**Supplementary Information**

**Manuscript title: Acyl ethanolamides in Diabetes and Diabetic Nephropathy: Novel targets from untargeted plasma metabolomic profiles of South Asian Indian men**

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**Supplementary Table 1**: The 16 metabolites significantly dysregulated between NGT and T2D, T2D and T2D-DN as well as NGT and T2D-DN (FDR adjusted $p$-value <0.05)]. (NGT: normal glucose tolerance, T2D: type 2 diabetes mellitus, T2D-DN: type 2 diabetes mellitus-diabetic nephropathy)

| Metabolite | Ratio T2D/NGT | Ratio T2D-DN/NGT | Ratio T2D-DN/T2D | Adjusted $p$-value T2D/NGT | Adjusted $p$-value T2D-DN/NGT | Adjusted $p$-value T2D-DN/T2D |
|---|---|---|---|---|---|---|
| (betaS)-beta-Hydroxy-L-tryptophan | 3.4 | 4.9 | 1.4 | 0.013 | <0.001 | 0.011 |
| (R)-3-hydroxybutyrylcarnitine | 1.5 | 2.0 | 1.3 | 0.001 | <0.001 | 0.008 |
| 2-Amino-9,10-epoxy-8-oxodecanoic acid | 1.4 | 1.9 | 1.3 | 0.015 | <0.001 | 0.046 |
| 6-Oxo-2-piperidinecarboxylic acid | 1.5 | 2.3 | 1.5 | 0.001 | <0.001 | <0.001 |
| Anagestone Acetate | 1.4 | 2.1 | 1.5 | 0.029 | <0.001 | 0.005 |
| Apronalide | 1.4 | 2.8 | 2.0 | 0.032 | <0.001 | <0.001 |
| Cholecalciferol | 0.7 | 0.5 | 0.8 | 0.006 | <0.001 | 0.043 |
| Diosgenin | 0.8 | 0.6 | 0.7 | 0.028 | <0.001 | 0.022 |
| DL-Dipalmitoylphosphatidylcholine | 1.5 | 2.6 | 1.7 | 0.029 | <0.001 | 0.002 |
| Imidazolelactate | 1.6 | 3.2 | 2.0 | 0.001 | <0.001 | <0.001 |
| Lauramide | 0.8 | 0.7 | 0.8 | 0.023 | <0.001 | 0.031 |
| N-Acetylornithine | 1.4 | 2.5 | 1.8 | 0.021 | <0.001 | <0.001 |
| Primobolan | 0.7 | 0.6 | 0.8 | 0.048 | <0.001 | 0.010 |
| Tetrahydrocorticosterone | 1.4 | 3.3 | 2.3 | 0.041 | <0.001 | <0.001 |
| Trigonelline | 1.4 | 2.4 | 1.7 | 0.035 | <0.001 | 0.002 |
| Xanthoaphin | 0.5 | 0.1 | 0.3 | 0.017 | <0.001 | <0.001 |

**Supplementary Table 2.** The 48 metabolites significantly associated with T2D irrespective of renal function of the subjects [significantly dysregulated (FDR adjusted *p*-value < 0.05) between NGT and T2D and between NGT and T2D-DN but not between T2D and T2D-DN]. (NGT: normal glucose tolerance, T2D: type 2 diabetes mellitus, T2D-DN: type 2 diabetes mellitus-diabetic nephropathy)

| Metabolite | Ratio T2D/NGT | Ratio T2D-DN/NGT | Ratio T2D-DN/T2D | Adjusted *p*-value T2D/NGT | Adjusted *p*-value T2D-DN/NGT | Adjusted *p*-value T2D-DN/T2D |
|---|---|---|---|---|---|---|
| (2E,4E,14E)-13-Hydroperoxy-N-(2-methylpropyl)icosa-2,4,14-trienamide | 0.5 | 0.5 | 1.1 | 0.023 | 0.013 | 1.000 |
| 18-hydroxy-5Z,8Z,11Z,14Z-eicosatetraenoic acid | 0.8 | 0.7 | 0.9 | 0.018 | <0.001 | 1.000 |
| 1-Linoleoyl glycerol | 1.6 | 1.6 | 1.0 | 0.001 | <0.001 | 1.000 |
| 1-Stearoylglycerol | 1.7 | 1.9 | 1.1 | <0.001 | <0.001 | 0.923 |
| 2-Linoleoyl glycerol | 1.7 | 1.7 | 1.0 | 0.007 | <0.001 | 1.000 |
| Cytidine 5'-diphosphocholine | 1.0 | 1.0 | 1.0 | 0.045 | 0.009 | 1.000 |
| D-Raffinose | 1.6 | 1.6 | 1.0 | <0.001 | <0.001 | 1.000 |
| Fingolimod | 0.5 | 0.2 | 0.4 | 0.035 | <0.001 | 0.285 |
| Jasmonic acid | 0.9 | 1.0 | 1.0 | 0.002 | 0.001 | 1.000 |
| Palmitoyl sphingomyelin | 1.4 | 1.7 | 1.2 | 0.035 | <0.001 | 0.754 |
| Sorbitane trioleate | 0.5 | 0.5 | 0.9 | <0.001 | <0.001 | 0.420 |
| Taurocholic acid | 0.3 | 0.2 | 0.7 | 0.042 | 0.001 | 1.000 |
| Cassine | 0.6 | 0.6 | 0.9 | <0.001 | <0.001 | 0.938 |
| 17α-Methyl-androstan-3-hydroxyimine-17β-ol | 0.3 | 0.3 | 0.8 | <0.001 | <0.001 | 0.188 |
| 1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine | 2.4 | 2.3 | 1.0 | <0.001 | <0.001 | 1.000 |
| 2,3-bis-O-(geranylgeranyl)-sn-glycero-3-phospho-L-serine | 1.4 | 1.3 | 0.9 | 0.004 | 0.001 | 1.000 |
| 2-[(5Z)-5-Tetradecen-1-yl]cyclobutanone | 0.4 | 0.2 | 0.5 | 0.031 | <0.001 | 0.134 |
| 3-dehydrosphingosine | 0.4 | 0.3 | 0.9 | <0.001 | <0.001 | 0.577 |
| 3-Oxalomalic acid | 0.9 | 0.8 | 0.9 | 0.008 | <0.001 | 1.000 |
| Diphenyl sulfoxide | 1.6 | 1.4 | 0.9 | <0.001 | 0.002 | 0.310 |
| Linoleamide | 0.7 | 0.6 | 0.9 | <0.001 | <0.001 | 0.467 |
| 9,10,18-Trihydroxystearic Acid | 0.7 | 0.7 | 0.9 | 0.001 | <0.001 | 0.800 |
| Lumichrome | 2.3 | 1.7 | 0.7 | 0.028 | 0.026 | 1.000 |
| Acetylcholine | 0.7 | 0.8 | 1.1 | <0.001 | <0.001 | 0.599 |
| Acetyl-L-leucyl-L-leucylargininal | 1.0 | 0.9 | 1.0 | 0.011 | 0.001 | 1.000 |
| Azelnidipine | 0.6 | 0.5 | 0.9 | 0.013 | 0.001 | 1.000 |
| Bardoxolone methyl | 1.4 | 1.4 | 1.0 | 0.033 | 0.001 | 1.000 |
| 2-Octenoic acid | 0.7 | 0.6 | 0.8 | 0.027 | <0.001 | 1.000 |

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| 4-Oxoretinoic acid | 0.6 | 0.4 | 0.7 | 0.001 | <0.001 | 0.220 |
| Cortisol | 1.4 | 1.3 | 0.9 | 0.017 | 0.022 | 1.000 |
| Drofenine | 0.4 | 0.2 | 0.6 | <0.001 | <0.001 | 0.192 |
| Epicillin | 1.2 | 1.2 | 1.0 | 0.017 | <0.001 | 1.000 |
| Epitestosterone | 0.7 | 0.8 | 1.1 | 0.011 | 0.018 | 0.969 |
| Gamma-Glutamyl-S-allylcysteine | 0.7 | 0.5 | 0.7 | 0.049 | <0.001 | 0.160 |
| Glimepiride | 1.2 | 1.2 | 1.0 | 0.006 | <0.001 | 1.000 |
| Glycerophospho-N-palmitoyl ethanolamine | 1.2 | 1.3 | 1.0 | 0.045 | 0.002 | 1.000 |
| Hexadecanamide | 0.6 | 0.4 | 0.7 | 0.001 | <0.001 | 0.143 |
| MDMA Methylene homolog | 2.1 | 2.6 | 1.2 | 0.038 | 0.001 | 1.000 |
| Metformin | 835.4 | 1.5 | 0.0 | <0.001 | <0.001 | 0.098 |
| N-benzoyl-D-arginine-4-nitroanilide | 0.5 | 0.7 | 1.2 | 0.001 | <0.001 | 1.000 |
| Oleamide | 0.5 | 0.4 | 0.8 | 0.022 | <0.001 | 0.848 |
| Palmitoleoyl ethanolamide | 0.4 | 0.4 | 0.8 | <0.001 | <0.001 | 0.523 |
| PC(18:3(9Z,12Z,15Z)/18:2(9Z,12Z)) | 2.2 | 1.7 | 0.8 | <0.001 | <0.001 | 0.686 |
| Stearamide | 0.6 | 0.4 | 0.7 | 0.006 | <0.001 | 0.068 |
| Tretinoin | 0.4 | 0.5 | 1.1 | 0.003 | <0.001 | 1.000 |
| Yersiniabactin | 4.3 | 3.0 | 0.7 | <0.001 | <0.001 | 0.761 |
| Sphinganine | 0.8 | 0.7 | 0.9 | 0.041 | <0.001 | 0.699 |
| γ-Linolenic acid ethyl ester | 1.2 | 1.3 | 1.0 | 0.013 | 0.001 | 1.000 |

**Supplementary Table 3.** The 192 metabolites specifically associated with T2D-DN [significantly dysregulated between NGT and T2D-DN as well as between T2D and T2D-DN (FDR adjusted *p*-value < 0.05) but not between NGT and T2D; and exhibiting a difference of ≥2 folds or ≤0.5 fold between the T2D-DN and T2D groups]. (NGT: normal glucose tolerance, T2D: type 2 diabetes mellitus, T2D-DN: type 2 diabetes mellitus-diabetic nephropathy)

| Metabolite | Ratio T2D/NGT | Ratio T2D-DN/NGT | Ratio T2D-DN/T2D | Adjusted *p*-value T2D/NGT | Adjusted *p*-value T2D-DN/NGT | Adjusted *p*-value T2D-DN/T2D |
|---|---|---|---|---|---|---|
| 12,13-dihydroxy-9Z-octadecenoic acid | 1.2 | 4.9 | 4.2 | 1.000 | <0.001 | <0.001 |
| Pantetheine | 0.7 | 3.7 | 5.4 | 1.000 | <0.001 | <0.001 |
| (2R,3S)-3-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid | 1.1 | 2.4 | 2.1 | 1.000 | <0.001 | 0.001 |
| (8aR,12S,12aR)-12-Hydroxy-4-methyl-4,5,6,7,8,8a,12,12a-octahydro-2H-3-benzoxecine-2,9(1H)-dione | 1.1 | 7.8 | 6.8 | 0.857 | <0.001 | <0.001 |
| 1-(2,4,5-Trimethoxyphenyl)-1,2-propanedione | 1.0 | 2.4 | 2.3 | 1.000 | <0.001 | 0.022 |
| 1-(2,4-Dihydroxyphenyl)-1-butanone | 1.0 | 3.1 | 3.0 | 1.000 | <0.001 | <0.001 |
| 1-(beta-D-ribofuranosyl)thymine | 1.1 | 3.1 | 2.9 | 1.000 | <0.001 | <0.001 |
| 1,4,5,6-Tetrahydro-2-methyl-4-pyrimidinecarboxylic acid | 1.2 | 2.7 | 2.2 | 0.207 | <0.001 | <0.001 |
| N-oleoyl tyrosine | 0.7 | 0.4 | 0.5 | 0.599 | <0.001 | 0.001 |
| 15-(tert-Butyl)-2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine | 0.6 | 1.6 | 2.6 | 0.440 | 0.030 | <0.001 |
| 16α-Hydroxydehydroepiandrosterone | 0.7 | 3.0 | 4.2 | 0.650 | <0.001 | <0.001 |
| 19(R)-HETE | 1.2 | 2.9 | 2.4 | 1.000 | <0.001 | <0.001 |
| 19-Nortestosterone | 1.0 | 2.5 | 2.4 | 1.000 | <0.001 | 0.009 |
| 1-alpha,24R,25-Trihydroxyvitamin D2 | 0.8 | 0.4 | 0.4 | 0.385 | <0.001 | 0.003 |
| 1-Naphthol | 1.1 | 2.3 | 2.1 | 0.493 | <0.001 | 0.009 |
| 1-Pentofuranosyl-2,4(1H,3H)-pyrimidinedione | 1.0 | 2.5 | 2.5 | 1.000 | <0.001 | <0.001 |
| 2-({2-[4-(4-Fluorophenyl)piperazino]-2-oxoethyl}sulfanyl)acetic acid | 1.5 | 0.5 | 0.4 | 1.000 | 0.006 | <0.001 |
| 2-(1H-Benzimidazol-2-ylsulfanyl)-N-(3-cyano-6-methyl-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)acetamide | 1.0 | 5.8 | 5.8 | 0.458 | <0.001 | <0.001 |
| 2-(Phenylsulfonyl)acetophenone | 1.1 | 2.2 | 2.0 | 1.000 | 0.001 | 0.001 |
| 2,6-quinolinediol | 1.3 | 3.9 | 3.0 | 0.410 | <0.001 | <0.001 |
| 2-[2-(3,4-dimethoxyphenyl)ethyl]-4-methoxy-2,3-dihydropyran-6-one | 0.9 | 2.0 | 2.1 | 1.000 | <0.001 | <0.001 |
| 2-Aminoadenosine | 0.9 | 3.2 | 3.4 | 1.000 | <0.001 | <0.001 |
| 2-Hydroxyhippuric acid | 1.4 | 3.4 | 2.4 | 0.422 | <0.001 | 0.040 |
| 2-methoxyacetaminophen sulfate | 0.9 | 2.1 | 2.4 | 0.979 | <0.001 | <0.001 |

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| 2-methylbutyrylcarnitine | 1.1 | 0.5 | 0.5 | 1.000 | <0.001 | <0.001 |
| 3-(2-Hydroxy-5-methoxybenzoyl)-2-(4-methylphenyl)isoindolin-1-one | 0.8 | 0.4 | 0.4 | 1.000 | <0.001 | <0.001 |
| 3,13,13,17-Tetramethyl-21-oxa-12-azahexacyclo[10.7.1.1~2,17~.0~5,20~.0~6,11~.0~14,19~]henicosa-1(20),2,4,6,8,10-hexaen-16-ol | 0.9 | 0.4 | 0.5 | 0.798 | <0.001 | 0.001 |
| 3,4,5-trimethoxydihydrocinnamic acid | 1.0 | 2.9 | 2.8 | 1.000 | 0.027 | 0.037 |
| 3',4'-Dimethoxyacetophenone | 1.0 | 2.8 | 2.9 | 1.000 | 0.035 | 0.039 |
| 3-Hydroxy-cis-5-tetradecenoylcarnitine | 0.9 | 2.1 | 2.2 | 1.000 | <0.001 | <0.001 |
| 4-methoxy-5-methyl-6-[(2S,3S)-2-methyl-3-[(2Z,4E)-4-methyl-5-[(1S,2S,4R,5R)-1,2,4-trimethyl-3,6-dioxabicyclo[3.1.0]hexan-4-yl]penta-2,4-dien-2-yl]oxiran-2-yl]pyran-2-one | 1.0 | 3.3 | 3.2 | 1.000 | <0.001 | <0.001 |
| Alpha-Farnesene | 1.2 | 0.5 | 0.4 | 1.000 | <0.001 | <0.001 |
| 5-(6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-2-methyl-pentanoic acid | 1.0 | 2.9 | 3.0 | 1.000 | <0.001 | <0.001 |
| 5-Butyl-1,3-oxazole | 1.5 | 3.3 | 2.2 | 0.101 | <0.001 | <0.001 |
| 5-guanidino-2-oxopentanoic acid | 1.1 | 2.4 | 2.1 | 1.000 | <0.001 | <0.001 |
| 5-Indolol | 1.2 | 3.7 | 3.2 | 0.472 | <0.001 | <0.001 |
| 5α-Dihydrotestosterone | 0.9 | 1.8 | 2.0 | 1.000 | 0.003 | <0.001 |
| 5α-Tetrahydrocortisol | 0.7 | 9.2 | 12.3 | 1.000 | <0.001 | <0.001 |
| 2,2'-[4-(2-Hydroxyethylamino)-3-nitrophenylimino]diethanol | 1.0 | 4.6 | 4.4 | 1.000 | <0.001 | <0.001 |
| 6-Hydroxy-5-methyl-4,11-dioxoundecanoic acid | 1.1 | 2.9 | 2.6 | 1.000 | <0.001 | <0.001 |
| 6-Ketoprostaglandin F1α | 0.7 | 1.7 | 2.3 | 0.923 | <0.001 | <0.001 |
| 6β-Hydroxyfluoxymesterone | 1.4 | 3.4 | 2.4 | 0.435 | <0.001 | <0.001 |
| [2-(Dimethoxymethyl)-1-heptenyl]benzene | 0.9 | 2.4 | 2.8 | 1.000 | <0.001 | <0.001 |
| N-Nitrosodibutylamine | 0.9 | 2.2 | 2.4 | 1.000 | <0.001 | <0.001 |
| Noroxycodone | 0.5 | 0.1 | 0.2 | 1.000 | <0.001 | 0.001 |
| 9-O-Demethyl-2alpha-hydroxyhomolycorine | 0.7 | 0.3 | 0.5 | 1.000 | 0.028 | 0.022 |
| Acamprosate | 1.1 | 2.5 | 2.3 | 1.000 | <0.001 | <0.001 |
| Acetyl-L-carnitine | 1.4 | 4.3 | 3.1 | 0.280 | <0.001 | <0.001 |
| Acetyllycopsamine | 1.2 | 3.0 | 2.5 | 1.000 | <0.001 | <0.001 |
| Actinonin | 0.8 | 1.7 | 2.1 | 1.000 | 0.001 | 0.010 |
| Aderbasib | 1.2 | 3.3 | 2.7 | 1.000 | <0.001 | <0.001 |
| Allixin | 1.1 | 2.6 | 2.5 | 1.000 | <0.001 | <0.001 |
| Alloxydim | 1.0 | 2.7 | 2.7 | 0.799 | <0.001 | <0.001 |
| Alminoprofen | 1.1 | 0.4 | 0.4 | 1.000 | <0.001 | <0.001 |
| Aloesin | 1.0 | 2.1 | 2.2 | 1.000 | 0.002 | 0.001 |
| Alpha-(4-methoxyphenyl)-6-methyl-2-pyridineacrylic acid | 1.0 | 2.2 | 2.1 | 1.000 | <0.001 | <0.001 |

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| Alpha-Cehc | 1.0 | 2.0 | 2.0 | 1.000 | <0.001 | <0.001 |
| Amidapsone | 1.0 | 4.4 | 4.6 | 1.000 | <0.001 | <0.001 |
| Amygdalin | 0.8 | 1.6 | 2.0 | 1.000 | 0.024 | 0.019 |
| Andrographolide | 0.7 | 2.1 | 3.0 | 1.000 | <0.001 | <0.001 |
| Androsterone | 1.5 | 3.5 | 2.4 | 0.053 | <0.001 | <0.001 |
| Apiol | 1.0 | 2.9 | 2.8 | 1.000 | 0.027 | 0.037 |
| Arachidonic acid | 1.3 | 2.7 | 2.0 | 0.538 | <0.001 | <0.001 |
| Artemisinin | 1.1 | 2.4 | 2.2 | 0.659 | <0.001 | <0.001 |
| Atractylone | 1.2 | 3.5 | 2.9 | 0.642 | <0.001 | <0.001 |
| Benfluralin | 0.9 | 11.3 | 12.0 | 0.276 | <0.001 | <0.001 |
| Benznidazole | 0.6 | 2.5 | 3.9 | 1.000 | <0.001 | <0.001 |
| Betaine | 1.1 | 2.3 | 2.1 | 1.000 | <0.001 | <0.001 |
| Buflomedil | 1.3 | 3.3 | 2.6 | 0.654 | <0.001 | 0.005 |
| Butabarbital | 1.1 | 2.6 | 2.4 | 1.000 | <0.001 | 0.001 |
| Callystatin A | 0.9 | 0.4 | 0.4 | 1.000 | <0.001 | 0.021 |
| Candoxatril | 1.2 | 2.6 | 2.3 | 1.000 | 0.004 | 0.028 |
| Cannabidivarin | 1.0 | 2.1 | 2.1 | 1.000 | <0.001 | <0.001 |
| Carbaprostacyclin | 1.4 | 3.4 | 2.4 | 0.075 | <0.001 | <0.001 |
| Carisoprodol | 1.3 | 3.4 | 2.6 | 0.658 | <0.001 | <0.001 |
| Carteolol | 1.0 | 3.1 | 3.2 | 1.000 | <0.001 | <0.001 |
| Cinnamoylglycine | 0.8 | 4.1 | 5.2 | 1.000 | <0.001 | <0.001 |
| Ciprostene | 0.9 | 0.4 | 0.4 | 1.000 | <0.001 | <0.001 |
| Clethodim sulfone | 1.2 | 2.8 | 2.4 | 0.946 | <0.001 | <0.001 |
| Clonazolam | 1.0 | 2.5 | 2.6 | 1.000 | <0.001 | <0.001 |
| Codeine | 1.0 | 0.3 | 0.3 | 0.932 | <0.001 | 0.004 |
| Coenzyme Q2 | 0.9 | 2.1 | 2.2 | 1.000 | <0.001 | <0.001 |
| Coronatine | 1.0 | 3.1 | 3.0 | 1.000 | <0.001 | <0.001 |
| Cyclooctatin | 1.9 | 4.8 | 2.5 | 0.182 | <0.001 | <0.001 |
| Glyol | 1.2 | 3.5 | 3.0 | 1.000 | <0.001 | <0.001 |
| Desonide | 0.5 | 3.4 | 7.2 | 1.000 | 0.001 | <0.001 |
| Dihydroberberine | 1.3 | 0.6 | 0.4 | 1.000 | 0.002 | 0.017 |
| Dihydrocodeine | 1.0 | 4.4 | 4.3 | 1.000 | <0.001 | <0.001 |
| DL-Glutamine | 1.3 | 7.7 | 5.9 | 0.500 | <0.001 | <0.001 |
| D-Maltose | 1.0 | 3.6 | 3.6 | 0.970 | <0.001 | <0.001 |
| Docosahexaenoic acid ethyl ester | 0.8 | 3.5 | 4.1 | 1.000 | <0.001 | <0.001 |
| Docosapentaenoic acid | 1.2 | 0.6 | 0.5 | 1.000 | 0.008 | 0.015 |
| Doramectin | 1.1 | 5.0 | 4.8 | 1.000 | <0.001 | <0.001 |

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| D-α-Tocopherol | 1.0 | 0.5 | 0.5 | 1.000 | <0.001 | 0.003 |
| 7-Methylxanthine | 0.9 | 1.9 | 2.1 | 1.000 | <0.001 | <0.001 |
| Epitestosterone glucuronide | 0.7 | 3.6 | 5.1 | 1.000 | <0.001 | <0.001 |
| Europine | 0.8 | 5.3 | 6.7 | 1.000 | <0.001 | <0.001 |
| Theasapogenol B | 0.9 | 0.2 | 0.2 | 0.262 | <0.001 | <0.001 |
| Salinosporamide B | 1.5 | 3.6 | 2.5 | 1.000 | <0.001 | <0.001 |
| Glycerol tripropionate | 1.1 | 4.0 | 3.6 | 1.000 | <0.001 | <0.001 |
| Flossonol | 1.2 | 2.6 | 2.3 | 0.510 | <0.001 | <0.001 |
| Gamma-glutamyltyramine | 1.1 | 3.0 | 2.9 | 1.000 | <0.001 | <0.001 |
| Genistin | 0.9 | 0.3 | 0.3 | 1.000 | <0.001 | 0.006 |
| Glaucarubinone | 0.9 | 2.0 | 2.3 | 1.000 | <0.001 | <0.001 |
| Hexanoylcarnitine | 1.3 | 2.8 | 2.2 | 1.000 | <0.001 | <0.001 |
| Hippuric acid | 1.0 | 2.1 | 2.2 | 1.000 | <0.001 | 0.001 |
| Homocitrulline | 0.9 | 2.3 | 2.5 | 0.807 | <0.001 | <0.001 |
| Hostmaniane | 1.2 | 2.4 | 2.1 | 0.739 | <0.001 | <0.001 |
| Hydroxypropionylcarnitine | 0.9 | 3.1 | 3.6 | 1.000 | <0.001 | <0.001 |
| Indane | 1.2 | 0.5 | 0.4 | 1.000 | 0.011 | 0.019 |
| Indol-2-one | 0.8 | 3.8 | 4.9 | 1.000 | <0.001 | <0.001 |
| Indol-4-one | 1.0 | 3.2 | 3.1 | 1.000 | <0.001 | <0.001 |
| Indolyl-3-acryloylglycine | 1.2 | 2.8 | 2.3 | 1.000 | 0.026 | 0.006 |
| Iobitridol | 0.8 | 6.2 | 7.5 | 1.000 | <0.001 | <0.001 |
| Kanamycin | 1.1 | 6.3 | 6.0 | 0.840 | <0.001 | <0.001 |
| L-Ergothioneine | 1.4 | 0.7 | 0.5 | 0.726 | <0.001 | <0.001 |
| Leucine | 1.1 | 2.8 | 2.7 | 1.000 | <0.001 | <0.001 |
| Leucylproline | 1.0 | 2.1 | 2.1 | 1.000 | <0.001 | <0.001 |
| L-Glutathione oxidized | 1.0 | 2.5 | 2.3 | 1.000 | <0.001 | <0.001 |
| Lincomycin | 1.2 | 3.1 | 2.6 | 0.784 | <0.001 | <0.001 |
| L-Kynurenine | 1.0 | 2.1 | 2.0 | 1.000 | <0.001 | <0.001 |
| L-Pyroglutamic acid | 1.5 | 3.7 | 2.4 | 0.292 | <0.001 | <0.001 |
| L-Tyrosine | 1.0 | 2.0 | 2.1 | 1.000 | <0.001 | <0.001 |
| Magnolol | 0.7 | 1.8 | 2.5 | 1.000 | 0.001 | <0.001 |
| Mephenytoin | 1.5 | 5.4 | 3.7 | 0.351 | <0.001 | <0.001 |
| Metharbital | 1.3 | 3.5 | 2.8 | 0.440 | <0.001 | <0.001 |
| Methasterone | 0.9 | 1.7 | 2.0 | 1.000 | <0.001 | <0.001 |
| Methionine | 1.8 | 12.5 | 6.9 | 0.213 | <0.001 | <0.001 |
| Methyl (3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)acetate | 0.6 | 3.1 | 5.0 | 1.000 | 0.012 | 0.002 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Methyl indole-3-acetate | 1.1 | 3.5 | 3.3 | 1.000 | <0.001 | <0.001 |
| Milbemycin A4 oxime | 0.9 | 1.9 | 2.0 | 1.000 | <0.001 | <0.001 |
| Miltirone | 0.5 | 3.4 | 6.9 | 1.000 | <0.001 | <0.001 |
| Morphinone | 0.7 | 0.2 | 0.2 | 1.000 | <0.001 | 0.001 |
| Myriocin | 0.8 | 1.6 | 2.1 | 1.000 | <0.001 | <0.001 |
| N-(4-coumaroyl)-L-homoserine lactone | 1.5 | 8.3 | 5.5 | 0.526 | <0.001 | <0.001 |
| N-(indol-3-ylacetyl)glutamine | 1.5 | 5.4 | 3.5 | 0.944 | <0.001 | <0.001 |
| N-(indole-3-acetyl)glutamic acid | 1.0 | 2.3 | 2.2 | 1.000 | <0.001 | <0.001 |
| N-[(9-beta-D-ribofuranosylpurin-6-yl)carbamoyl]threonine | 0.9 | 2.6 | 2.8 | 1.000 | <0.001 | <0.001 |
| N1-(2-Pyridylmethyl)-4-methylbenzene-1-sulfonamide | 1.4 | 3.2 | 2.3 | 0.453 | <0.001 | <0.001 |
| N4-Acetyl sulfamethazine | 0.7 | 5.5 | 7.8 | 1.000 | <0.001 | <0.001 |
| N-Acetylhistamine | 0.8 | 2.6 | 3.3 | 1.000 | 0.011 | 0.005 |
| N-Acetylvaline | 1.1 | 2.4 | 2.1 | 1.000 | <0.001 | <0.001 |
| Nalorphine | 0.7 | 0.2 | 0.2 | 0.519 | <0.001 | 0.002 |
| N-Butyl salicylate | 1.2 | 2.3 | 2.0 | 0.619 | <0.001 | 0.002 |
| N-Caffeoylputrescine | 1.1 | 3.9 | 3.6 | 1.000 | <0.001 | <0.001 |
| N-Phenylacetylglutamic acid | 0.8 | 2.0 | 2.5 | 1.000 | <0.001 | <0.001 |
| N-Phenylacetylglutamine | 1.4 | 8.0 | 5.8 | 0.391 | <0.001 | <0.001 |
| O-3-methylglutarylcarnitine | 1.2 | 3.1 | 2.6 | 0.480 | <0.001 | <0.001 |
| Oleyl anilide | 1.0 | 2.3 | 2.3 | 1.000 | <0.001 | <0.001 |
| Ophthalmic acid | 1.1 | 2.7 | 2.5 | 0.863 | <0.001 | <0.001 |
| Ornithinoalanine | 1.4 | 4.0 | 2.8 | 0.496 | <0.001 | <0.001 |
| Palmitoylcarnitine | 0.8 | 0.1 | 0.1 | 1.000 | 0.001 | 0.008 |
| Pantoprazole | 1.0 | 2.0 | 2.0 | 0.460 | <0.001 | 0.003 |
| Phenisopham | 1.3 | 10.2 | 7.8 | 0.889 | <0.001 | <0.001 |
| Piperanine | 1.2 | 0.4 | 0.3 | 1.000 | 0.007 | 0.003 |
| Piperine | 0.7 | 0.2 | 0.2 | 1.000 | <0.001 | 0.001 |
| Prednisone | 0.9 | 2.2 | 2.5 | 1.000 | <0.001 | <0.001 |
| Pregnanetriol | 0.9 | 2.1 | 2.3 | 1.000 | <0.001 | <0.001 |
| Pregnenolone | 0.9 | 1.9 | 2.0 | 1.000 | 0.001 | 0.001 |
| Proacaciberin | 1.0 | 2.3 | 2.3 | 1.000 | <0.001 | <0.001 |
| Probenazole | 0.9 | 2.3 | 2.5 | 1.000 | <0.001 | <0.001 |
| Progesterone | 1.3 | 3.0 | 2.2 | 0.169 | <0.001 | <0.001 |
| Promolate | 1.0 | 3.0 | 2.9 | 1.000 | <0.001 | <0.001 |
| Propionylcarnitine | 1.0 | 2.0 | 2.0 | 1.000 | <0.001 | <0.001 |
| Pulcherriminic acid | 0.9 | 2.6 | 2.7 | 1.000 | <0.001 | <0.001 |

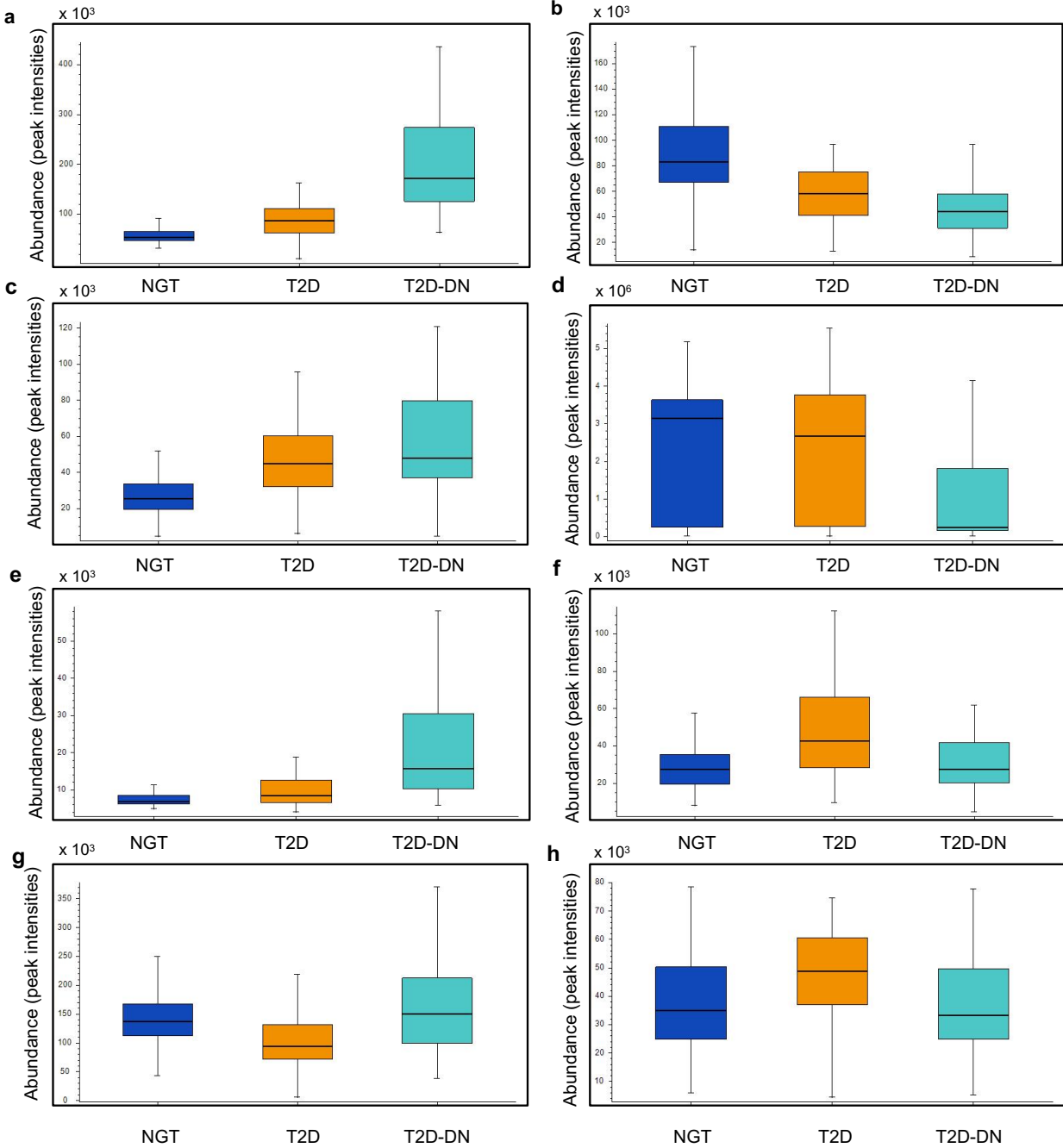| | | | | | | |
|---|---|---|---|---|---|---|
| Pumiliotoxin 251D | 0.7 | 1.5 | 2.3 | 0.325 | 0.001 | <0.001 |
| Ricinoleic Acid | 0.8 | 0.4 | 0.5 | 0.511 | <0.001 | 0.002 |
| Roxatidine | 1.1 | 8.1 | 7.4 | 1.000 | <0.001 | <0.001 |
| Ryania | 0.5 | 3.5 | 7.3 | 1.000 | <0.001 | <0.001 |
| Salinomycin | 0.6 | 1.5 | 2.4 | 0.539 | 0.013 | <0.001 |
| Secobarbital | 1.0 | 2.1 | 2.2 | 1.000 | <0.001 | <0.001 |
| Sesamin | 1.2 | 9.4 | 7.9 | 0.513 | <0.001 | <0.001 |
| Siaresinol | 1.0 | 0.2 | 0.2 | 0.265 | <0.001 | <0.001 |
| Soyasaponin I | 1.4 | 3.5 | 2.4 | 0.599 | <0.001 | <0.001 |
| Stylisterol B | 0.8 | 0.2 | 0.3 | 0.314 | <0.001 | 0.001 |
| Sucrose acetate isobutyrate | 1.0 | 2.7 | 2.7 | 1.000 | <0.001 | <0.001 |
| Telmisartan | 0.8 | 3.2 | 3.9 | 0.188 | <0.001 | 0.027 |
| Tetrahydrocortisone | 1.0 | 3.1 | 3.2 | 1.000 | <0.001 | <0.001 |
| Tetranor 12-HETE | 0.7 | 1.5 | 2.0 | 0.811 | 0.004 | <0.001 |
| thr-tyr | 1.2 | 3.6 | 2.9 | 0.998 | <0.001 | <0.001 |
| 2-Tetrahydrothiopheneacetic acid | 1.2 | 2.6 | 2.2 | 0.985 | <0.001 | <0.001 |
| N-Acetyl-L-tryptophan | 1.0 | 2.7 | 2.6 | 1.000 | 0.007 | 0.001 |
| Lophophorine | 1.2 | 2.7 | 2.2 | 0.979 | <0.001 | <0.001 |
| N-Acetylthreonine | 1.0 | 2.6 | 2.5 | 1.000 | <0.001 | <0.001 |
| Valyltyrosine | 1.1 | 2.3 | 2.2 | 1.000 | <0.001 | <0.001 |
| Valylvaline | 1.5 | 3.7 | 2.5 | 1.000 | <0.001 | <0.001 |
| Veliflapon | 0.8 | 0.3 | 0.3 | 0.617 | <0.001 | <0.001 |
| Zalcitabine | 0.8 | 2.2 | 2.6 | 1.000 | <0.001 | <0.001 |
| Zopiclone | 1.1 | 7.9 | 7.4 | 0.918 | <0.001 | <0.001 |
| α-Hydroxyhippuric acid | 0.9 | 6.0 | 6.7 | 1.000 | <0.001 | <0.001 |
| α-Zearalanol | 1.0 | 5.1 | 5.0 | 0.094 | <0.001 | 0.012 |
| β-Cortolone | 1.0 | 2.3 | 2.3 | 1.000 | <0.001 | <0.001 |

**Supplementary Table 4**. Spearman's correlation between renal function, expressed as estimated Glomerular Filtration Rate (eGFR), and the 20 metabolites with least FDR adjusted *p*-value in difference in abundance between T2D and T2D-DN. (NGT: normal glucose tolerance, T2D: type 2 diabetes mellitus, T2D-DN: type 2 diabetes mellitus-diabetic nephropathy)

| Metabolite | eGFR (mL/min/1.73m$^2$) | | | | | |
|---|---|---|---|---|---|---|
| | **NGT** | | **T2D** | | **T2D-DN** | |
| | **rho** | ***p*-value** | **rho** | ***p*-value** | **rho** | ***p*-value** |
| Imidazolelactate | -0.20 | 0.286 | -0.42 | 0.025 | -0.62 | <0.001 |
| L-Pyroglutamic acid | -0.30 | 0.107 | -0.29 | 0.129 | -0.60 | <0.001 |
| Mephenytoin | -0.26 | 0.163 | -0.14 | 0.474 | -0.66 | <0.001 |
| N-Phenylacetylglutamine | -0.31 | 0.094 | -0.29 | 0.131 | -0.61 | <0.001 |
| N-Phenylacetylglutamic acid | -0.33 | 0.080 | -0.39 | 0.037 | -0.64 | <0.001 |
| 2,6-quinolinediol | 0.11 | 0.575 | -0.55 | 0.002 | -0.70 | <0.001 |
| DL-Glutamine | -0.30 | 0.106 | -0.26 | 0.167 | -0.60 | <0.001 |
| Ornithinoalanine | -0.33 | 0.079 | -0.24 | 0.207 | -0.65 | <0.001 |
| Secobarbital | -0.41 | 0.027 | -0.21 | 0.267 | -0.71 | <0.001 |
| α-Hydroxyhippuric acid | 0.15 | 0.444 | -0.13 | 0.505 | -0.63 | <0.001 |
| N-Acetylthreonine | -0.11 | 0.571 | 0.11 | 0.567 | -0.53 | 0.002 |
| N-Caffeoylputrescine | -0.05 | 0.783 | -0.10 | 0.599 | -0.74 | <0.001 |
| N-[(9-beta-D-ribofuranosylpurin-6-yl)carbamoyl]threonine | -0.42 | 0.022 | -0.38 | 0.042 | -0.79 | <0.001 |
| Indol-4-one | -0.26 | 0.158 | -0.08 | 0.677 | -0.59 | <0.001 |
| Glycerol tripropionate | -0.23 | 0.223 | -0.20 | 0.298 | -0.59 | <0.001 |
| EUROPINE | -0.12 | 0.528 | -0.18 | 0.355 | -0.72 | <0.001 |
| Aderbasib | -0.21 | 0.259 | -0.19 | 0.321 | -0.59 | 0.001 |
| [2-(Dimethoxymethyl)-1-heptenyl]benzene | -0.03 | 0.884 | -0.50 | 0.006 | -0.60 | <0.001 |
| 1-(beta-D-ribofuranosyl)thymine | 0.24 | 0.208 | -0.43 | 0.019 | -0.69 | <0.001 |
| 2-methoxyacetaminophen sulfate | -0.40 | 0.032 | 0.00 | 0.994 | -0.68 | <0.001 |

**Supplementary Table 5**. The 3 metabolites specifically associated with T2D [significantly dysregulated between NGT and T2D as well as between T2D and T2D-DN (FDR adjusted *p*-value < 0.05) but not between NGT and T2D-DN. (NGT: normal glucose tolerance, T2D: type 2 diabetes mellitus, T2D-DN: type 2 diabetes mellitus-diabetic nephropathy)

| Metabolite | Ratio T2D/NGT | Ratio T2D-DN/NGT | Ratio T2D-DN/T2D | Adjusted *p*-value T2D/NGT | Adjusted *p*-value T2D-DN/NGT | Adjusted *p*-value T2D-DN/T2D |
|---|---|---|---|---|---|---|
| 1-arachidonoyl-sn-glycero-3-phosphocholine | 1.5 | 1.0 | 0.6 | 0.015 | 0.859 | 0.035 |
| 4-(8-Methyl-8,9-dihydro-7H-[1,3]dioxolo[4,5-h][2,3]benzodiazepin-5-yl)aniline | 1.4 | 0.9 | 0.7 | 0.044 | 1.000 | 0.004 |
| Phenylalanylproline | 0.7 | 1.1 | 1.6 | 0.009 | 1.000 | <0.001 |

**Supplementary Figure 1.** Box plots depicting levels of (a) imidazolelactate, (b) cholecalciferol (c) 1-Stearoylglycerol, (d) palmitoylcarnitine, (e) choline, (f) 1-arachidonoyl-sn-glycero-3-phosphocholine, (g) phenylalanylproline and (h) 4-(8-Methyl-8,9-dihydro-7H-[1,3]dioxolo[4,5-h][2,3]benzodiazepin-5-yl)aniline in normal glucose tolerance (dark blue), type 2 diabetes mellitus (orange) and type 2 diabetes mellitus-diabetic nephropathy (light blue) subjects.

**Supplementary Figure 2.** Biochemical pathway and chemical relationships network of the 192 metabolites specifically associated with T2D-DN [significantly dysregulated between NGT and T2D-DN as well as between T2D and T2D-DN (FDR adjusted *P* value < 0.05; and exhibiting a difference in ratio of ≥2 or ≤0.5 between the T2D-DN and T2D groups) but not between NGT and T2D]. Blue represents downregulated and red represents upregulated metabolites in T2D-DN compared to T2D and to NGT. (NGT: normal glucose tolerance, T2D: type 2 diabetes mellitus, T2D-DN: type 2 diabetes mellitus-diabetic nephropathy