a C20:3 | 0.0 | <LOD | 5.2 |
| lysoPC a C20:4 | 0.0 | <LOD | 5.9 |
| lysoPC a C24:0 | 0.0 | <LOD | 9.9 |
| **Sphingolipids** | | | |

| | | | |
|---|---|---|---|
| SM C16:0 | 0.0 | <LOD | 6.1 |
| SM C16:1 | 0.0 | <LOD | 6.3 |
| SM C18:0 | 0.0 | <LOD | 7.2 |
| SM C18:1 | 0.0 | <LOD | 6.4 |
| SM C20:2 | 0.0 | <LOD | 9.7 |
| SM C24:0 | 0.0 | <LOD | 6.0 |
| SM C24:1 | 0.0 | <LOD | 6.5 |
| SM C26:0 | 9.0 | <LOD | 11.7 |
| SM C26:1 | 1.0 | <LOD | 10.7 |
| SM (OH) C14:1 | 0.0 | <LOD | 6.5 |
| SM (OH) C16:1 | 0.0 | <LOD | 6.2 |
| SM (OH) C22:1 | 0.0 | <LOD | 7.0 |
| SM (OH) C22:2 | 0.0 | <LOD | 5.8 |
| SM (OH) C24:1 | 0.0 | <LOD | 9.9 |
| **Hexose** | | | |
| Hexose | 0.0 | <LLOQ (< 1500 µmol/L) | 3.4 |

[1]Metabolites in gray were excluded from the statistical analysis because more than 20% or the measures were outside the measurable range.
[2]Limit of detection (LOD) is applicable to acylcarnitines, glycerophospholipids, sphingolipids. Lower limit of quantification (LLOQ) or upper limit of quantification (ULOQ) is applicable to amino acids, biogenic amines and hexose. No metabolites had values both under LLOQ and over ULOQ.
[3]Mean intra- and inter-batch coefficients of variation (CVs) based on two quality control samples measured in duplicate in each batch.
[4]CV for serotonin not calculated because measures in quality controls were lower than LLOQ.

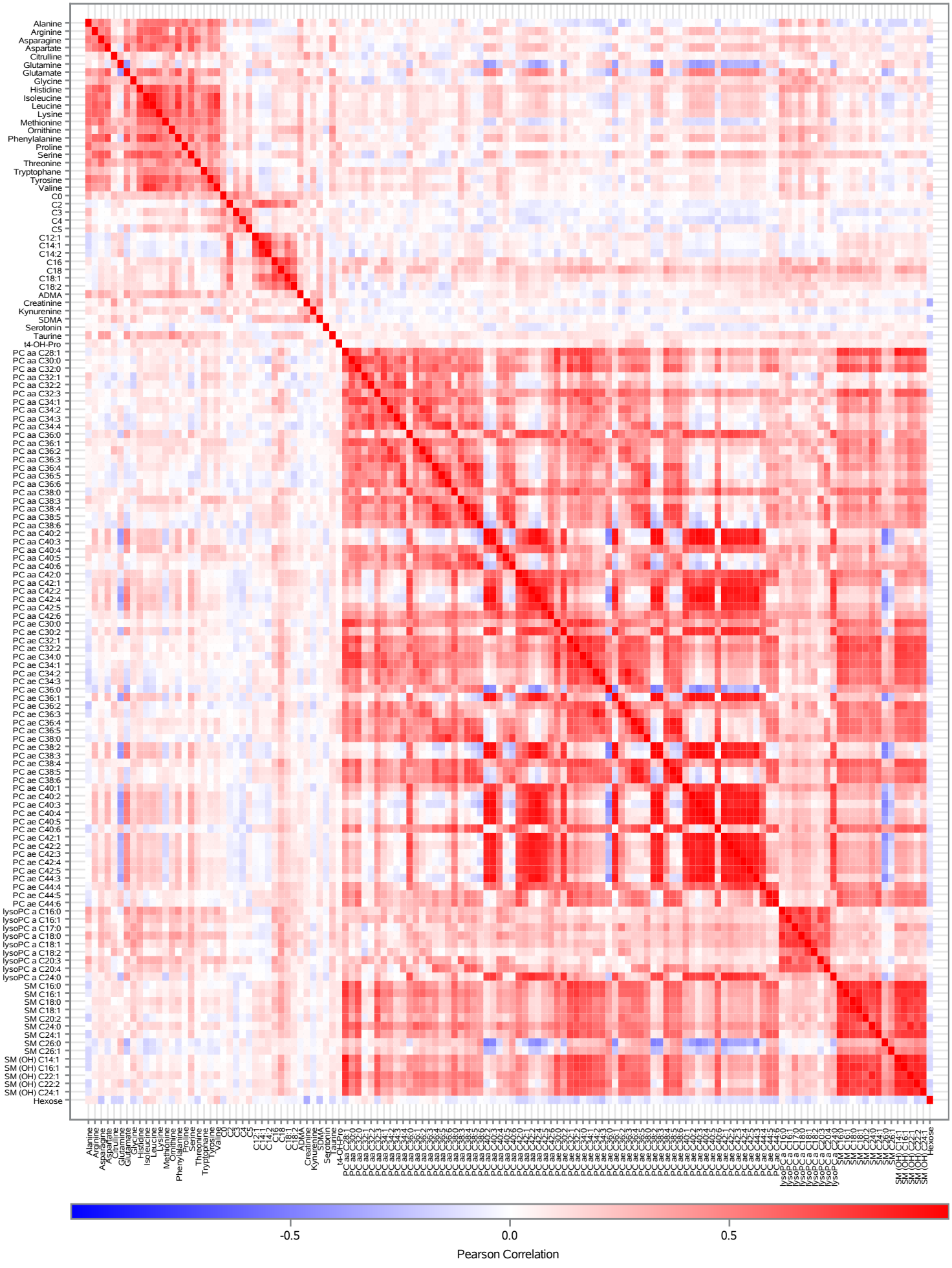
Supplementary Table 2. Geometric means of metabolites concentrations

| | | |
|---|---|---|
| **Variable** | **N** | **Geometric mean (95% CI) (µmol/L)** |
| **C0** | 573 | 32.18 (31.69-32.69) |
| **C2** | 573 | 5.31 (5.19-5.44) |
| **C3** | 573 | 0.30 (0.29-0.31) |
| **C4** | 573 | 0.15 (0.14-0.15) |
| **C5** | 573 | 0.11 (0.11-0.12) |
| **C12:1** | 573 | 0.21 (0.21-0.21) |
| **C14:1** | 573 | 0.06 (0.06-0.06) |
| **C14:2** | 573 | 0.03 (0.03-0.03) |
| **C16** | 573 | 0.11 (0.11-0.11) |
| **C18** | 573 | 0.05 (0.04-0.05) |
| **C18:1** | 573 | 0.12 (0.12-0.13) |
| **C18:2** | 573 | 0.06 (0.06-0.06) |
| **Alanine** | 573 | 469.21 (461.08-477.48) |
| **Arginine** | 573 | 157.23 (153.14-161.43) |
| **Asparagine** | 573 | 51.05 (50.19-51.92) |
| **Aspartate** | 573 | 51.50 (50.28-52.75) |
| **Citrulline** | 573 | 25.86 (25.32-26.41) |
| **Glutamine** | 573 | 491.29 (483.10-499.62) |
| **Glutamate** | 573 | 153.86 (148.98-158.90) |
| **Glycine** | 573 | 348.92 (341.28-356.73) |
| **Histidine** | 573 | 99.11 (97.83-100.41) |
| **Isoleucine** | 573 | 76.22 (74.96-77.51) |
| **Leucine** | 573 | 155.26 (152.62-157.94) |
| **Lysine** | 573 | 247.69 (243.53-251.93) |
| **Methionine** | 573 | 23.47 (22.99-23.95) |
| **Ornithine** | 573 | 93.29 (90.95-95.68) |
| **Phenylalanine** | 573 | 99.09 (97.54-100.66) |
| **Proline** | 573 | 201.05 (196.96-205.23) |
| **Serine** | 573 | 179.38 (176.39-182.41) |
| **Threonine** | 573 | 133.40 (130.66-136.19) |
| **Tryptophane** | 573 | 63.24 (62.40-64.09) |
| **Tyrosine** | 573 | 73.30 (72.02-74.61) |
| **Valine** | 573 | 231.29 (227.26-235.39) |
| **ADMA** | 573 | 0.47 (0.47-0.48) |
| **Creatinine** | 573 | 53.09 (52.37-53.83) |
| **Kynurenine** | 573 | 2.08 (2.04-2.12) |
| **SDMA** | 573 | 0.42 (0.41-0.42) |
| **Serotonin** | 573 | 0.67 (0.64-0.70) |
| **Taurine** | 573 | 147.71 (144.49-151.00) |
| **t4-OH-Pro** | 573 | 10.59 (10.18-11.01) |
| **PC aa C28:1** | 573 | 1.78 (1.73-1.82) |
| **PC aa C30:0** | 573 | 2.31 (2.25-2.37) |
| **PC aa C32:0** | 573 | 17.31 (16.97-17.65) |

| | | |
|---|---|---|
| **PC aa C32:1** | 573 | 18.59 (17.95-19.24) |
| **PC aa C32:2** | 573 | 6.75 (6.58-6.94) |
| **PC aa C32:3** | 573 | 0.99 (0.97-1.01) |
| **PC aa C34:1** | 573 | 238.47 (234.24-242.78) |
| **PC aa C34:2** | 573 | 525.26 (518.64-531.96) |
| **PC aa C34:3** | 573 | 25.11 (24.62-25.61) |
| **PC aa C34:4** | 573 | 2.36 (2.29-2.42) |
| **PC aa C36:0** | 573 | 2.64 (2.58-2.70) |
| **PC aa C36:1** | 573 | 44.09 (43.19-45.00) |
| **PC aa C36:2** | 573 | 288.26 (283.94-292.64) |
| **PC aa C36:3** | 573 | 177.98 (175.08-180.92) |
| **PC aa C36:4** | 573 | 197.37 (193.37-201.45) |
| **PC aa C36:5** | 573 | 16.77 (16.21-17.34) |
| **PC aa C36:6** | 573 | 0.94 (0.91-0.97) |
| **PC aa C38:0** | 573 | 2.30 (2.25-2.35) |
| **PC aa C38:3** | 573 | 49.27 (48.27-50.29) |
| **PC aa C38:4** | 573 | 99.18 (97.06-101.34) |
| **PC aa C38:5** | 573 | 48.30 (47.22-49.41) |
| **PC aa C38:6** | 573 | 59.60 (58.12-61.12) |
| **PC aa C40:2** | 573 | 0.48 (0.45-0.52) |
| **PC aa C40:3** | 573 | 0.62 (0.59-0.65) |
| **PC aa C40:4** | 573 | 3.43 (3.35-3.51) |
| **PC aa C40:5** | 573 | 7.31 (7.14-7.48) |
| **PC aa C40:6** | 573 | 18.15 (17.70-18.61) |
| **PC aa C42:0** | 573 | 0.29 (0.28-0.29) |
| **PC aa C42:1** | 573 | 0.16 (0.16-0.16) |
| **PC aa C42:2** | 573 | 0.16 (0.15-0.17) |
| **PC aa C42:4** | 573 | 0.18 (0.17-0.19) |
| **PC aa C42:5** | 573 | 0.26 (0.25-0.26) |
| **PC aa C42:6** | 573 | 0.28 (0.28-0.29) |
| **PC ae C30:0** | 573 | 0.21 (0.20-0.21) |
| **PC ae C30:2** | 573 | 0.08 (0.08-0.09) |
| **PC ae C32:1** | 573 | 3.41 (3.34-3.49) |
| **PC ae C32:2** | 573 | 1.04 (1.02-1.06) |
| **PC ae C34:0** | 573 | 1.64 (1.60-1.68) |
| **PC ae C34:1** | 573 | 12.64 (12.41-12.88) |
| **PC ae C34:2** | 573 | 16.59 (16.24-16.94) |
| **PC ae C34:3** | 573 | 10.13 (9.88-10.39) |
| **PC ae C36:0** | 573 | 0.61 (0.58-0.63) |
| **PC ae C36:1** | 573 | 14.13 (13.54-14.74) |
| **PC ae C36:2** | 573 | 19.10 (18.72-19.49) |
| **PC ae C36:3** | 573 | 10.47 (10.26-10.68) |
| **PC ae C36:4** | 573 | 20.80 (20.34-21.28) |
| **PC ae C36:5** | 573 | 11.87 (11.57-12.18) |
| **PC ae C38:0** | 573 | 1.70 (1.66-1.73) |
| **PC ae C38:2** | 573 | 4.49 (4.25-4.76) |

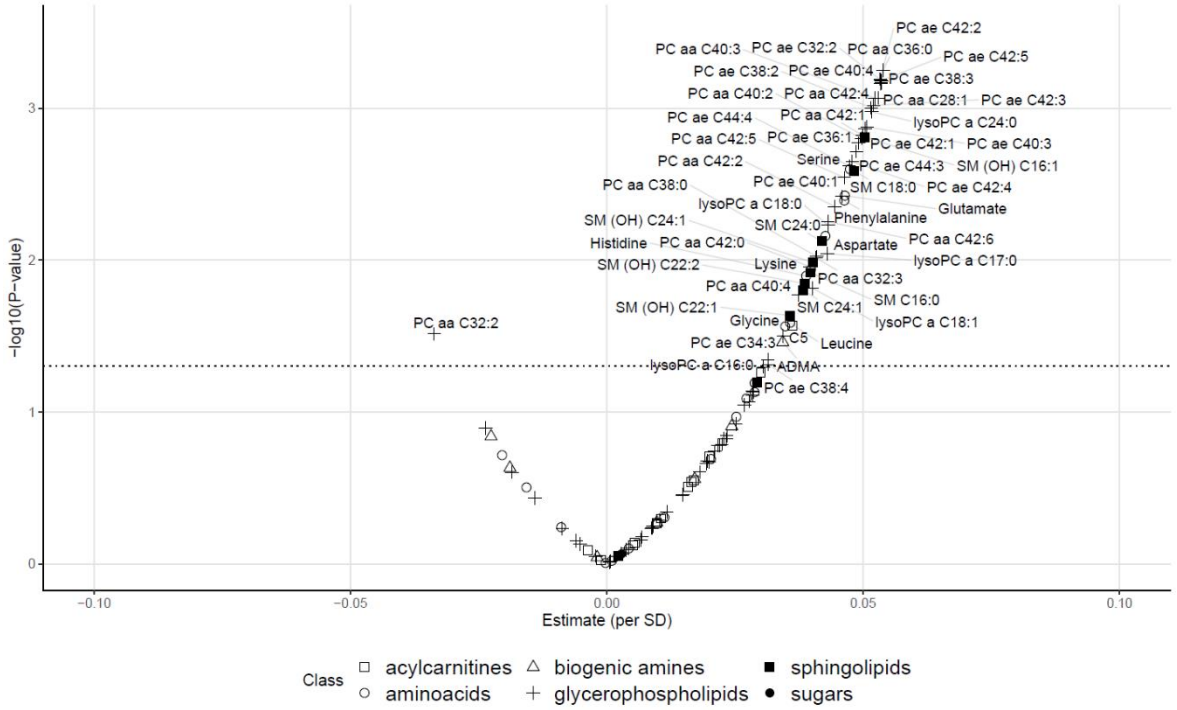
| | | |
|---|---|---|
| **PC ae C38:3** | 573 | 8.33 (7.93-8.75) |
| **PC ae C38:4** | 573 | 14.14 (13.86-14.41) |
| **PC ae C38:5** | 573 | 17.94 (17.56-18.32) |
| **PC ae C38:6** | 573 | 6.55 (6.39-6.70) |
| **PC ae C40:1** | 573 | 1.02 (0.99-1.05) |
| **PC ae C40:2** | 573 | 1.77 (1.70-1.84) |
| **PC ae C40:3** | 573 | 2.20 (2.05-2.36) |
| **PC ae C40:4** | 573 | 3.12 (3.00-3.26) |
| **PC ae C40:5** | 573 | 4.60 (4.43-4.77) |
| **PC ae C40:6** | 573 | 3.54 (3.47-3.62) |
| **PC ae C42:1** | 573 | 0.42 (0.40-0.43) |
| **PC ae C42:2** | 573 | 0.42 (0.41-0.43) |
| **PC ae C42:3** | 573 | 0.61 (0.59-0.63) |
| **PC ae C42:4** | 573 | 0.74 (0.71-0.76) |
| **PC ae C42:5** | 573 | 1.74 (1.69-1.79) |
| **PC ae C44:3** | 573 | 0.09 (0.08-0.09) |
| **PC ae C44:4** | 573 | 0.20 (0.19-0.20) |
| **PC ae C44:5** | 573 | 0.68 (0.66-0.69) |
| **PC ae C44:6** | 573 | 0.57 (0.56-0.59) |
| **lysoPC a C16:0** | 573 | 156.23 (152.58-159.96) |
| **lysoPC a C16:1** | 573 | 4.30 (4.20-4.41) |
| **lysoPC a C17:0** | 573 | 2.96 (2.88-3.04) |
| **lysoPC a C18:0** | 573 | 47.71 (46.49-48.96) |
| **lysoPC a C18:1** | 573 | 25.45 (24.89-26.02) |
| **lysoPC a C18:2** | 573 | 25.22 (24.68-25.77) |
| **lysoPC a C20:3** | 573 | 2.08 (2.03-2.13) |
| **lysoPC a C20:4** | 573 | 5.91 (5.75-6.07) |
| **lysoPC a C24:0** | 573 | 0.11 (0.11-0.12) |
| **SM C16:0** | 573 | 67.14 (65.77-68.54) |
| **SM C16:1** | 573 | 10.49 (10.29-10.69) |
| **SM C18:0** | 573 | 12.19 (11.92-12.46) |
| **SM C18:1** | 573 | 6.78 (6.63-6.93) |
| **SM C20:2** | 573 | 0.28 (0.27-0.28) |
| **SM C24:0** | 573 | 6.60 (6.47-6.73) |
| **SM C24:1** | 573 | 13.11 (12.82-13.40) |
| **SM C26:0** | 573 | 0.03 (0.03-0.03) |
| **SM C26:1** | 573 | 0.06 (0.06-0.07) |
| **SM (OH) C14:1** | 573 | 3.84 (3.74-3.94) |
| **SM (OH) C16:1** | 573 | 2.02 (1.97-2.07) |
| **SM (OH) C22:1** | 573 | 5.16 (5.05-5.27) |
| **SM (OH) C22:2** | 573 | 3.64 (3.56-3.73) |
| **SM (OH) C24:1** | 573 | 0.39 (0.38-0.40) |
| **Hexose** | 573 | 4423.7 (4334.1-4515.2) |

# Supplementary Figure 1. Pearson's partial correlations between metabolites adjusted for age, state, and batch



**Supplementary Figure 2. Associations between metabolites and non-dense area. A: Raw P-values. B: Adjusted P-values.** Estimates per standard deviation increase in residuals of metabolites on batch were obtained from linear regression adjusted for age, BMI, age at menarche, family history of cancer, history of benign breast disease, use of oral contraceptive, number of full-term pregnancies, age at first full-term pregnancy, breastfeeding, alcohol intake, smoking status, socioeconomic status, and physical activity. Dotted lines represent statistical significance thresholds for raw P-values (A) and for P-values adjusted by permutation-based stepdown *minP* (B). Abbreviations: ae: acyl-alkyl; aa: acyl-acyl; PC: phosphatidylcholine; SM: sphingomyelin; SD: standard deviation.

A.




B.