

# Supplementary Materials for

## **Serum Metabolomics Study to Screen Potential Biomarkers of Lung Cancer Risk in High Natural Background Radiation Areas of Thailand: A Pilot Study**

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**Supplementary Table S1.** Key metabolites for comparing the LC and **the** low-radon groups (VIP >1, FC > 1 or < 0.5 and  $P < 0.05$  ).

| Metabolites   | VIP  | FC     | <i>P</i> value        | Type |
|---|------|--------|-----------------------|------|
| 1. Triethyl phosphate   | 2.71 | 3.87   | $2.6 \times 10^{-37}$ | up   |
| 2. 2-Methylnaphthalene  | 2.55 | 2.93   | $4.2 \times 10^{-28}$ | up   |
| 3. 2,3-Octadiene-5,7-diyn-1-ol  | 2.51 | 2.53   | $1.9 \times 10^{-26}$ | up   |
| 4. 2-[(5E,8E)-5,8-Tetradecadien-1-yl]cyclobutanone  | 2.32 | 2.04   | $3.1 \times 10^{-20}$ | up   |
| 5. UNII:6S7S02945H  | 2.25 | 1.64   | $2.6 \times 10^{-18}$ | up   |
| 6. (-)-Lupinine   | 2.15 | 1.60   | $3.1 \times 10^{-16}$ | up   |
| 7. Estrane  | 2.10 | 1.58   | $1.1 \times 10^{-14}$ | up   |
| 8. Oleamide   | 2.02 | 1.46   | $9.9 \times 10^{-14}$ | up   |
| 9. (2,7-Dimethyloctahydro-1H-cyclopenta[c]pyridin-4-yl)methanol                                   | 1.99 | 1.52   | $3.6 \times 10^{-13}$ | up   |
| 10. 2-[(5Z)-5-tetradecenyl]cyclobutanone  | 1.97 | 1.47   | $5.9 \times 10^{-13}$ | up   |
| 11. PEG Monolaurate n6  | 1.96 | 1.34   | $8.7 \times 10^{-13}$ | up   |
| 12. Hexylbenzene  | 1.96 | 1.60   | $8.9 \times 10^{-13}$ | up   |
| 13. 4-[(1S)-1-Cyclohexyl-2-(2-piperidiny)ethyl]cyclohexanol                                       | 1.86 | 3.00   | $2.9 \times 10^{-11}$ | up   |
| 14. (2E,4Z)-N-Isobutyl-2,4-octadecadienamide  | 1.85 | 1.80   | $3.9 \times 10^{-11}$ | up   |
| 15. NP-021018   | 1.75 | 13.4   | $7.5 \times 10^{-10}$ | up   |
| 16. Hydrocortisone succinate  | 1.60 | 27.9   | $3.1 \times 10^{-8}$  | up   |
| 17. 2-(4-Methylthiazol-5-yl)ethyl butyrate  | 1.59 | 633.5  | $3.9 \times 10^{-8}$  | up   |
| 18. UROBILIN, (-)-  | 1.59 | 5.89   | $4.6 \times 10^{-8}$  | up   |
| 19. Furfural  | 1.51 | 1.72   | $2.3 \times 10^{-7}$  | up   |
| 20. N-Acetyl-L-Citrulline   | 1.44 | 2.22   | $1.0 \times 10^{-6}$  | up   |
| 21. (4S)-4-[(2E)-2-Octenoyloxy]-4-(trimethylammonio)butanoate                                     | 1.40 | 2.85   | $2.0 \times 10^{-6}$  | up   |
| 22. N1-(2-Cyanoethyl)-N1-(3-pyridylmethyl)-4-methyl-1-benzenesulfonamide                          | 1.39 | 47.7   | $2.9 \times 10^{-6}$  | up   |
| 23. Sorbitan, monododecanoate   | 1.35 | 60.7   | $5.4 \times 10^{-6}$  | up   |
| 24. 2-(Propylthio)nicotinic acid  | 1.35 | 1050   | $5.8 \times 10^{-6}$  | up   |
| 25. Tetradecanedioic acid   | 1.33 | 141.5  | $7.6 \times 10^{-6}$  | up   |
| 26. Anhydroecgonine   | 1.33 | 90.0   | $8.8 \times 10^{-6}$  | up   |
| 27. 5-Hydroxyomeprazole   | 1.32 | 253.8  | $9.7 \times 10^{-6}$  | up   |
| 28. 4-[(Z)-[(4E,7Z,16Z,19Z)-1-Hydroxy-4,7,10,13,16,19-docosaheptaen-1-ylidene]amino]butanoic acid | 1.32 | 3.47   | $1.0 \times 10^{-5}$  | up   |
| 29. ISOFENPHOS  | 1.32 | 2739.2 | $1.0 \times 10^{-5}$  | up   |
| 30. Stearidonic acid  | 1.26 | 3.83   | $2.4 \times 10^{-5}$  | up   |
| 31. Chlordiazepoxide  | 1.26 | 1.37   | $2.4 \times 10^{-5}$  | up   |
| 32. 1-(4-methoxyphenyl)-2-(propylthio)-1,4-dihydropyrido[2,3-d]pyrimidin-4-one                    | 1.26 | 82.2   | $2.5 \times 10^{-5}$  | up   |
| 33. (2E)-decenoic acid  | 1.25 | 4.92   | $3.1 \times 10^{-5}$  | up   |
| 34. 2-[(3S)-1-(1,3-Benzodioxol-5-ylmethyl)-3-pyrrolidinyl]-5-(2-methoxyphenyl)-1,3,4-oxadiazole   | 1.22 | 257.6  | $4.8 \times 10^{-5}$  | up   |

|  |      |       |                       |      |
|--|------|-------|-----------------------|------|
| 35. 3-Methylglutaryl carnitine   | 1.21 | 2.7   | 5.2×10 <sup>-5</sup>  | up   |
| 36. DB2700000  | 1.20 | 20.6  | 6.1×10 <sup>-5</sup>  | up   |
| 37. Nicotinuric acid   | 1.21 | 1.80  | 6.3×10 <sup>-5</sup>  | up   |
| 38. O-Ethyl (4-hydroxyphenyl)carbamothioate  | 1.20 | 10.68 | 7.6×10 <sup>-5</sup>  | up   |
| 39. (6S)-2,6-Anhydro-6-[(1S)-2-isopropyl-5-methylcyclohexyl]-L-gulonic acid  | 1.18 | 37.6  | 9.5×10 <sup>-5</sup>  | up   |
| 40. 7-O-geranyl-2-O,3-dimethylflavolin   | 1.16 | 16.3  | 1.1×10 <sup>-4</sup>  | up   |
| 41. RH0365500  | 1.16 | 2.48  | 1.1×10 <sup>-4</sup>  | up   |
| 42. 2-methyl-4-ethyl-5-propyloxazole   | 1.12 | 93.5  | 2.2×10 <sup>-4</sup>  | up   |
| 43. 3-amino-2-phenyl-2H-pyrazolo[4,3-c]pyridine-4,6-diol   | 1.12 | 2.09  | 2.3×10 <sup>-4</sup>  | up   |
| 44. Omeprazole   | 1.11 | 56.7  | 2.5×10 <sup>-4</sup>  | up   |
| 45. Idanpramine  | 1.10 | 40.0  | 2.8×10 <sup>-4</sup>  | up   |
| 46. Pantothenate   | 1.08 | 2.12  | 3.7×10 <sup>-4</sup>  | up   |
| 47. Pirenzepine  | 1.08 | 45.5  | 3.9×10 <sup>-4</sup>  | up   |
| 48. N-Pentacosanoylglycine   | 1.06 | 1.23  | 4.8×10 <sup>-4</sup>  | up   |
| 49. (2-[(1S,4S)-4-{3,5-Dimethyl-1-[4-(2-methyl-2-propanyl)phenyl]-1H-pyrazol-4-yl}-2-cyclopenten-1-yl]amino)-2-oxoethoxy)acetic acid   | 1.06 | 952.7 | 4.9×10 <sup>-4</sup>  | up   |
| 50. cyclandelate   | 1.06 | 1.24  | 5.1×10 <sup>-4</sup>  | up   |
| 51. 4-Methoxychalcone  | 1.05 | 62.6  | 5.7×10 <sup>-3</sup>  | up   |
| 52. 12a-Hydroxy-3-oxo-4,6-choladien-24-oic acid  | 1.04 | 1.55  | 6.8×10 <sup>-4</sup>  | up   |
| 53. 3-[2-[(E)-[3-(2-carboxyethyl)-5-[(4-ethyl-3-methyl-5-oxo-pyrrolidin-2-yl)methyl]-4-methyl-pyrrol-2-ylidene]methyl]-5-[(3-ethyl-4-methyl-5-oxo-pyrrolidin-2-yl)methyl]-4-methyl-1H-pyrrol-3-yl]propanoic acid | 1.02 | 18.35 | 8.4×10 <sup>-4</sup>  | up   |
| 54. Canrenone  | 1.01 | 11.87 | 9.0×10 <sup>-4</sup>  | up   |
| 55. D-Sphingosine  | 2.94 | 0.01  | 8.9×10 <sup>-95</sup> | down |
| 56. Benzylideneacetone   | 2.75 | 0.15  | 2.7×10 <sup>-41</sup> | down |
| 57. Hippuric acid  | 2.64 | 0.01  | 7.6×10 <sup>-33</sup> | down |
| 58. Cyprodenate  | 2.53 | 0.39  | 1.5×10 <sup>-27</sup> | down |
| 59. Gabapentin   | 2.42 | 0.15  | 3.5×10 <sup>-23</sup> | down |
| 60. L-Aspartylphenylalanine  | 2.37 | 0.13  | 1.2×10 <sup>-21</sup> | down |
| 61. Aspartame  | 2.27 | 0.30  | 7.5×10 <sup>-19</sup> | down |
| 62. 2GKY1ALK5L   | 2.03 | 0.45  | 6.4×10 <sup>-14</sup> | down |
| 63. 2-Aminoheptanoic acid  | 1.96 | 0.40  | 9.4×10 <sup>-13</sup> | down |
| 64. 8-Azabicyclo[3.2.1]octane-3,6-diol   | 1.92 | 0.18  | 4.2×10 <sup>-12</sup> | down |
| 65. Propamocarb  | 1.88 | 0.11  | 1.2×10 <sup>-11</sup> | down |
| 66. L-Glu-Gly  | 1.73 | 0.37  | 1.2×10 <sup>-9</sup>  | down |
| 67. 4-[(2R)-2-(Aminomethyl)-2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]-3-(3-pentanylamino)benzoic acid  | 1.68 | 0.27  | 4.4×10 <sup>-9</sup>  | down |
| 68. Paraxanthine   | 1.67 | 0.46  | 6.3×10 <sup>-9</sup>  | down |
| 69. MFCD00020424   | 1.64 | 0.35  | 1.2×10 <sup>-8</sup>  | down |
| 70. N-Methylhexanamide   | 1.64 | 0.27  | 1.2×10 <sup>-8</sup>  | down |
| 71. Cinnamoylglycine   | 1.55 | 0.18  | 9.8×10 <sup>-8</sup>  | down |
| 72. (2E)-2-Cyano-N-(ethylcarbamoyl)-2-(methoxyimino)acetamide  | 1.54 | 0.19  | 1.2×10 <sup>-7</sup>  | down |
| 73. 6-[(1Z)-1-Propen-1-yl]-2,3,4,5-tetrahydropyridine  | 1.54 | 0.39  | 1.3×10 <sup>-7</sup>  | down |
| 74. 2-HYDROXYHIPPURIC ACID   | 1.54 | 0.1   | 1.4×10 <sup>-7</sup>  | down |

|   |      |      |                      |      |
|---|------|------|----------------------|------|
| 75. ??-Oxo-3-pyridinebutanal                                      | 1.54 | 0.15 | $1.4 \times 10^{-7}$ | down |
| 76. 4-(allyloxy)-1,2-dihydroquinolin-2-one                        | 1.51 | 0.24 | $2.4 \times 10^{-7}$ | down |
| 77. 3-Methylxanthine  | 1.50 | 0.44 | $3.3 \times 10^{-7}$ | down |
| 78. Pregabalin  | 1.47 | 0.48 | $5.5 \times 10^{-7}$ | down |
| 79. 2,4-Quinolinediol   | 1.46 | 0.18 | $6.5 \times 10^{-7}$ | down |
| 80. Pivagabine  | 1.45 | 0.40 | $8.5 \times 10^{-7}$ | down |
| 81. 1,7-Dimethyluric acid   | 1.44 | 0.19 | $1.1 \times 10^{-6}$ | down |
| 82. 2-Hydroxyquinoline  | 1.44 | 0.15 | $1.1 \times 10^{-6}$ | down |
| 83. Piperidione   | 1.42 | 0.42 | $1.5 \times 10^{-6}$ | down |
| 84. 2-Propionylthiazole   | 1.40 | 0.07 | $2.6 \times 10^{-6}$ | down |
| 85. 3-Methyloxindole  | 1.36 | 0.16 | $4.5 \times 10^{-6}$ | down |
| 86. 1-Methyl-4-[(8E)-10-methyl-6-methylene-8-undecen-2-yl]benzene | 1.36 | 0.30 | $4.6 \times 10^{-6}$ | down |
| 87. Ruspolinone   | 1.28 | 0.04 | $1.8 \times 10^{-5}$ | down |
| 88. AG6542800   | 1.11 | 0.09 | $2.5 \times 10^{-4}$ | down |
| 89. MDMA Methylene homolog  | 1.02 | 0.36 | $8.0 \times 10^{-4}$ | down |
| 90. 1-Isopropenyl-3-isopropylbenzene                              | 1.00 | 0.43 | $1.0 \times 10^{-3}$ | down |

**Supplementary Table S2.** Key metabolites for comparing the LC and **the** high radon groups (VIP >1, FC > 1 or < 0.5 and  $P < 0.05$  ).

| Metabolites  | VIP  | FC    | <i>P</i> value        | Type |
|--|------|-------|-----------------------|------|
| 1. UNII:6S7S02945H   | 2.06 | 1.52  | $8.0 \times 10^{-15}$ | up   |
| 2. MFCD00004231  | 2.06 | 22.7  | $1.0 \times 10^{-14}$ | up   |
| 3. (-)-Lupinine  | 2.04 | 1.57  | $1.9 \times 10^{-14}$ | up   |
| 4. Metaxyl   | 1.95 | 4.15  | $6.3 \times 10^{-13}$ | up   |
| 5. NP-021018   | 1.95 | 17.5  | $7.8 \times 10^{-13}$ | up   |
| 6. Oleamide  | 1.95 | 1.42  | $8.5 \times 10^{-13}$ | up   |
| 7. Estrane   | 1.94 | 1.48  | $1.1 \times 10^{-12}$ | up   |
| 8. 2-[(5E,8E)-5,8-Tetradecadien-1-yl]cyclobutanone   | 1.93 | 1.77  | $1.4 \times 10^{-12}$ | up   |
| 9. 4-Methoxysalicylic acid   | 1.91 | 18.8  | $3.4 \times 10^{-12}$ | up   |
| 10. (2,7-Dimethyloctahydro-1H-cyclopenta[c]pyridin-4-yl)methanol   | 1.87 | 1.49  | $1.1 \times 10^{-11}$ | up   |
| 11. pseudouridine  | 1.87 | 1.52  | $1.2 \times 10^{-11}$ | up   |
| 12. 2-[(5Z)-5-tetradecenyl]cyclobutanone   | 1.86 | 1.44  | $1.6 \times 10^{-11}$ | up   |
| 13. Betaine  | 1.85 | 1.49  | $2.7 \times 10^{-11}$ | up   |
| 14. cyclandelate   | 1.83 | 1.61  | $4.5 \times 10^{-11}$ | up   |
| 15. Hexylbenzene   | 1.80 | 1.53  | $1.3 \times 10^{-10}$ | up   |
| 16. N-Phenylacetylglutamine  | 1.74 | 2.80  | $7.3 \times 10^{-10}$ | up   |
| 17. 4-[(1S)-1-Cyclohexyl-2-(2-piperidiny)ethyl]cyclohexanol  | 1.72 | 3.02  | $1.3 \times 10^{-9}$  | up   |
| 18. (4S)-4-[(2E)-2-Octenoyloxy]-4-(trimethylammonio)butanoate  | 1.67 | 3.67  | $4.5 \times 10^{-9}$  | up   |
| 19. Guvacoline   | 1.67 | 1.97  | $4.8 \times 10^{-9}$  | up   |
| 20. 3-amino-2-phenyl-2H-pyrazolo[4,3-c]pyridine-4,6-diol   | 1.65 | 2.92  | $6.4 \times 10^{-9}$  | up   |
| 21. 2-Hydroxy-4,5',8a'-trimethyl-1'-oxo-4-vinyloctahydro-1'H-spiro[cyclopentane-1,2'-naphthalene]-5'-carboxylic acid | 1.64 | 1.68  | $9.7 \times 10^{-9}$  | up   |
| 22. Decanamide   | 1.62 | 1.36  | $1.6 \times 10^{-8}$  | up   |
| 23. 4-[(Z)-[(4E,7Z,16Z,19Z)-1-Hydroxy-4,7,10,13,16,19-docosahexaen-1-ylidene]amino]butanoic acid                     | 1.59 | 6.95  | $3.2 \times 10^{-8}$  | up   |
| 24. 2-(4-Methylthiazol-5-yl)ethyl butyrate   | 1.59 | 647.9 | $3.3 \times 10^{-8}$  | up   |
| 25. (2E,4Z)-N-Isobutyl-2,4-octadecadienamide   | 1.56 | 1.63  | $6.5 \times 10^{-8}$  | up   |
| 26. Stearidonic acid   | 1.51 | 4.93  | $1.9 \times 10^{-7}$  | up   |
| 27. 3-Methylglutaryl carnitine   | 1.51 | 4.66  | $2.0 \times 10^{-7}$  | up   |
| 28. 5-Methylangelicin  | 1.51 | 19.9  | $2.1 \times 10^{-7}$  | up   |
| 29. Piperine   | 1.50 | 15.8  | $2.3 \times 10^{-7}$  | up   |
| 30. RH0365500  | 1.49 | 3.09  | $3.2 \times 10^{-7}$  | up   |
| 31. (2E)-decenoic acid   | 1.48 | 7.13  | $3.4 \times 10^{-7}$  | up   |
| 32. 2-[2-[5-(Ethoxycarbonyl)-2-morpholinoanilino]-2-oxoethoxy]acetic acid  | 1.48 | 1.53  | $3.8 \times 10^{-7}$  | up   |
| 33. O-Ethyl (4-hydroxyphenyl)carbamothioate  | 1.47 | 20.4  | $4.9 \times 10^{-7}$  | up   |

|  |      |        |                      |    |
|--|------|--------|----------------------|----|
| 34. N-Acetylvaline   | 1.45 | 2.64   | 6.6×10 <sup>-7</sup> | up |
| 35. LU3453000  | 1.45 | 1.49   | 7.4×10 <sup>-7</sup> | up |
| 36. Hydrocortisone succinate   | 1.43 | 23.2   | 9.7×10 <sup>-7</sup> | up |
| 37. N1-(2-Cyanoethyl)-N1-(3-pyridylmethyl)-4-methyl-1-benzenesulfonamide   | 1.43 | 51.7   | 1.1×10 <sup>-6</sup> | up |
| 38. Prolylleucine  | 1.42 | 1.72   | 1.4×10 <sup>-6</sup> | up |
| 39. 5-Hydroxyomeprazole  | 1.40 | 305.5  | 1.8×10 <sup>-6</sup> | up |
| 40. N-Undecanoylglycine  | 1.40 | 1.28   | 1.8×10 <sup>-6</sup> | up |
| 41. UROBILIN, (-)-   | 1.39 | 6.03   | 2.1×10 <sup>-6</sup> | up |
| 42. 1-Dodecyl-2-pyrrolidinone  | 1.38 | 1.14   | 2.5×10 <sup>-6</sup> | up |
| 43. N-(tert-Butoxycarbonyl)-L-leucine  | 1.35 | 1.50   | 4.9×10 <sup>-6</sup> | up |
| 44. 2-(Propylthio)nicotinic acid   | 1.34 | 1063.9 | 5.4×10 <sup>-6</sup> | up |
| 45. Tetradecanedioic acid  | 1.34 | 142.7  | 5.7×10 <sup>-6</sup> | up |
| 46. Anhydroecgonine  | 1.34 | 94.1   | 5.8×10 <sup>-6</sup> | up |
| 47. MFCD11045309   | 1.34 | 1.43   | 5.9×10 <sup>-6</sup> | up |
| 48. Acetyl-L-carnitine   | 1.34 | 1.69   | 6.0×10 <sup>-6</sup> | up |
| 49. 1-(4-methoxyphenyl)-2-(propylthio)-1,4-dihydropyrido[2,3-d]pyrimidin-4-one   | 1.33 | 92.7   | 7.0×10 <sup>-6</sup> | up |
| 50. Normorphine  | 1.33 | 69.8   | 7.2×10 <sup>-6</sup> | up |
| 51. Pantothenate   | 1.32 | 2.54   | 7.5×10 <sup>-6</sup> | up |
| 52. ISOFENPHOS   | 1.31 | 2788.6 | 9.1×10 <sup>-6</sup> | up |
| 53. NSC 92778  | 1.30 | 2.63   | 1.1×10 <sup>-5</sup> | up |
| 54. 5-methylthioribose   | 1.30 | 1.41   | 1.3×10 <sup>-5</sup> | up |
| 55. Theobromine  | 1.29 | 1.01   | 1.3×10 <sup>-5</sup> | up |
| 56. promacyl   | 1.26 | 1.27   | 2.1×10 <sup>-5</sup> | up |
| 57. carbapenem MM22383   | 1.26 | 9.80   | 2.3×10 <sup>-5</sup> | up |
| 58. 5-(N,N-Dimethylcarbamimidamido)-2-oxopentanoic acid  | 1.25 | 3.36   | 2.9×10 <sup>-5</sup> | up |
| 59. 6-Methyl[1,2,4]triazolo[4,3-b]pyridazin-8-ol   | 1.24 | 1.57   | 3.2×10 <sup>-5</sup> | up |
| 60. Shogaol  | 1.24 | 1.36   | 3.4×10 <sup>-5</sup> | up |
| 61. nalorphine   | 1.23 | 18.1   | 4.0×10 <sup>-5</sup> | up |
| 62. Sorbitan, monododecanoate  | 1.20 | 51.6   | 6.0×10 <sup>-5</sup> | up |
| 63. L-Glutamine  | 1.19 | 1.20   | 6.9×10 <sup>-5</sup> | up |
| 64. fenoxycarb   | 1.19 | 68.3   | 7.1×10 <sup>-5</sup> | up |
| 65. Hexadecanamide   | 1.16 | 1.28   | 1.0×10 <sup>-4</sup> | up |
| 66. Nornorcapsaicin  | 1.14 | 26.0   | 1.4×10 <sup>-4</sup> | up |
| 67. methyl 3,4,5-trihydroxycyclohex-1-ene-1-carboxylate  | 1.14 | 4.63   | 1.4×10 <sup>-4</sup> | up |
| 68. 3-Methyl-9H-carbazol-1-ol  | 1.14 | 19.8   | 1.5×10 <sup>-4</sup> | up |
| 69. 3-[2-[(E)-[3-(2-carboxyethyl)-5-[(4-ethyl-3-methyl-5-oxo-pyrrolidin-2-yl)methyl]-4-methyl-pyrrol-2-ylidene)methyl]-5-[(3-ethyl-4-methyl-5-oxo-pyrrolidin-2-yl)methyl]-4-methyl-1H-pyrrol-3-yl]propanoic acid | 1.12 | 12.4   | 1.8×10 <sup>-4</sup> | up |
| 70. 1-Hexadecanoylpyrrolidine  | 1.12 | 1.23   | 1.8×10 <sup>-4</sup> | up |
| 71. (E)-doxepin  | 1.12 | 1.26   | 2.0×10 <sup>-4</sup> | up |
| 72. Pirenzepine  | 1.11 | 47.1   | 2.2×10 <sup>-4</sup> | up |
| 73. 2-[(3S)-1-(1,3-Benzodioxol-5-ylmethyl)-3-pyrrolidinyl]-5-(2-methoxyphenyl)-1,3,4-oxadiazole  | 1.10 | 227.0  | 2.3×10 <sup>-4</sup> | up |

|   |      |       |                       |      |
|---|------|-------|-----------------------|------|
| 74. (6S)-2,6-Anhydro-6-[(1S)-2-isopropyl-5-methylcyclohexyl]-L-gulonic acid                         | 1.10 | 34.8  | 2.4×10 <sup>-4</sup>  | up   |
| 75. 7-O-geranyl-2-O,3-dimethylflaviolin   | 1.10 | 15.4  | 2.8×10 <sup>-4</sup>  | up   |
| 76. DL-Stachydrine  | 1.08 | 2.81  | 3.2×10 <sup>-4</sup>  | up   |
| 77. DL-Carnitine  | 1.08 | 1.60  | 3.4×10 <sup>-4</sup>  | up   |
| 78. Propionylcarnitine  | 1.07 | 1.43  | 4.0×10 <sup>-4</sup>  | up   |
| 79. 3-oxolauric acid  | 1.05 | 33.5  | 5.4×10 <sup>-4</sup>  | up   |
| 80. Epitestosterone   | 1.04 | 1.87  | 5.9×10 <sup>-4</sup>  | up   |
| 81. L-Pyroglutamic acid   | 1.04 | 1.16  | 6.0×10 <sup>-4</sup>  | up   |
| 82. 3,6-Anhydro-1-O-stearoylhexitol   | 1.03 | 26.7  | 6.5×10 <sup>-4</sup>  | up   |
| 83. Omeprazole  | 1.03 | 49.5  | 6.9×10 <sup>-4</sup>  | up   |
| 84. 2-methyl-4-ethyl-5-propyloxazole  | 1.02 | 79.4  | 7.7×10 <sup>-4</sup>  | up   |
| 85. O-Desmethyl-cis-tramadol  | 1.02 | 530.0 | 8.0×10 <sup>-4</sup>  | up   |
| 86. Codeine   | 1.01 | 129.2 | 8.4×10 <sup>-4</sup>  | up   |
| 87. Idanpramine   | 1.00 | 36.2  | 8.8×10 <sup>-4</sup>  | up   |
| 88. 5-Pentyl-2(5H)-furanone   | 1.00 | 12.4  | 9.2×10 <sup>-4</sup>  | up   |
| 89. N,O-DIDESMETHYLVENLAFAXINE-GLUCURONIDE  | 1.00 | 538.6 | 9.7×10 <sup>-4</sup>  | up   |
| 90. D-Sphingosine   | 2.45 | 0.04  | 1.0×10 <sup>-24</sup> | down |
| 91. Hippuric acid   | 2.38 | 0.05  | 2.8×10 <sup>-22</sup> | down |
| 92. 1-Methyl-4-[(8E)-10-methyl-6-methylene-8-undecen-2-yl]benzene                                   | 1.78 | 0.06  | 2.0×10 <sup>-10</sup> | down |
| 93. Propamocarb   | 1.64 | 0.08  | 7.9×10 <sup>-9</sup>  | down |
| 94. Aspartame   | 2.13 | 0.11  | 5.3×10 <sup>-16</sup> | down |
| 95. 13,14-Dihydroretinol  | 1.67 | 0.12  | 6.3×10 <sup>-9</sup>  | down |
| 96. L-Aspartylphenylalanine   | 2.30 | 0.12  | 3.4×10 <sup>-20</sup> | down |
| 97. 1-Isopropenyl-3-isopropylbenzene  | 1.13 | 0.13  | 1.7×10 <sup>-4</sup>  | down |
| 98. 8-Azabicyclo[3.2.1]octane-3,6-diol  | 1.63 | 0.14  | 1.2×10 <sup>-8</sup>  | down |
| 99. 4-[(2R)-2-(Aminomethyl)-2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]-3-(3-pentanylamino)benzoic acid | 1.40 | 0.31  | 1.9×10 <sup>-6</sup>  | down |
| 100. 2GKY1ALK5L   | 1.80 | 0.32  | 1.0×10 <sup>-10</sup> | down |
| 101. N-Methylhexanamide   | 1.27 | 0.33  | 2.0×10 <sup>-5</sup>  | down |
| 102. MFCD00020424   | 1.61 | 0.35  | 2.1×10 <sup>-8</sup>  | down |
| 103. 2-Aminoheptanoic acid  | 1.55 | 0.36  | 8.3×10 <sup>-8</sup>  | down |
| 104. threonylphenylalanine  | 1.08 | 0.40  | 3.4×10 <sup>-4</sup>  | down |
| 105. Gabapentin   | 1.65 | 0.42  | 6.4×10 <sup>-9</sup>  | down |
| 106. 1-[(9Z)-hexadecenoyl]-sn-glycero-3-phosphocholine  | 2.02 | 0.45  | 5.3×10 <sup>-14</sup> | down |
| 107. L-alpha-lysophosphatidylcholine  | 1.95 | 0.45  | 7.7×10 <sup>-13</sup> | down |
| 108. Benzylideneacetone   | 1.12 | 0.46  | 1.9×10 <sup>-4</sup>  | down |
| 109. (2R)-3-[(2-Aminoethoxy)(hydroxy)phosphoryl]oxy-2-hydroxypropyl (9Z)-9-hexadecenoate            | 1.54 | 0.47  | 8.9×10 <sup>-8</sup>  | down |
| 110. DMU  | 1.51 | 0.48  | 1.8×10 <sup>-7</sup>  | down |
| 111. 1-[(8Z,11Z,14Z)-icosatrienoyl]-sn-glycero-3-phosphocholine                                     | 1.68 | 0.49  | 2.9×10 <sup>-9</sup>  | down |

**Supplementary Table S3.** The top 25 metabolic pathways distinguishing the LC and the low-radon groups.

| Pathways  | Total | Hits | Hits compound | <i>P</i> value |
|---|-------|------|---------------|----------------|
| 1. SARS-CoV-2 and COVID-19 pathway                                  | 5     | 1    | D-Sphingosine | 0.006          |
| 2. GDNF signaling   | 7     | 1    | D-Sphingosine | 0.008          |
| 3. Conjugation of benzoate with glycine                             | 8     | 1    | Hippuric acid | 0.009          |
| 4. Pirenzepine Action Pathway                                       | 10    | 1    | Pirenzepine   | 0.012          |
| 5. Amino acid conjugation of benzoic acid                           | 10    | 1    | Hippuric acid | 0.012          |
| 6. Modulation of PI3K-Akt-mTOR signaling by bioactive sphingolipids | 10    | 1    | D-Sphingosine | 0.012          |
| 7. VEGFR2 mediated cell proliferation                               | 11    | 1    | D-Sphingosine | 0.013          |
| 8. Sphingolipid metabolism in senescence                            | 14    | 1    | D-Sphingosine | 0.016          |
| 9. Degradation pathway of sphingolipids, including diseases         | 14    | 1    | D-Sphingosine | 0.016          |
| 10. Amino Acid conjugation  | 16    | 1    | Hippuric acid | 0.019          |
| 11. Conjugation of carboxylic acids                                 | 16    | 1    | Hippuric acid | 0.019          |
| 12. Phenylalanine metabolism  | 20    | 1    | Aspartame     | 0.023          |
| 13. Glucose homeostasis   | 21    | 1    | Hippuric acid | 0.024          |
| 14. Synthesis of ceramides and 1-deoxyceramides                     | 23    | 1    | D-Sphingosine | 0.027          |
| 15. Sphingolipid pathway  | 24    | 1    | D-Sphingosine | 0.028          |
| 16. Extra-nuclear estrogen signaling                                | 27    | 1    | D-Sphingosine | 0.031          |
| 17. Sphingolipid metabolism overview                                | 27    | 1    | D-Sphingosine | 0.031          |
| 18. Signaling by VEGF   | 28    | 1    | D-Sphingosine | 0.032          |
| 19. VEGFA-VEGFR2 Pathway  | 28    | 1    | D-Sphingosine | 0.032          |
| 20. 10q11.21q11.23 copy number variation syndrome                   | 30    | 1    | D-Sphingosine | 0.035          |
| 21. ESR-mediated signaling  | 33    | 1    | D-Sphingosine | 0.038          |
| 22. Metabolism of sphingolipids in ER and Golgi apparatus           | 34    | 1    | D-Sphingosine | 0.039          |
| 23. Glycosphingolipid metabolism                                    | 35    | 1    | D-Sphingosine | 0.040          |
| 24. Fabry disease   | 35    | 1    | D-Sphingosine | 0.040          |
| 25. Gaucher Disease   | 35    | 1    | D-Sphingosine | 0.040          |



**Supplementary Table S4.** The top 25 metabolic pathways distinguishing the LC and the high radon groups.

| Pathways  | Total | Hits | Hits compound   | P value              |
|---|-------|------|---|----------------------|
| 1. Amino Acid conjugation   | 16    | 2    | N-Phenylacetylglutamine, Hippuric acid                      | 4.6×10 <sup>-4</sup> |
| 2. Conjugation of carboxylic acids                                  | 16    | 2    | N-Phenylacetylglutamine, Hippuric acid                      | 4.6×10 <sup>-4</sup> |
| 3. SARS-CoV-2 and COVID-19 pathway                                  | 5     | 1    | D-Sphingosine   | 0.011                |
| 4. GDNF signaling   | 7     | 1    | D-Sphingosine   | 0.015                |
| 5. Conjugation of benzoate with glycine                             | 8     | 1    | Hippuric acid   | 0.017                |
| 6. Conjugation of phenylacetate with glutamine                      | 9     | 1    | N-Phenylacetylglutamine                                     | 0.019                |
| 7. Pirenzepine Action Pathway                                       | 10    | 1    | Pirenzepine   | 0.021                |
| 8. Amino acid conjugation of benzoic acid                           | 10    | 1    | Hippuric acid   | 0.021                |
| 9. Modulation of PI3K-Akt-mTOR signaling by bioactive sphingolipids | 10    | 1    | D-Sphingosine   | 0.021                |
| 10. VEGFR2 mediated cell proliferation                              | 11    | 1    | D-Sphingosine   | 0.023                |
| 11. Biological oxidations   | 317   | 3    | 5-Hydroxyomeprazole, N-Phenylacetylglutamine, Hippuric acid | 0.024                |
| 12. Omeprazole Action Pathway                                       | 12    | 1    | 5-Hydroxyomeprazole   | 0.025                |
| 13. Cocaine metabolism  | 13    | 1    | Anhydroecgonine   | 0.027                |
| 14. Sphingolipid metabolism in senescence                           | 14    | 1    | D-Sphingosine   | 0.029                |
| 15. Degradation pathway of sphingolipids, including diseases        | 14    | 1    | D-Sphingosine   | 0.029                |
| 16. Phase II - Conjugation of compounds                             | 146   | 2    | N-Phenylacetylglutamine, Hippuric acid                      | 0.036                |
| 17. Phenylalanine metabolism  | 20    | 1    | Aspartame   | 0.041                |
| 18. Glucose homeostasis   | 21    | 1    | Hippuric acid   | 0.043                |
| 19. Synthesis of ceramides and 1-deoxyceramides                     | 23    | 1    | D-Sphingosine   | 0.047                |
| 20. Sphingolipid pathway  | 24    | 1    | D-Sphingosine   | 0.049                |
| 21. Extra-nuclear estrogen signaling                                | 27    | 1    | D-Sphingosine   | 0.049                |
| 22. Sphingolipid metabolism overview                                | 27    | 1    | D-Sphingosine   | 0.049                |

|   |    |   |                         |       |
|---|----|---|-------------------------|-------|
| 23. Phenylalanine and Tyrosine Metabolism | 28 | 1 | N-Phenylacetylglutamine | 0.049 |
| 24. Signaling by VEGF                     | 28 | 1 | D-Sphingosine           | 0.049 |
| 25. VEGFA-VEGFR2 Pathway                  | 28 | 1 | D-Sphingosine           | 0.049 |

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