**SUPPLEMENT**

**Online Supplement**

Contents:



## Supplemental Methods

*Construction of Phenotype Pools*

We assigned sex-specific tertiles scores of 1, 2 or 3 for the changes in weight, waist circumference, and truncal adiposity, and we summed the tertile scores for each indicator to create an overall phenotype score (minimum score 3, indicating the participant was in the lowest tertile of change on all 3 indicators of adipose change, maximum 9, indicating the participant was in the highest tertile of change on all 3 indicators of adiposity change). The three subgroups of the incident central adiposity gain group were defined by tertiles of the composite score to investigate the potential for dose-response between the concentration of a metabolomic marker and phenotype.

*GC-MS quantification of selected ions*

For precise absolute quantification, GC-MS measurements of the derivatives of interest were additionally performed in selected ion monitoring mode, with the following settings for each selected ion: m/z 117.1, 191.1, 219.1 (dwell times: 30 ms) for Lactic acid 2TMS; m/z 144.1, 218.1, 246.1 (dwell times: 30 ms) for Valine 2TMS; m/z 158.1, 232.1, 260.1 (dwell times: 30 ms) for Leucine 2TMS; m/z 158.1, 218.1, 260.1 (dwell times: 30 ms) for Isoleucine 2TMS; m/z 217.1, 307.1, 320.1 (dwell times: 30 ms) for Erythritol 4TMS; m/z 220.1, 248.1, 310.1 (dwell times: 40 ms) for U13C-Ribitol 5TMS; m/z 307.1, 277.1, 364.2 (dwell times: 20 ms) for Fructose 1MeOX 5TMS.

*DBS experiments*

Automated sample derivatization was performed using a GERSTEL multi-purpose sampler (Muehlheim an der Ruhr, Germany). Dried samples were dissolved in 15 µl pyridine, containing 20 mg/ml methoxyamine hydrochloride, at 40 °C for 90 min under shaking. After adding 15 µl N-methyl-N-trimethylsilyl-triflouroacetamide (MSTFA) samples were incubated at 40 °C for 30 min under continuous shaking.

For DBS experiments, GC-MS analysis was performed by using an Agilent 7890A GC coupled to an Agilent 5975C inert XL Mass Selective Detector (Agilent Technologies, Germany). A sample volume of 1 µl was injected into a Split/Splitless inlet in split mode (3:1) at 270 °C. The gas chromatograph was equipped with a 30 m DB-35MS (I.D. 250 µm, film 0.25 µm) capillary column + 5 m DuraGuard capillary in front of the analytical column (Agilent J&W GC Column). Helium was used as carrier gas with a constant flow rate of 1.2 ml/min. The GC oven temperature was held at 90 °C for 1 min and increased to 320 °C at 15 °C/min, then held at that temperature for 8 min. The total run time for each sample was 24.333 min. The transfer line temperature was set constantly to 280 °C. The MSD was operating under electron ionization at 70 eV. The MS source was held at 230 °C and the quadrupole at 150 °C.

For MID determination, measurements of Erythritol 4TMS were performed in SIM mode using the following settings: m/z 320.2, 321.2, 322.2, 323.2, 324.2, 325.2, 326.2, 327.2. A dwell time of 15 ms for each ion was applied.

MetaboliteDetector software (Version 3.02015123Ra). Compounds were identified using an in-house mass spectral library. The following deconvolution settings were applied: Peak threshold: 1; Minimum peak height: 1; Bins per scan: 10; Deconvolution width: 8 scans; No baseline adjustment; Minimum 2 peaks per spectrum; No minimum required base peak intensity.

*Blood incubation experiments*

Automated sample derivatization was performed using a GERSTEL multi-purpose sampler (Muehlheim an der Ruhr, Germany). Dried samples were dissolved in 15 µl pyridine, containing 20 mg/ml methoxyamine hydrochloride, at 40 °C for 90 min under shaking. After adding 15 µl N-methyl-N-trimethylsilyl-triflouroacetamide (MSTFA) samples were incubated at 40 °C for 30 min under continuous shaking.

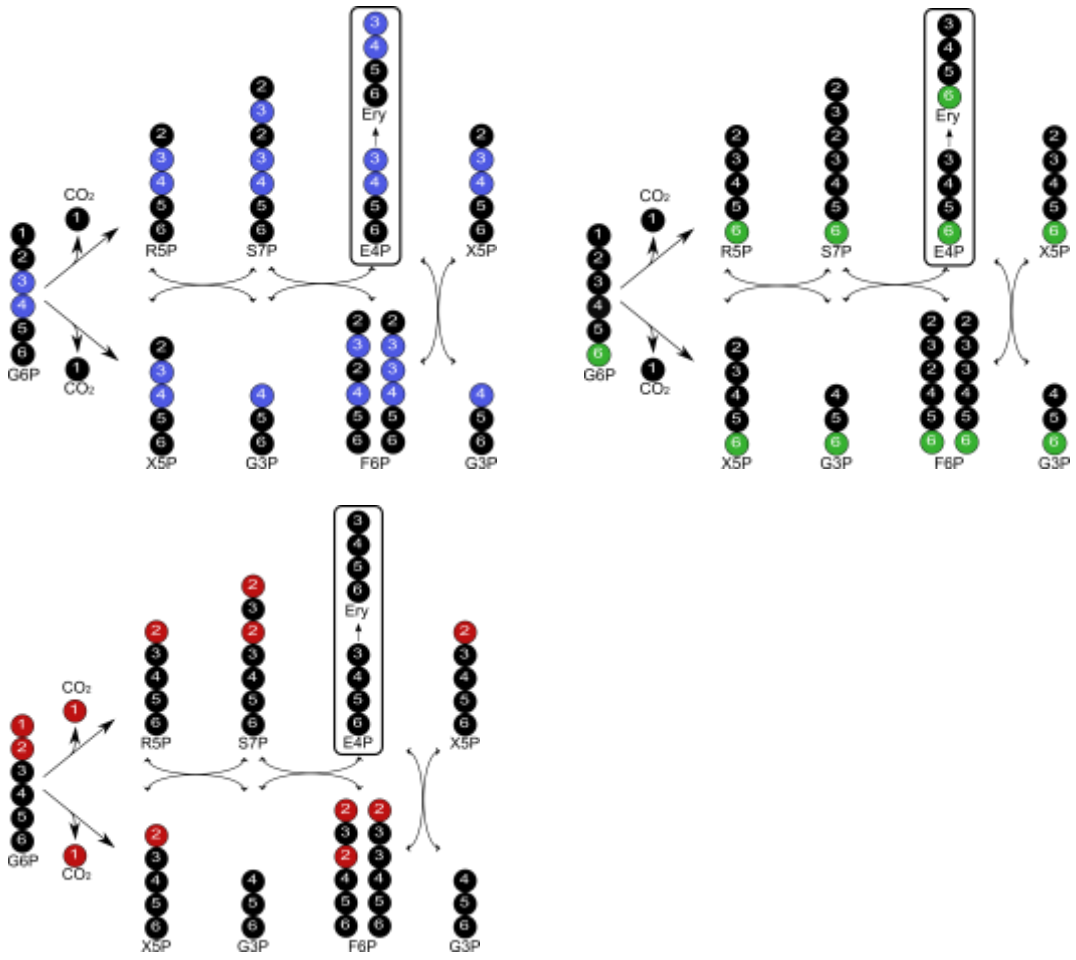
GC-MS analysis was performed by using an Agilent 7890B GC coupled to an Agilent 5977A Mass Selective Detector (Agilent Technologies, Germany). A sample volume of 2 µl were injected into a Split/Splitless inlet in split mode (10:1) at 270 °C. The gas chromatograph was equipped with a 20 m DB-5MS (I.D. 180 µm, film 0.18 µm) capillary column (Agilent J&W GC Column). Helium was used as carrier gas with a constant flow rate of 1.0 ml/min. The GC oven temperature was held at 90 °C for 0.5 min and increased to 220 °C at 13 °C/min, then increased to 325 °C at 100 °C/min and held at that temperature for 3.5 min. The total run time for each sample was 15.05 min. The transfer line temperature was set constantly to 280 °C. The MSD was operating under electron ionization at 70 eV. The MS source was held at 230 °C and the quadrupole at 150 °C.

For MID determination, measurements of Erythritol 4TMS were performed in SIM mode using the following settings: m/z 320.2, 321.2, 322.2, 323.2, 324.2, 325.2, 326.2, 327.2. A dwell time of 15 ms for each ion was applied.

MetaboliteDetector software (Version 3.02015123Ra). Compounds were identified using an in-house mass spectral library. The following deconvolution settings were applied: Peak threshold: 1; Minimum peak height: 1; Bins per scan: 10; Deconvolution width: 7 scans; No

baseline adjustment; Minimum 2 peaks per spectrum; No minimum required base peak intensity.

MID determination (sum formula fragment: C13H32O3Si3, MID size: 5) and correction for natural isotope abundance (Carbon) were performed.




**Supplemental Figure 1. Labelled carbon atom transitions from different glucose tracers within the PPP.** Erythritol (Ery) is synthesized from glucose *via* PPP from glucose-6-phosphate (G6P) that can be shown by **A** 3,4-$^{13}C_2$-Glucose yielding in 2 times labeled erythritol (M2 erythritol), **B** 6-$^{13}C_1$ Glucose yielding 1 times labelled erythritol (M1 erythritol) and **C** 1,2-$^{13}C_2$-

Glucose that will not transfer labelled carbon atoms to erythritol.

## Supplemental Results

**Supplemental Table 1** Metabolite quantification* for incident central adiposity phenotype compared to stable adiposity phenotype groups (nominal P-values)

| | Increased Central Adiposity[a] | | Stable Adiposity[b] | | |
|---|---|---|---|---|---|
| **Metabolite** | **Mean*** | **SE** | **Mean*** | **SE** | **Nominal P-Value** |
| Meso-Erythritol | 60.77 | 3.14 | 4.12 | 0.00 | **<0.0001** |
| Fructose | 46.18 | 0.92 | 27.77 | 1.60 | **0.0022** |
| Isoleucine | 47.62 | 0.95 | 45.12 | 4.47 | 0.6392 |
| Lactic Acid | 1547.21 | 5.07 | 1422.93 | 20.75 | **0.0283** |
| Leucine | 78.74 | 2.48 | 75.45 | 9.15 | 0.7614 |
| Valine | 152.95 | 6.23 | 143.97 | 11.76 | 0.5483 |

* concentration (µmol/L)

[a] Defined as change in three indicators (weight increase >0.5kg, DXA truncal adiposity increase >200g, and waist circumference increase >0.5cm; N = 66)

[b] Defined as minimal change in three indicators (weight, DXA truncal adiposity and waist circumference; N = 16)

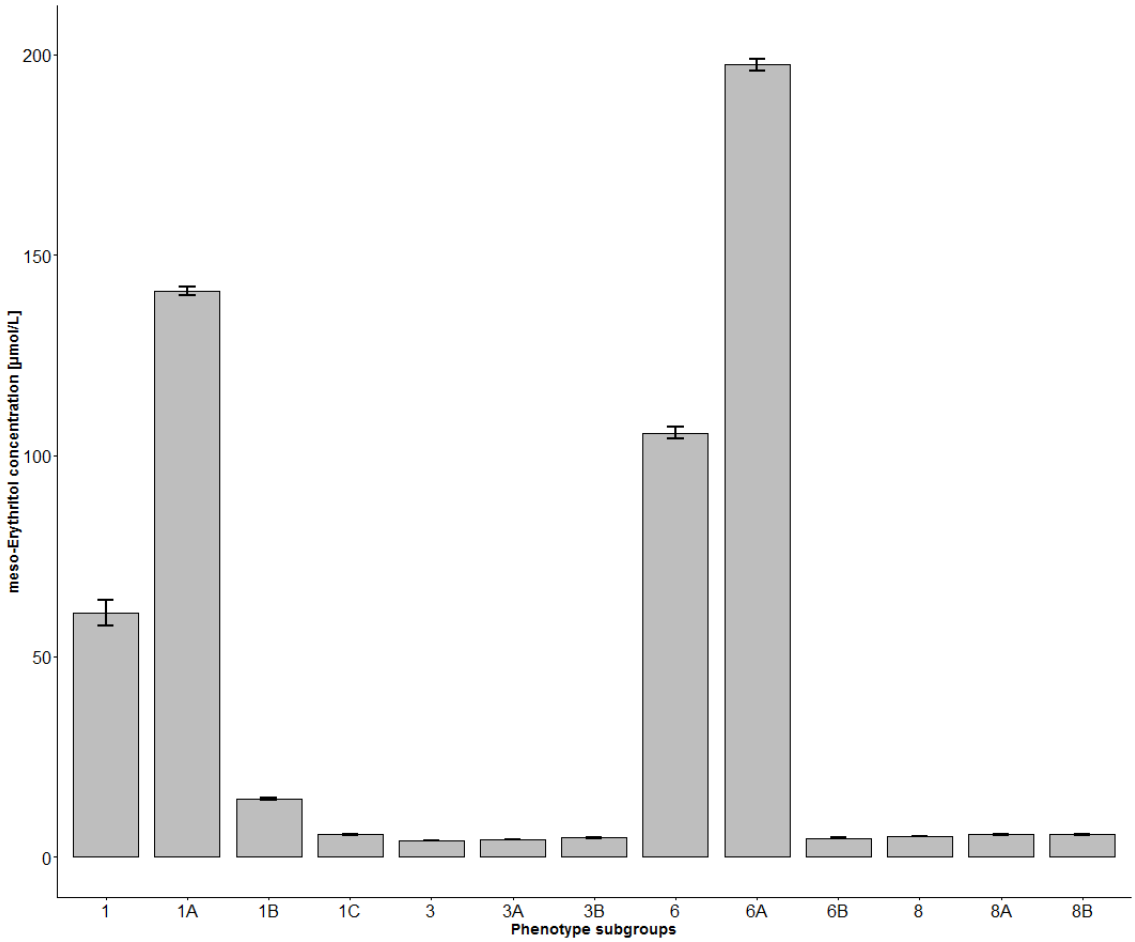
**Supplemental Table 2** Metabolite quantification* for higher baseline glycemia phenotype compared to lower glycemia phenotype (nominal P-values)

| | Higher Baseline Glycemia [a] | | Lower Baseline Glycemia [b] | | |
|---|---|---|---|---|---|
| **Metabolite** | **Mean*** | **SE** | **Mean*** | **SE** | **Nominal P-Value** |
| Meso-Erythritol | 105.62 | 1.44 | 5.12 | 0.07 | **0.0024** |
| Fructose | 42.62 | 3.24 | 76.62 | 6.67 | **0.0444** |
| Isoleucine | 52.64 | 3.49 | 42.52 | 3.21 | 0.0996 |
| Lactic Acid | 1499.10 | 18.94 | 1909.41 | 39.11 | **0.0088** |
| Leucine | 86.50 | 7.65 | 67.16 | 6.28 | 0.1458 |
| Valine | 160.28 | 9.63 | 129.15 | 5.89 | 0.0702 |

105 * concentration (µmol/L)

[a] Defined as top 25% of baseline HbA1c (N = 21, HbA1c > 5.05%; mean 5.66% [SD 0.18])

[b] Defined as bottom 10% of baseline HbA1c (N = 7, HbA1c < 4.92%; mean 4.80% [SD 0.08




**Supplemental Figure 2. Quantification of meso-erythritol by phenotype pool, and by phenotype sub-group pools, defined as follows:** 1: all incident central adiposity gain, with 1A, 1B and 1C denoting low, middle and high amount of central adiposity change (N=26, N = 24 and N = 16, respectively); 3: all stable adiposity, with 3A and 3B denoting above and below the median; 6: higher usual glycemia at baseline, with 6A and 6B denoting above and below median (median HbA1c, 5.64%); 8: lower usual glycemia at baseline, with 8A and 8B denoting above and below median (median HbA1c, 4.85%)

**Supplemental Table 3** Comparison of semi-quantitative metabolite level[a] in the central adiposity gain group versus the stable adiposity group: 107 metabolites

| Metabolite | Incident Central Adiposity[b] | Stable Adiposity[c] | P-value | FDR_Q |
|---|---|---|---|---|
| meso.Erythritol_4TMS | 0.139496073 | 0.010409447 | 0.000406654 | 0.04214742 |
| No.match..1742.91 | 0.018366709 | 0.00787385 | 0.006031768 | 0.21709209 |
| Fructose_1MeOX_ 5TMS_MP | 0.058660655 | 0.027127042 | 0.006391786 | 0.220824354 |
| No.match..1297.82[d] | 0.009708415 | 0.013542487 | 0.012021597 | 0.311492898 |
| No.match..2470.91 | 0.008893111 | 0.005977686 | 0.030840536 | 0.532324329 |
| No.match..2470.69 | 0.010048109 | 0.006363204 | 0.05856035 | 0.677577402 |
| Lactic_acid_2TMS | 2.137415816 | 1.944666965 | 0.065906523 | 0.701308765 |
| No.match..1359.44 | 0.007257791 | 0.008772946 | 0.078595585 | 0.734412555 |
| No.match..1927.70 | 0.002527556 | 0.004705395 | 0.090321451 | 0.758556559 |
| No.match..1556 | 0.020273696 | 0.030265328 | 0.092792448 | 0.763033958 |
| No.match..1952 | 0.017833177 | 0.020326106 | 0.108730486 | 0.78795354 |
| No.match..3757.78 | 0.002660148 | 0.001276173 | 0.11047771 | 0.790330145 |
| Serine_3TMS | 0.089710209 | 0.075406737 | 0.126424743 | 0.80949571 |
| Fructose_1MEOX_5TMS_BP | 0.061862848 | 0.015351731 | 0.146515321 | 0.828583405 |
| Alanine_2TMS | 0.703988982 | 0.643950089 | 0.152558704 | 0.833482526 |
| No.match..1103.63 | 0.030083763 | 0.074473905 | 0.158136544 | 0.837718142 |
| No.match..1220.07 | 0.006162478 | 0.007848049 | 0.173430414 | 0.848113445 |
| Urea_2TMS | 4.499865651 | 4.301155398 | 0.179506066 | 0.85181268 |
| No.match..1817.73 | 0.078535378 | 0.022117578 | 0.182770334 | 0.853711052 |
| Threonine_3TMS | 0.096213376 | 0.084908934 | 0.183529635 | 0.854144133 |
| No.match..1971.55 | 0.035430913 | 0.055609066 | 0.19166511 | 0.85859432 |
| No.match..1255.79 | 0.074897923 | 0.166373884 | 0.20778787 | 0.866496672 |
| No.match..1259.59 | 0.002544887 | 0.003317306 | 0.210790806 | 0.867849402 |
| No.match..1543.65 | 0.004371679 | 0.001089337 | 0.220027014 | 0.871802649 |
| No.match..1913.81 | 6.683909614 | 7.614975804 | 0.220137626 | 0.871848191 |
| Octadecanoic_acid_1TMS | 0.173289528 | 0.189346561 | 0.220514664 | 0.872003122 |
| Glycerol_3TMS | 0.152588868 | 0.159917553 | 0.220786499 | 0.872114529 |
| No.match..1732.80 | 0.005219795 | 0.00914687 | 0.225121127 | 0.874267316 |
| Unknown_coeluting_ with_Glutaconic_acid_2TMS | 0.003941668 | 0.005736521 | 0.231087842 | 0.87711481 |
| Methionine_2TMS | 0.015884144 | 0.013413046 | 0.238569665 | 0.880508133 |
| No.match..2278.34 | 0.102984536 | 0.095764221 | 0.268300745 | 0.892323562 |
| Glycine_3TMS | 0.107651634 | 0.149645806 | 0.293269105 | 0.9005795 |

| Metabolite | Incident Central Adiposity[b] | Stable Adiposity[c] | P-value | FDR_Q |
|---|---|---|---|---|
| No.match..1428.03 | 0.00382517 | 0.007304264 | 0.300068646 | 0.902612964 |
| Glucose_5TMS_BP1 | 5.144867074 | 5.726094588 | 0.300905066 | 0.902857372 |
| No.match..1141.73 | 0.064142159 | 0.067957048 | 0.321048039 | 0.908393902 |
| No.match..2187.44 | 0.283715192 | 0.298809195 | 0.325318953 | 0.909487688 |
| Lysine_4TMS | 0.036956918 | 0.049689613 | 0.32539239 | 0.909506267 |
| No.match..1611.12 | 0.014645364 | 0.011023369 | 0.331844041 | 0.911109239 |
| Carbonic_acid_1MeOX _2TMS | 3.305949579 | 2.672350607 | 0.357524827 | 0.916964025 |
| Ethylenediaminetetraacetic acid_.EDTA._4TMS | 18.19170867 | 19.66327479 | 0.358795629 | 0.917233785 |
| Octadecenoic_acid_1TMS | 0.249588219 | 0.240602442 | 0.382553184 | 0.921972723 |
| No.match..1394.21 | 0.007010714 | 0.006102799 | 0.38305064 | 0.922066158 |
| No.match..1515 | 0.052394032 | 0.06414949 | 0.400050409 | 0.925129935 |
| Phosphoric_acid_3TMS | 3.452282316 | 3.62017775 | 0.40238229 | 0.92553151 |
| Isoleucine_2TMS | 0.117264776 | 0.107856535 | 0.427385386 | 0.929581314 |
| No.match..1492.69 | 0.00394002 | 0.009280005 | 0.436906531 | 0.93101002 |
| No.match..2009.52 | 0.009070961 | 0.006339202 | 0.437300324 | 0.931067864 |
| No.match..1619.47 | 0.024857077 | 0.02845617 | 0.472368147 | 0.935857025 |
| No.match..1559.00 | 0.002834278 | 0.003276818 | 0.477997381 | 0.936564499 |
| Leucine_2TMS | 0.197698085 | 0.183013859 | 0.49557033 | 0.938675981 |
| No.match..1309.23 | 0.002066315 | 0.004494198 | 0.519013724 | 0.941283291 |
| No.match..1737.67 | 0.02796783 | 0.02312219 | 0.525422007 | 0.94195786 |
| No.match..1585.87 | 0.014212769 | 0.01343711 | 0.52824357 | 0.942249983 |
| No.match..1137.45 | 0.041214212 | 0.038236764 | 0.53070704 | 0.942502637 |
| No.match..2749.80 | 0.014913957 | 0.010905572 | 0.533446336 | 0.942780998 |
| No.match..1178.27 | 0.045968212 | 0.038928921 | 0.533944153 | 0.942831295 |
| X5.hydroxypentanoic_ acid_2TMS | 0.021708559 | 0.020057396 | 0.545322052 | 0.943957247 |
| Glucose_1MEOX_5TMS _BP | 2.117060854 | 1.973315313 | 0.57241421 | 0.946467737 |
| Mannose_1MeOX_5TMS _MP | 0.057870992 | 0.054780873 | 0.57886809 | 0.947032962 |
| No.match..1211.26 | 0.006796954 | 0.007897809 | 0.580239225 | 0.947151512 |
| No.match..2970.22 | 0.005584235 | 0.004177439 | 0.582852299 | 0.947375976 |
| No.match..1825.62 | 0.277552994 | 0.296783221 | 0.609616017 | 0.949569796 |
| No.match..1198.43 | 0.009475781 | 0.008714261 | 0.617432547 | 0.95017642 |
| No.match..2335.24 | 0.110638152 | 0.115765777 | 0.620992852 | 0.950447917 |

| Metabolite | Incident Central Adiposity[b] | Stable Adiposity[c] | P-value | FDR_Q |
|---|---|---|---|---|
| No.match..2331.37 | 0.001848896 | 0.00200985 | 0.625442451 | 0.950783096 |
| Hexadecanoic_acid_ 1TMS | 0.732127602 | 0.706137889 | 0.627799092 | 0.950958786 |
| No.match..1164.14 | 0.060793921 | 0.054255013 | 0.62886028 | 0.95103749 |
| N.Carboxy.L.valine_3TMS | 0.015696078 | 0.014773345 | 0.638639858 | 0.951751084 |
| No.match..2147.51 | 0.016444516 | 0.017715983 | 0.648832739 | 0.95247303 |
| No.match..2465.13 | 0.012469217 | 0.015176386 | 0.654160145 | 0.952841831 |
| No.match..1872.96 | 0.040648823 | 0.03709986 | 0.660746169 | 0.953289927 |
| Valine_2TMS | 0.426952407 | 0.405912012 | 0.662800133 | 0.953427936 |
| Glucose_1MEOX_5TMS_MP | 11.01314878 | 10.4209253 | 0.680085354 | 0.954557834 |
| Phenylalanine_2TMS | 0.013757549 | 0.013003585 | 0.696262422 | 0.955566731 |
| No.match..1175.43 | 0.13272981 | 0.13614129 | 0.697788218 | 0.955659582 |
| No.match..2293.86 | 0.01757471 | 0.014247482 | 0.722729211 | 0.957124139 |
| No.match..2408.36 | 0.021445781 | 0.017839503 | 0.734850231 | 0.957801513 |
| No.match..2377.12 | 0.004946601 | 0.004693921 | 0.74128993 | 0.958152757 |
| Aspartic_acid_3TMS | 0.020265696 | 0.019260392 | 0.747662529 | 0.958494632 |
| No.match..1811.69 | 0.025497872 | 0.020362551 | 0.754041562 | 0.958831303 |
| N.Carboxy.L.threonine_4TMS | 0.00792922 | 0.007703445 | 0.75972577 | 0.959126734 |
| No.match..2836.11 | 0.011815793 | 0.010380529 | 0.764845346 | 0.959389213 |
| Glycine_2TMS | 0.011303574 | 0.009905016 | 0.76649694 | 0.959473172 |
| No.match..1894.58 | 0.194676006 | 0.183706283 | 0.771614938 | 0.959731156 |
| Pyroglutamic_acid_2TMS | 0.08026979 | 0.083075189 | 0.77608874 | 0.959953992 |
| No.match..1237.02 | 0.002372468 | 0.002569758 | 0.780256162 | 0.96015936 |
| No.match..1679.44 | 0.051172303 | 0.044346624 | 0.786589876 | 0.960467479 |
| No.match..2058.85 | 0.030799796 | 0.027476587 | 0.792949779 | 0.960772114 |
| No.match..3076.59 | 0.002934196 | 0.002532108 | 0.800791511 | 0.961141325 |
| No.match..2720.68 | 0.012084723 | 0.010652772 | 0.814908639 | 0.961788773 |
| No.match..1526.95 | 0.003933045 | 0.003784695 | 0.818692732 | 0.961958671 |
| No.match..2175.27 | 0.02651608 | 0.023140204 | 0.819802161 | 0.962008196 |
| No.match..2637.59 | 0.005240751 | 0.004748597 | 0.824102371 | 0.962198946 |
| No.match..1591.58 | 0.021762799 | 0.018639444 | 0.825294254 | 0.962251477 |
| No.match..2524.75 | 0.013264691 | 0.01212948 | 0.843021509 | 0.963015904 |
| Cholesterol_1TMS | 1.641734621 | 1.682714522 | 0.844575687 | 0.96308145 |
| No.match..2860.30 | 0.013687037 | 0.012465374 | 0.853959039 | 0.963472295 |
| No.match..2365.76 | 0.010181634 | 0.009265513 | 0.855088227 | 0.963518772 |
| No.match..2950.24 | 0.005970379 | 0.005523559 | 0.855110029 | 0.963519668 |

| Metabolite | Incident Central Adiposity[b] | Stable Adiposity[c] | P-value | FDR_Q |
|---|---|---|---|---|
| N.Carboxy.L.proline_2TMS | 0.07164912 | 0.070451765 | 0.898221586 | 0.965209683 |
| Myo.inositol_6TMS | 0.075513883 | 0.077124301 | 0.90671956 | 0.965524505 |
| No.match..2023.20 | 0.004191801 | 0.004307858 | 0.936782375 | 0.966593918 |
| No.match..1779.99 | 0.051347704 | 0.050656906 | 0.944173807 | 0.966846766 |
| No.match..2120.10 | 0.009989034 | 0.009666347 | 0.960071613 | 0.967377841 |
| No.match..2204.33 | 0.005886845 | 0.005735533 | 0.963365016 | 0.967485738 |
| N.Carboxyalanine_3TMS | 0.037862772 | 0.038002594 | 0.984066577 | 0.968147946 |
| No.match..2245.01 | 0.015321581 | 0.015192203 | 0.989305044 | 0.968311261 |

[a] metabolite semi-quantitative findings are reported for the optimized assay, which validated results based on the non-targeted assay

125 [b]Defined as change in three indicators (weight increase >0.5kg, DXA truncal adiposity increase >200g, and waist circumference increase >0.5cm; N = 66)

[c]Defined as minimal change in three indicators (weight, DXA truncal adiposity and waist circumference; N = 16)

[e]unidentified metabolites represented with their corresponding retention indices

130 **Supplemental Table 4** Comparison of semi-quantitative metabolite level[a] in the HbA1c groups: 107 metabolites

| Metabolite | Higher Baseline Glycemia [b] | Lower Baseline Glycemia [c] | P-value | FDR_Q |
|---|---|---|---|---|
| meso.Erythritol_4TMS | 0.276762442 | 0.012386419 | 1.51E-06 | 0.000147993 |
| Fructose_1MeOX_5TMS_MP | 0.050414727 | 0.11619351 | 0.000563605 | 0.027700977 |
| Octadecenoic_acid_1TMS | 0.203311778 | 0.283717496 | 0.022664541 | 0.413921516 |
| Lactic_acid_2TMS | 1.987027959 | 2.720958789 | 0.023286837 | 0.417892106 |
| Glycerol_3TMS | 0.139987298 | 0.181361917 | 0.025958582 | 0.433479341 |
| Valine_2TMS | 0.435651286 | 0.34967887 | 0.042994997 | 0.497576824 |
| No.match..1175.43[d] | 0.09426782 | 0.153913294 | 0.046796433 | 0.506853505 |
| No.match..2278.34 | 0.095865156 | 0.116823113 | 0.047097849 | 0.507538423 |
| Leucine_2TMS | 0.215698348 | 0.158546066 | 0.047502143 | 0.508446306 |
| Isoleucine_2TMS | 0.125710946 | 0.096869603 | 0.062044389 | 0.534555076 |
| No.match..2335.24 | 0.134164308 | 0.105980382 | 0.063303965 | 0.536345107 |
| No.match..2749.80 | 0.013048695 | 0.014888148 | 0.074637373 | 0.550123901 |
| Phosphoric_acid_3TMS | 3.697251187 | 3.379745631 | 0.0816438 | 0.556982769 |
| Fructose_1MEOX_5TMS_BP | 0.045795529 | 0.128886152 | 0.087876598 | 0.562279572 |
| No.match..3757.78 | 0.003376407 | 0.004985906 | 0.091363696 | 0.564965687 |
| No.match..1742.91 | 0.010686064 | 0.031076416 | 0.092039825 | 0.565465769 |
| Hexadecanoic_acid_1TMS | 0.647573224 | 0.818942281 | 0.10578677 | 0.591264482 |
| Mannose_1MeOX_5TMS_MP | 0.067451217 | 0.053081991 | 0.115892451 | 0.607444474 |
| Phenylalanine_2TMS | 0.016819233 | 0.0133391 | 0.123028537 | 0.617708075 |
| Glucose_1MEOX_5TMS_MP | 11.85849871 | 10.09830935 | 0.148996319 | 0.648733213 |

| Metabolite | Higher Baseline Glycemia [b] | Lower Baseline Glycemia [c] | P-value | FDR_Q |
|---|---|---|---|---|
| No.match..2293.86 | 0.016522209 | 0.01923787 | 0.155573689 | 0.655326091 |
| Pyroglutamic_acid_2TMS | 0.103519446 | 0.0820215 | 0.157282413 | 0.656969211 |
| No.match..1927.70 | 0.004096564 | 0.00779712 | 0.160665473 | 0.660142433 |
| Methionine_2TMS | 0.018531292 | 0.015027572 | 0.181581531 | 0.677671273 |
| Glucose_1MEOX_5TMS_BP | 2.282966017 | 1.943518326 | 0.188504306 | 0.682785755 |
| No.match..1137.45 | 0.042759133 | 0.057518011 | 0.191457632 | 0.684877098 |
| Octadecanoic_acid_1TMS | 0.167776087 | 0.190514485 | 0.193791391 | 0.686493349 |
| No.match..1309.23 | 0.003236505 | 0.001362909 | 0.193858715 | 0.686539508 |
| No.match..1952 | 0.020075439 | 0.016528468 | 0.210937113 | 0.704417008 |
| No.match..1141.73 | 0.05738698 | 0.064243101 | 0.211069994 | 0.704548116 |
| No.match..1737.67 | 0.021851926 | 0.034845997 | 0.21331463 | 0.706745343 |
| No.match..2637.59 | 0.005093486 | 0.00584431 | 0.273664787 | 0.755610872 |
| No.match..1164.14 | 0.043906318 | 0.058858485 | 0.303756341 | 0.774358362 |
| No.match..1515 | 0.049609262 | 0.053756967 | 0.308685342 | 0.77715845 |
| No.match..1825.62 | 0.245087007 | 0.297210744 | 0.316403691 | 0.78140617 |
| Cholesterol_1TMS | 1.652561066 | 1.745359963 | 0.339207572 | 0.793060504 |
| N.Carboxyalanine_3TMS | 0.031207567 | 0.041792956 | 0.342347038 | 0.794568374 |
| No.match..2524.75 | 0.013172658 | 0.015703177 | 0.354990092 | 0.800424677 |
| Aspartic_acid_3TMS | 0.023250875 | 0.027701392 | 0.357272143 | 0.801446339 |

| Metabolite | Higher Baseline Glycemia [b] | Lower Baseline Glycemia [c] | P-value | FDR_Q |
|---|---|---|---|---|
| No.match..1817.73 | 0.027105933 | 0.268323683 | 0.362367536 | 0.803690195 |
| Urea_2TMS | 4.417762063 | 4.14145831 | 0.364719969 | 0.804709112 |
| No.match..2187.44 | 0.291234094 | 0.270196459 | 0.376853694 | 0.809801033 |
| No.match..1394.21 | 0.006803274 | 0.00783614 | 0.388711579 | 0.81452703 |
| No.match..1559.00 | 0.001768333 | 0.002847565 | 0.395585896 | 0.817160794 |
| No.match..2175.27 | 0.026541317 | 0.030423476 | 0.407612604 | 0.821593054 |
| No.match..2058.85 | 0.028172338 | 0.032368749 | 0.441241424 | 0.832918349 |
| Serine_3TMS | 0.091177637 | 0.082604578 | 0.445511559 | 0.83425436 |
| X5.hydroxypentanoic_ acid_2TMS | 0.046558497 | 0.02049241 | 0.445944553 | 0.83438864 |
| No.match..2860.30 | 0.014453606 | 0.016843246 | 0.456172914 | 0.837498571 |
| No.match..1237.02 | 0.003029198 | 0.003874599 | 0.464840129 | 0.840043848 |
| No.match..1556 | 0.022778435 | 0.021037972 | 0.510529419 | 0.852243809 |
| No.match..1971.55 | 0.04274086 | 0.031727769 | 0.513847126 | 0.853057629 |
| No.match..2970.22 | 0.005788045 | 0.006442427 | 0.519137808 | 0.854337026 |
| No.match..2204.33 | 0.005708534 | 0.004680873 | 0.535687403 | 0.858199033 |
| No.match..1297.82 | 0.011055293 | 0.012321708 | 0.553236941 | 0.862076782 |
| Ethylenediaminetetraacetic _acid_.EDTA._4TMS | 17.58953746 | 18.30727899 | 0.580417191 | 0.867680943 |
| Glucose_5TMS_BP1 | 4.433300535 | 4.71811155 | 0.583883752 | 0.868363119 |

| Metabolite | Higher Baseline Glycemia [b] | Lower Baseline Glycemia [c] | P-value | FDR_Q |
|---|---|---|---|---|
| No.match..1492.69 | 0.007209866 | 0.00932569 | 0.592301164 | 0.869990646 |
| No.match..1732.80 | 0.008648679 | 0.009422018 | 0.597075382 | 0.87089599 |
| Lysine_4TMS | 0.046381968 | 0.03907726 | 0.606305457 | 0.87261103 |
| No.match..2377.12 | 0.005070634 | 0.005436552 | 0.608452541 | 0.873003467 |
| No.match..1259.59 | 0.00215093 | 0.002472524 | 0.615817374 | 0.874331409 |
| No.match..1611.12 | 0.013542077 | 0.015035363 | 0.625177894 | 0.875979636 |
| No.match..2465.13 | 0.017455623 | 0.023932479 | 0.63004591 | 0.876819837 |
| No.match..2470.69 | 0.009655722 | 0.0113154 | 0.630106478 | 0.876830219 |
| N.Carboxy.L.proline_2TMS | 0.0626688 | 0.069418154 | 0.635487205 | 0.877745611 |
| No.match..1591.58 | 0.020599228 | 0.025856306 | 0.64139996 | 0.87873595 |
| No.match..1894.58 | 0.126873982 | 0.156471292 | 0.648451885 | 0.879896312 |
| No.match..1679.44 | 0.054022576 | 0.060055364 | 0.655919565 | 0.881101118 |
| No.match..1526.95 | 0.004138469 | 0.004519227 | 0.659538993 | 0.881676408 |
| No.match..1543.65 | 0.003728436 | 0.002838009 | 0.662646515 | 0.882165909 |
| Glycine_3TMS | 0.152201718 | 0.124030279 | 0.685315327 | 0.885617788 |
| No.match..1872.96 | 0.027263203 | 0.03224095 | 0.687523695 | 0.885943286 |
| No.match..2245.01 | 0.015493542 | 0.0186071 | 0.694830825 | 0.887007223 |
| No.match..2836.11 | 0.01053692 | 0.012497251 | 0.703537645 | 0.888249326 |

| Metabolite | Higher Baseline Glycemia [b] | Lower Baseline Glycemia [c] | P-value | FDR_Q |
|---|---|---|---|---|
| No.match..1779.99 | 0.040889217 | 0.044377215 | 0.704552626 | 0.888392347 |
| No.match..2408.36 | 0.021062069 | 0.022579173 | 0.717337156 | 0.890162965 |
| No.match..1811.69 | 0.028296822 | 0.026660073 | 0.72208455 | 0.890806244 |
| No.match..1619.47 | 0.022700106 | 0.020019138 | 0.723029902 | 0.890933442 |
| No.match..2365.76 | 0.009200905 | 0.011107566 | 0.732263968 | 0.892160486 |
| No.match..2147.51 | 0.013738259 | 0.01463906 | 0.734337135 | 0.892432187 |
| Threonine_3TMS | 0.104160714 | 0.101715279 | 0.756344423 | 0.895234173 |
| No.match..3076.59 | 0.003209314 | 0.003285 | 0.785841062 | 0.898768488 |
| No.match..1255.79 | 0.111221205 | 0.088476364 | 0.787183969 | 0.89892373 |
| No.match..2470.91 | 0.008590949 | 0.009546804 | 0.791351556 | 0.89940249 |
| No.match..2009.52 | 0.00697263 | 0.007768269 | 0.797273336 | 0.900075019 |
| No.match..2120.10 | 0.010327734 | 0.01197815 | 0.804345313 | 0.900866486 |
| No.match..1211.26 | 0.007098945 | 0.007672199 | 0.831246919 | 0.903765997 |
| No.match..2023.20 | 0.002609373 | 0.002768516 | 0.833609427 | 0.904012552 |
| N.Carboxy.L.valine_3TMS | 0.013616099 | 0.013080252 | 0.852401225 | 0.9059296 |
| N.Carboxy.L.threonine_4TMS | 0.006273651 | 0.006647296 | 0.859583519 | 0.90664223 |
| No.match..2950.24 | 0.0064123 | 0.006087734 | 0.868631604 | 0.907524761 |

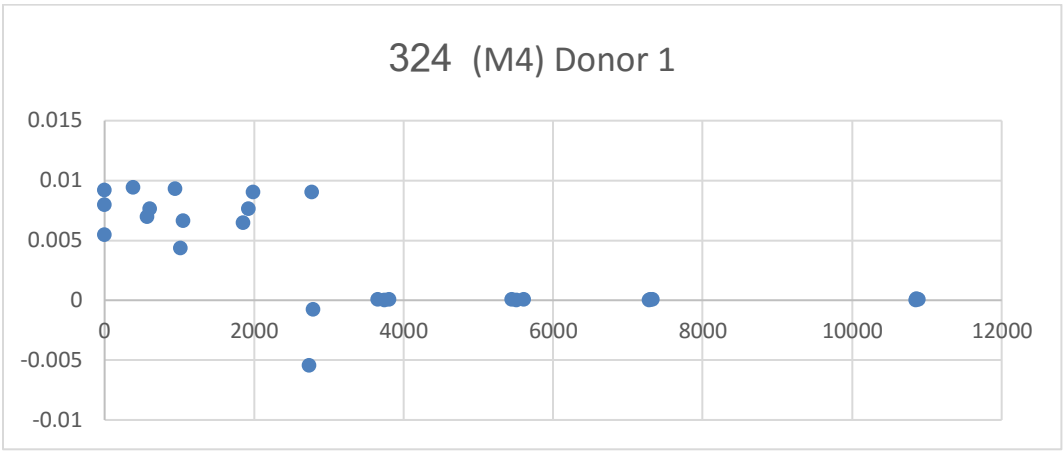
| Metabolite | Higher Baseline Glycemia [b] | Lower Baseline Glycemia [c] | P-value | FDR_Q |
|---|---|---|---|---|
| No.match..1198.43 | 0.008482761 | 0.008724508 | 0.87463704 | 0.908101364 |
| No.match..2720.68 | 0.012897103 | 0.013773827 | 0.874747444 | 0.908111897 |
| Unknown_coeluting_ with_Glutaconic_acid_2TMS | 0.004930411 | 0.005193494 | 0.884911024 | 0.909071307 |
| No.match..1178.27 | 0.039731085 | 0.040574359 | 0.897921791 | 0.910270629 |
| No.match..1220.07 | 0.006892838 | 0.007223481 | 0.900969122 | 0.910546971 |
| No.match..1428.03 | 0.005662198 | 0.006175462 | 0.916644838 | 0.911942017 |
| No.match..2331.37 | 0.002915579 | 0.002869867 | 0.943286894 | 0.91421576 |
| No.match..1913.81 | 6.01701924 | 6.059394679 | 0.946363109 | 0.914470758 |
| Alanine_2TMS | 0.70983466 | 0.707727106 | 0.953421869 | 0.91505019 |
| No.match..1103.63 | 0.048607381 | 0.051471787 | 0.957609782 | 0.915390268 |
| Carbonic_acid_1MeOX _2TMS | 3.108320624 | 3.078816988 | 0.957716573 | 0.915398904 |
| Glycine_2TMS | 0.015626795 | 0.015821096 | 0.960624888 | 0.915633427 |
| No.match..1585.87 | 0.015534807 | 0.015358718 | 0.96252642 | 0.915786062 |
| Myo.inositol_6TMS | 0.086436941 | 0.085948902 | 0.972516997 | 0.916579015 |
| No.match..1359.44 | 0.007816233 | 0.007905812 | 0.979924979 | 0.917157412 |

[a] metabolite semi-quantitative findings are reported for the optimized assay, which validated results based on the non-targeted assay

[b]Defined as top 25% of baseline HbA1c (N = 21, HbA1c > 5.05%; mean 5.66% [SD 0.18])

[c]Defined as bottom 10% of baseline HbA1c (N = 7, HbA1c < 4.92%; mean 4.80% [SD 0.084])

[d]unidentified metabolites represented with their corresponding retention indices


324 (M4) Donor 1
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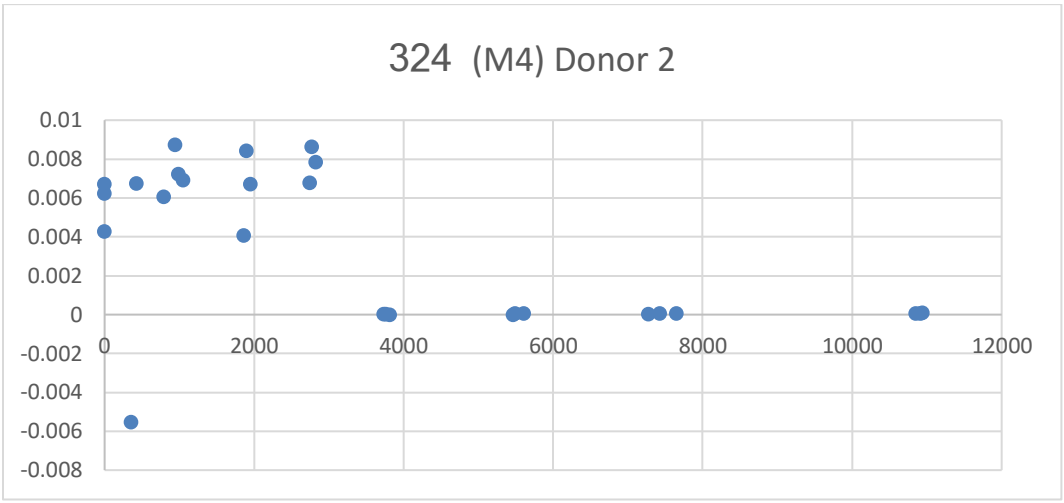
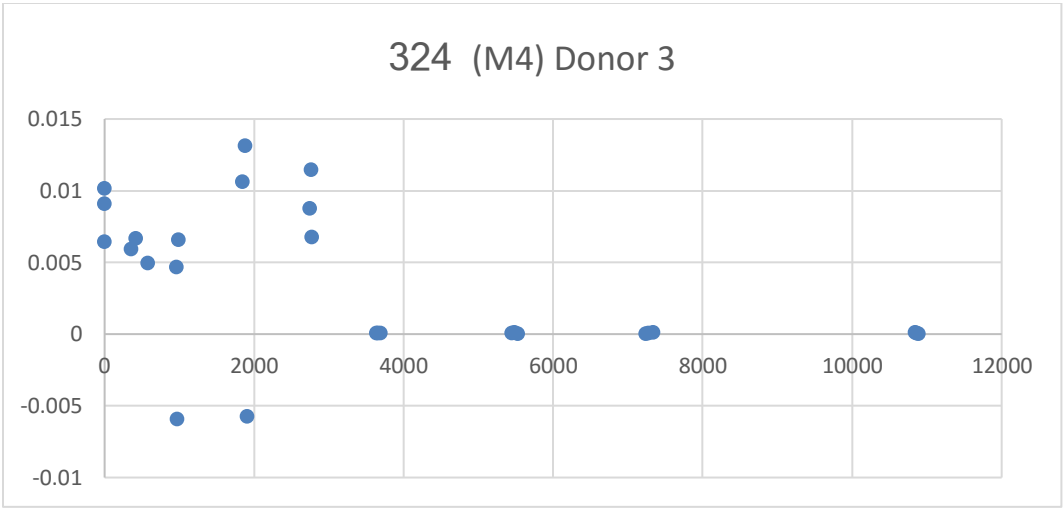
0.01
0.005
0
-0.005
-0.01
0
2000
4000
6000
8000
10000
12000


324 (M4) Donor 2
0.01
0.008
0.006
0.004
0.002
0
-0.002
-0.004
-0.006
-0.008
0
2000
4000
6000
8000
10000
12000


324 (M4) Donor 3
0.015
0.01
0.005
0
-0.005
-0.01
0
2000
4000
6000
8000
10000
12000

**Supplemental Figure 3.** M4 mass isotopomer of erythritol in human plasma (for 3 donors) after oral intake of 2g of a [U13C6]-glucose tracer. 45 minutes (2700 s) post intake, 50g of unlabeled erythritol were administered.