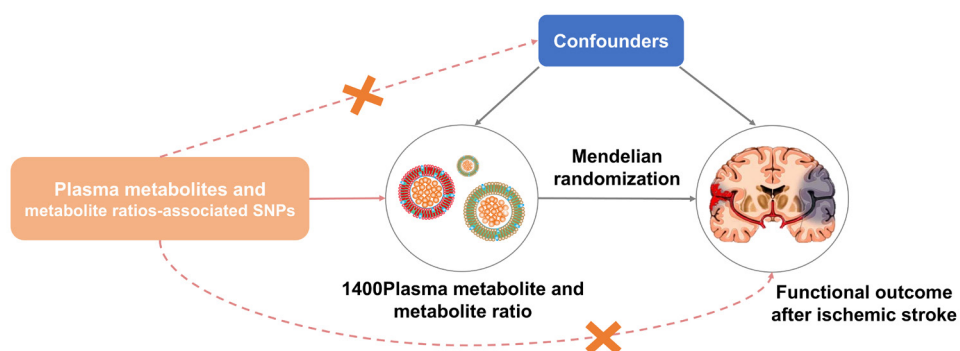




**Figure S1** Graphical abstract.

**Table S1** Cochran’s Q test for heterogeneity of causal associations between plasma metabolites and ischemic stroke functional outcomes

| Exposure                                                  | Cochran’s Q                 |                             |                       |                       |
|-----------------------------------------------------------|-----------------------------|-----------------------------|-----------------------|-----------------------|
|                                                           | Q <sub>I<sup>2</sup>W</sub> | P <sub>I<sup>2</sup>W</sub> | Q <sub>MR-Egger</sub> | P <sub>MR-Egger</sub> |
| X-17146 levels                                            | 22.20424                    | 0.88                        | 22.03426              | 0.85                  |
| ADP to EDTA ratio                                         | 16.39024                    | 0.63                        | 15.47919              | 0.63                  |
| C20:2 levels                                              | 29.00596                    | 0.31                        | 28.77597              | 0.27                  |
| Phosphate to threonine ratio                              | 33.8577                     | 0.62                        | 32.09467              | 0.65                  |
| Picolinate levels                                         | 29.10905                    | 0.36                        | 26.54464              | 0.43                  |
| X-15461 levels                                            | 10.17567                    | 0.93                        | 10.14007              | 0.90                  |
| AMP to citrate ratio                                      | 17.36111                    | 0.30                        | 16.60594              | 0.28                  |
| X-12261 levels                                            | 26.11279                    | 0.46                        | 22.60732              | 0.60                  |
| X-22834 levels                                            | 21.17844                    | 0.51                        | 18.56471              | 0.61                  |
| 3-CMPFP levels                                            | 5.591283                    | 0.96                        | 4.766109              | 0.97                  |
| 5,6-dihydrothymine levels                                 | 9.67353                     | 0.72                        | 9.105141              | 0.69                  |
| C20:3n3 or 6 levels                                       | 16.00679                    | 0.82                        | 15.81915              | 0.78                  |
| 2-hydroxypalmitate levels                                 | 11.79072                    | 0.69                        | 11.65073              | 0.63                  |
| X-23974 levels                                            | 21.17513                    | 0.39                        | 21.07188              | 0.33                  |
| Ceramide (d18:1/24:1) levels                              | 16.76296                    | 0.86                        | 16.16997              | 0.85                  |
| 3-acetylphenol sulfate levels                             | 23.2262                     | 0.39                        | 23.22061              | 0.33                  |
| X-23654 levels                                            | 17.00882                    | 0.76                        | 16.20906              | 0.76                  |
| Methyl vanillate sulfate levels                           | 11.04679                    | 0.96                        | 8.507044              | 0.99                  |
| Tryptophan betaine levels                                 | 27.67688                    | 0.12                        | 26.34744              | 0.12                  |
| Homostachydrine levels                                    | 36.70919                    | 0.06                        | 35.95315              | 0.055                 |
| 17:1n7 levels                                             | 20.61441                    | 0.30                        | 20.56767              | 0.25                  |
| Phosphate to 5-oxoproline ratio                           | 14.7347                     | 0.74                        | 11.65859              | 0.86                  |
| Glucose-to-mannose ratio                                  | 23.68505                    | 0.21                        | 23.67988              | 0.17                  |
| Uridine levels                                            | 21.62922                    | 0.60                        | 20.87174              | 0.59                  |
| ADP to citrate ratio                                      | 9.338536                    | 0.97                        | 8.34688               | 0.97                  |
| Alpha-hydroxyisovalerate levels                           | 19.11015                    | 0.58                        | 18.29092              | 0.57                  |
| HVA levels                                                | 23.56169                    | 0.49                        | 22.24441              | 0.51                  |
| N-palmitoyl-sphinganine (d18:0/16:0) levels               | 21.67721                    | 0.65                        | 20.57677              | 0.66                  |
| X-24801 levels                                            | 11.54144                    | 0.40                        | 11.5408               | 0.32                  |
| Alanine levels                                            | 10.61915                    | 0.78                        | 10.60799              | 0.72                  |
| ADP to valine ratio                                       | 10.67691                    | 0.91                        | 10.64592              | 0.87                  |
| Sphingomyelin (d18:1/20:1, d18:2/20:0) levels             | 28.93693                    | 0.36                        | 26.853                | 0.42                  |
| Dihomo-linolenoyl-choline levels                          | 16.856                      | 0.72                        | 16.61531              | 0.68                  |
| 1-(1-enyl-palmitoyl)-2-linoleoyl-GPE (p-16:0/18:2) levels | 11.34044                    | 0.79                        | 10.10675              | 0.81                  |
| N-acetylcitrulline levels                                 | 21.36785                    | 0.50                        | 21.27194              | 0.44                  |
| Taurolithocholate 3-sulfate levels                        | 14.15301                    | 0.36                        | 11.70632              | 0.47                  |
| Phosphocholine levels                                     | 30.87122                    | 0.08                        | 29.40601              | 0.08                  |
| Salicylate to oxalate (ethanedioate) ratio                | 12.23807                    | 0.93                        | 11.87163              | 0.92                  |
| Hypotaurine levels                                        | 19.6949                     | 0.18                        | 19.07697              | 0.16                  |
| 2-linoleoylglycerol (18:2) levels                         | 17.28626                    | 0.57                        | 14.809                | 0.68                  |
| X-23680 levels                                            | 20.59368                    | 0.48                        | 19.9808               | 0.46                  |
| X-24556 levels                                            | 11.14155                    | 0.74                        | 8.673448              | 0.85                  |
| Ceramide (d18:1/17:0, d17:1/18:0) levels                  | 18.84191                    | 0.47                        | 15.92161              | 0.60                  |
| Mannose levels                                            | 10.56109                    | 0.91                        | 10.32382              | 0.89                  |
| Isovalerylglycine levels                                  | 22.31748                    | 0.72                        | 20.76493              | 0.75                  |
| ADP to pantothenate ratio                                 | 29.56788                    | 0.59                        | 29.50145              | 0.54                  |
| X-12701 levels                                            | 18.40509                    | 0.68                        | 17.19976              | 0.70                  |
| Pyrraline levels                                          | 18.88608                    | 0.71                        | 18.05557              | 0.70                  |
| Umbelliferone sulfate levels                              | 22.23635                    | 0.27                        | 21.93909              | 0.23                  |
| C17 levels                                                | 24.02938                    | 0.15                        | 21.95839              | 0.19                  |
| ADP to FAD ratio                                          | 16.09896                    | 0.76                        | 12.4586               | 0.90                  |
| 3-CMPFP levels                                            | 18.47823                    | 0.73                        | 18.47582              | 0.68                  |
| Arachidate (20:0) levels                                  | 10.44431                    | 0.92                        | 10.40763              | 0.89                  |
| X-25271 levels                                            | 25.14324                    | 0.20                        | 25.13519              | 0.16                  |
| Serine to alpha-ketobutyrate ratio                        | 11.29774                    | 0.91                        | 10.59541              | 0.91                  |
| C8-DC levels                                              | 20.05591                    | 0.64                        | 18.35923              | 0.68                  |
| X-23648 levels                                            | 13.11734                    | 0.52                        | 11.79383              | 0.54                  |
| Carnitine C14 levels                                      | 20.06264                    | 0.39                        | 18.59158              | 0.42                  |
| Histidine to phosphate ratio                              | 23.38842                    | 0.22                        | 23.38708              | 0.18                  |
| X-17146 levels                                            | 22.20424                    | 0.88                        | 22.03426              | 0.85                  |

17:1n7, 10-heptadecenoate; 3-CMPFP, 3-carboxy-4-methyl-5-pentyl-2-furanpropionate; ADP, adenosine 5'-diphosphate; AMP, adenosine 5'-monophosphate; C17, margaroylcarnitine; C20:2, dihomol-linoleoylcarnitine; C20:3n3 or 6, dihomol-linolenoyl carnitine; C8-DC, suberate; EDTA, ethylenediaminetetraacetic acid; FAD, flavin adenine dinucleotide; HVA, homovanillate; IWV, inverse-variance weighted; MR, Mendelian randomization.

| Table S2 Egger’s regression analysis for assessing pleiotropy in causal associations between plasma metabolites and ischemic stroke functional outcomes                                                                                                                                                                                                                                      |                 |        |      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|--------|------|
| Exposure                                                                                                                                                                                                                                                                                                                                                                                     | Egger intercept | SE     | P    |
| X-17146 levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0055          | 0.0517 | 0.92 |
| ADP to EDTA ratio                                                                                                                                                                                                                                                                                                                                                                            | −0.0586         | 0.0367 | 0.13 |
| C20:2 levels                                                                                                                                                                                                                                                                                                                                                                                 | −0.0223         | 0.0290 | 0.45 |
| Phosphate to threonine ratio                                                                                                                                                                                                                                                                                                                                                                 | −0.0432         | 0.0347 | 0.22 |
| Picolinate levels                                                                                                                                                                                                                                                                                                                                                                            | −0.0061         | 0.0321 | 0.85 |
| X-15461 levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0306          | 0.0336 | 0.37 |
| AMP to citrate ratio                                                                                                                                                                                                                                                                                                                                                                         | 0.0245          | 0.0405 | 0.55 |
| X-12261 levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0425          | 0.0564 | 0.47 |
| X-22834 levels                                                                                                                                                                                                                                                                                                                                                                               | −0.0242         | 0.0490 | 0.63 |
| 3-CMPFP levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0370          | 0.0322 | 0.26 |
| 5,6-dihydrothymine levels                                                                                                                                                                                                                                                                                                                                                                    | −0.0178         | 0.0476 | 0.71 |
| C20:3n3 or 6 levels                                                                                                                                                                                                                                                                                                                                                                          | −0.0334         | 0.0211 | 0.13 |
| 2-hydroxypalmitate levels                                                                                                                                                                                                                                                                                                                                                                    | 0.0521          | 0.0469 | 0.28 |
| X-23974 levels                                                                                                                                                                                                                                                                                                                                                                               | −0.0602         | 0.0504 | 0.25 |
| Ceramide (d18:1/24:1) levels                                                                                                                                                                                                                                                                                                                                                                 | 0.0385          | 0.0271 | 0.17 |
| 3-acetylphenol sulfate levels                                                                                                                                                                                                                                                                                                                                                                | −0.0030         | 0.0486 | 0.95 |
| X-23654 levels                                                                                                                                                                                                                                                                                                                                                                               | −0.0286         | 0.0215 | 0.19 |
| Methyl vanillate sulfate levels                                                                                                                                                                                                                                                                                                                                                              | −0.0161         | 0.0522 | 0.76 |
| Tryptophan betaine levels                                                                                                                                                                                                                                                                                                                                                                    | −0.0068         | 0.0265 | 0.80 |
| Homostachydrine levels                                                                                                                                                                                                                                                                                                                                                                       | −0.0154         | 0.0344 | 0.66 |
| 17:1n7 levels                                                                                                                                                                                                                                                                                                                                                                                | −0.0475         | 0.0567 | 0.41 |
| Phosphate to 5-oxoproline ratio                                                                                                                                                                                                                                                                                                                                                              | −0.0482         | 0.0483 | 0.33 |
| Glucose-to-mannose ratio                                                                                                                                                                                                                                                                                                                                                                     | 0.0264          | 0.0295 | 0.38 |
| Uridine levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0084          | 0.0428 | 0.85 |
| ADP to citrate ratio                                                                                                                                                                                                                                                                                                                                                                         | −0.0906         | 0.0516 | 0.10 |
| Alpha-hydroxyisovalerate levels                                                                                                                                                                                                                                                                                                                                                              | 0.0160          | 0.0329 | 0.63 |
| HVA levels                                                                                                                                                                                                                                                                                                                                                                                   | −0.0485         | 0.0372 | 0.21 |
| N-palmitoyl-sphinganine (d18:0/16:0) levels                                                                                                                                                                                                                                                                                                                                                  | 0.0217          | 0.0443 | 0.63 |
| X-24801 levels                                                                                                                                                                                                                                                                                                                                                                               | −0.0114         | 0.0276 | 0.68 |
| Alanine levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0656          | 0.0384 | 0.10 |
| ADP to valine ratio                                                                                                                                                                                                                                                                                                                                                                          | 0.0077          | 0.0439 | 0.86 |
| Sphingomyelin (d18:1/20:1, d18:2/20:0) levels                                                                                                                                                                                                                                                                                                                                                | −0.0351         | 0.0319 | 0.28 |
| Dihomo-linolenoyl-choline levels                                                                                                                                                                                                                                                                                                                                                             | −0.0383         | 0.0440 | 0.39 |
| 1-(1-enyl-palmitoyl)-2-linoleoyl-GPE (p-16:0/18:2) levels                                                                                                                                                                                                                                                                                                                                    | 0.0016          | 0.0507 | 0.97 |
| N-acetylcitrulline levels                                                                                                                                                                                                                                                                                                                                                                    | −0.0450         | 0.0286 | 0.14 |
| Taurolithocholate 3-sulfate levels                                                                                                                                                                                                                                                                                                                                                           | −0.0318         | 0.0333 | 0.35 |
| Phosphocholine levels                                                                                                                                                                                                                                                                                                                                                                        | 0.0705          | 0.0376 | 0.07 |
| Salicylate to oxalate (ethanedioate) ratio                                                                                                                                                                                                                                                                                                                                                   | −0.0464         | 0.0510 | 0.38 |
| Hypotaurine levels                                                                                                                                                                                                                                                                                                                                                                           | 0.0411          | 0.0392 | 0.30 |
| 2-linoleoylglycerol (18:2) levels                                                                                                                                                                                                                                                                                                                                                            | −0.0721         | 0.0446 | 0.12 |
| X-23680 levels                                                                                                                                                                                                                                                                                                                                                                               | −0.0064         | 0.0334 | 0.85 |
| X-24556 levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0020          | 0.0403 | 0.96 |
| Ceramide (d18:1/17:0, d17:1/18:0) levels                                                                                                                                                                                                                                                                                                                                                     | 0.0833          | 0.0437 | 0.07 |
| Mannose levels                                                                                                                                                                                                                                                                                                                                                                               | −0.0130         | 0.0301 | 0.67 |
| Isovalerylglycine levels                                                                                                                                                                                                                                                                                                                                                                     | −0.0122         | 0.0399 | 0.76 |
| ADP to pantothenate ratio                                                                                                                                                                                                                                                                                                                                                                    | −0.0808         | 0.0517 | 0.14 |
| X-12701 levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0013          | 0.0565 | 0.98 |
| Pyrraline levels                                                                                                                                                                                                                                                                                                                                                                             | 0.0323          | 0.0357 | 0.38 |
| Umbelliferone sulfate levels                                                                                                                                                                                                                                                                                                                                                                 | −0.0458         | 0.0468 | 0.34 |
| C17 levels                                                                                                                                                                                                                                                                                                                                                                                   | −0.0334         | 0.0426 | 0.44 |
| ADP to FAD ratio                                                                                                                                                                                                                                                                                                                                                                             | 0.0026          | 0.0367 | 0.94 |
| 3-CMPFP levels                                                                                                                                                                                                                                                                                                                                                                               | −0.0425         | 0.0632 | 0.51 |
| Arachidate (20:0) levels                                                                                                                                                                                                                                                                                                                                                                     | 0.0698          | 0.0444 | 0.13 |
| X-25271 levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0622          | 0.0541 | 0.27 |
| Serine to alpha-ketobutyrate ratio                                                                                                                                                                                                                                                                                                                                                           | −0.0396         | 0.0497 | 0.44 |
| C8-DC levels                                                                                                                                                                                                                                                                                                                                                                                 | −0.0040         | 0.0514 | 0.94 |
| X-23648 levels                                                                                                                                                                                                                                                                                                                                                                               | 0.0450          | 0.0452 | 0.33 |
| Carnitine C14 levels                                                                                                                                                                                                                                                                                                                                                                         | 0.0673          | 0.0531 | 0.22 |
| Histidine to phosphate ratio                                                                                                                                                                                                                                                                                                                                                                 | 0.0288          | 0.0406 | 0.48 |
| 17:1n7, 10-heptadecenoate; 3-CMPFP, 3-carboxy-4-methyl-5-pentyl-2-furanpropionate; ADP, adenosine 5'-diphosphate; AMP, adenosine 5'-monophosphate; C17, margaroylcarnitine; C20:2, dihomol-linoleoylcarnitine; C20:3n3 or 6, dihomol-linolenoyl carnitine; C8-DC, suberate; EDTA, ethylenediaminetetraacetic acid; FAD, flavin adenine dinucleotide; HVA, homovanillate; SE, standard error. |                 |        |      |