## Sheet1
| Unnamed: 0 | Table S7. Path analysis demonstrating the relationship between macronutrient intake with BMIz and HOMA-CP through metabolome clusters, adjusting for age, sex and puberty onset. Association between energy-adjusted fat and carbohydrate intake (mean 0, standard deviation 1) and metabolome clusters (β1), adjusting for age, sex and puberty onset. Association between metabolome clusters and BMIz and HOMA-CP (β2), adjusting for sex, age and puberty onset. Unadjusted p-value<0.05 highlighted in red. Path analysis demonstrating the indirect relationship between macronutrient intake with BMIz and HOMA-CP through metabolome clusters (Sobel testing, Path 2). Unadjusted p-value<0.05 highlighted in red. AC, acylcarnitine; BCAA, branched chain amino acid; BMIz, BMI z-score; Cer, ceramide; DG, diglyceride; DiC, dicarboxylic group; FA, fatty acid; HOMA-CP, homeostatic model assessment of insulin resistance using C-peptide; keto, ketone; LC, long chain; LysoPC, lysophosphatidylcholine; LysoPE, lysophosphatidylethanolamine; MC, medium chain; OH, hydroxyl group; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin; StdErr, standard error; TG, triglyceride; VLC, very long chain. | Unnamed: 2 | Unnamed: 3 | Unnamed: 4 | Unnamed: 5 | Unnamed: 6 | Unnamed: 7 | Unnamed: 8 | Unnamed: 9 | Unnamed: 10 | Unnamed: 11 | Unnamed: 12 | Unnamed: 13 | Unnamed: 14 | Unnamed: 15 | Unnamed: 16 | Unnamed: 17 | Unnamed: 18 | Unnamed: 19 | Unnamed: 20 | Unnamed: 21 | Unnamed: 22 | Unnamed: 23 | Unnamed: 24 | Unnamed: 25 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN |
| Cluster Number | Type of metabolites | Regression Analysis | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | NaN | Sobel Testing | NaN | NaN | NaN | NaN | NaN | NaN | NaN |
| NaN | NaN | Fat intake and metabolome cluster | NaN | NaN | NaN | Carbohydrate intake and metabolome cluster | NaN | NaN | NaN | Metabolome cluster and BMIz | NaN | NaN | NaN | Metabolome cluster and HOMA-CP | NaN | NaN | NaN | Fat intake and BMIz | NaN | Fat intake and HOMA-CP | NaN | Carbohydrate intake and BMIz | NaN | Carbohydrate intake and HOMA-CP | NaN |
| NaN | NaN | β1 | StdErr | z-value | p-value | β1 | StdErr | z-value | p-value | β2 | StdErr | z-value | p-value | β2 | StdErr | z-value | p-value | t-statistic | p-value | t-statistic | p-value | t-statistic | p-value | t-statistic | p-value |
| 1 | LC and VLC-FA (DiC),VLC-FA, PC/PE | 0.01 | 0.038 | 0.268 | 0.789 | -0.01 | 0.038 | -0.254 | 0.799 | -0.148 | 0.164 | -0.901 | 0.368 | 0.118 | 0.257 | 0.459 | 0.646 | -0.256877 | 0.797274 | 0.231438 | 0.816975 | 0.244471 | 0.806866 | -0.222241 | 0.824126 |
| 2 | LC-FA | 0.033 | 0.065 | 0.516 | 0.606 | -0.049 | 0.065 | -0.757 | 0.449 | 0.12 | 0.092 | 1.312 | 0.189 | -0.052 | 0.145 | -0.362 | 0.717 | 0.480197 | 0.631088 | -0.296346 | 0.766966 | -0.655686 | 0.512026 | 0.32658 | 0.743986 |
| 3 | LC-FA | 0.09 | 0.065 | 1.377 | 0.169 | -0.093 | 0.065 | -1.435 | 0.151 | 0.068 | 0.093 | 0.735 | 0.462 | -0.017 | 0.146 | -0.116 | 0.908 | 0.648412 | 0.516718 | -0.115591 | 0.907977 | -0.654182 | 0.512995 | 0.115623 | 0.907951 |
| 4 | Cer | 0.022 | 0.065 | 0.339 | 0.735 | -0.027 | 0.065 | -0.422 | 0.673 | 0.015 | 0.092 | 0.168 | 0.866 | 0.024 | 0.144 | 0.168 | 0.866 | 0.150529 | 0.880347 | 0.150529 | 0.880347 | -0.156086 | 0.875965 | -0.156086 | 0.875965 |
| 5 | TG, Cer | 0.036 | 0.062 | 0.582 | 0.56 | -0.041 | 0.062 | -0.67 | 0.503 | 0.003 | 0.096 | 0.035 | 0.972 | -0.012 | 0.151 | -0.081 | 0.936 | 0.034937 | 0.97213 | -0.080227 | 0.936057 | -0.034952 | 0.972118 | 0.080414 | 0.935908 |
| 6 | VLC-FA, VLC-FA (DiC), VLC-FA (OH) | 0.025 | 0.062 | 0.393 | 0.694 | -0.024 | 0.062 | -0.383 | 0.702 | -0.108 | 0.096 | -1.127 | 0.26 | 0.055 | 0.151 | 0.365 | 0.715 | -0.371085 | 0.710574 | 0.267445 | 0.789126 | 0.362632 | 0.71688 | -0.264228 | 0.791604 |
| 7 | LysoPE, FA | 0.01 | 0.062 | 0.164 | 0.87 | -0.021 | 0.062 | -0.337 | 0.736 | 0.032 | 0.096 | 0.333 | 0.739 | -0.021 | 0.062 | -0.333 | 0.739 | 0.147125 | 0.883033 | -0.147125 | 0.883033 | -0.236868 | 0.812759 | 0.236868 | 0.812759 |
| 8 | LC-FA, odd-chain LC-FA, Cer | 0.037 | 0.032 | 1.174 | 0.24 | -0.039 | 0.032 | -1.235 | 0.217 | 0.315 | 0.202 | 1.557 | 0.119 | -0.556 | 0.319 | -1.744 | 0.081 | 0.937391 | 0.348558 | -0.973896 | 0.330108 | -0.967578 | 0.333255 | 1.007881 | 0.313512 |
| 9 | bile acids, glucose, PS | -0.005 | 0.009 | -0.577 | 0.564 | 0.007 | 0.01 | 0.753 | 0.452 | 0.933 | 1.173 | 0.795 | 0.427 | -0.941 | 1.628 | -0.578 | 0.563 | -0.466971 | 0.640521 | 0.408354 | 0.683014 | 0.546697 | 0.584587 | -0.458499 | 0.646594 |
| 10 | malate intermediates, PA, MC-FA (DiC) | 0.094 | 0.041 | 2.319 | 0.02 | -0.088 | 0.041 | -2.168 | 0.03 | 0.063 | 0.151 | 0.414 | 0.679 | 0.235 | 0.238 | 0.99 | 0.322 | 0.407556 | 0.683599 | 0.910501 | 0.362558 | -0.406652 | 0.684264 | -0.90055 | 0.367828 |
| 11 | Glucose metabolites, BCAA metabolites, xanthine | 0.114 | 0.066 | 1.715 | 0.086 | -0.104 | 0.066 | -1.562 | 0.118 | 0.063 | 0.091 | 0.695 | 0.487 | 0.056 | 0.143 | 0.392 | 0.695 | 0.644119 | 0.519498 | 0.382145 | 0.702354 | -0.634982 | 0.52544 | -0.38021 | 0.70379 |
| 12 | Glucose metabolites, acetyl-amino acids | 0.03 | 0.038 | 0.8 | 0.424 | -0.028 | 0.038 | -0.752 | 0.452 | 0.105 | 0.179 | 0.584 | 0.559 | -0.026 | 0.281 | -0.092 | 0.927 | 0.471689 | 0.637149 | -0.091398 | 0.927177 | -0.461246 | 0.644622 | 0.091319 | 0.927239 |
| 13 | MC-FA (DiC) | 0.159 | 0.054 | 2.936 | 0.003 | -0.166 | 0.054 | -3.074 | 0.002 | 0.071 | 0.108 | 0.66 | 0.509 | -0.023 | 0.17 | -0.133 | 0.894 | 0.643931 | 0.51962 | -0.132864 | 0.894301 | -0.645294 | 0.518737 | 0.132876 | 0.894292 |
| 14 | MC-FA (DiC OH), LC-FA (DiC, OH) | 0.179 | 0.055 | 3.254 | 0.001 | -0.18 | 0.055 | -3.274 | 0.001 | 0.15 | 0.107 | 1.407 | 0.159 | 0.178 | 0.168 | 1.062 | 0.288 | 1.291444 | 0.19655 | 1.009592 | 0.312691 | -1.292685 | 0.19612 | -1.010184 | 0.312407 |
| 15 | odd-chain MC-FA (DiC) | 0.131 | 0.055 | 2.391 | 0.017 | -0.114 | 0.055 | -2.081 | 0.037 | 0.201 | 0.108 | 1.868 | 0.062 | 0.361 | 0.169 | 2.133 | 0.033 | 1.47202 | 0.141015 | 1.591687 | 0.111455 | -1.3901 | 0.164499 | -1.489534 | 0.136347 |
| 16 | BCAA, BCAA metabolite | 0.075 | 0.034 | 2.216 | 0.027 | -0.067 | 0.033 | -1.999 | 0.046 | 0.312 | 0.23 | 1.357 | 0.175 | 0.282 | 0.354 | 0.795 | 0.427 | 1.157258 | 0.247167 | 0.748302 | 0.454278 | -1.122745 | 0.261546 | -0.738724 | 0.460075 |
| 17 | homocysteine, phenylalanine metabolite | 0.033 | 0.066 | 0.493 | 0.622 | -0.017 | 0.066 | -0.256 | 0.798 | 0.284 | 0.109 | 2.599 | 0.009 | 0.155 | 0.168 | 0.923 | 0.356 | 0.484363 | 0.628128 | 0.434856 | 0.663667 | -0.254767 | 0.798903 | -0.246687 | 0.80515 |
| 18 | BCAA, BCAA metabolites, aromatic amino acids, methionine | 0.067 | 0.036 | 1.879 | 0.06 | -0.062 | 0.036 | -1.724 | 0.085 | 0.467 | 0.174 | 2.683 | 0.007 | 0.487 | 0.268 | 1.814 | 0.07 | 1.539094 | 0.123781 | 1.305066 | 0.19187 | -1.450385 | 0.146951 | -1.249658 | 0.211424 |
| 19 | DG, PC/PE, LysoPC | -0.012 | 0.06 | -0.2 | 0.841 | -0.015 | 0.06 | -0.25 | 0.803 | 0.419 | 0.098 | 4.289 | 0 | 0.423 | 0.156 | 2.715 | 0.007 | -0.199783 | 0.84165 | -0.19946 | 0.841903 | -0.249576 | 0.802915 | -0.248947 | 0.803402 |
| 20 | DG, PC/PE, PS | -0.075 | 0.056 | -1.336 | 0.181 | 0.043 | 0.056 | 0.776 | 0.438 | 0.26 | 0.114 | 2.289 | 0.022 | 0.435 | 0.179 | 2.432 | 0.015 | -1.153844 | 0.248564 | -1.17095 | 0.241619 | 0.734917 | 0.46239 | 0.739279 | 0.459738 |
| 21 | polar metabolites, urate | -0.01 | 0.012 | -0.877 | 0.38 | 0.015 | 0.013 | 1.21 | 0.226 | -0.402 | 0.585 | -0.687 | 0.492 | -0.848 | 0.952 | -0.891 | 0.373 | 0.540821 | 0.588631 | 0.625024 | 0.531956 | -0.597423 | 0.550225 | -0.717469 | 0.473085 |
| 22 | dipeptides, cortisol, vitamin metabolites | 0.005 | 0.032 | 0.165 | 0.869 | 0 | 0.032 | 0.008 | 0.994 | 0.258 | 0.189 | 1.37 | 0.171 | -0.271 | 0.294 | -0.923 | 0.356 | 0.163816 | 0.869876 | -0.162425 | 0.870971 | 0.008 | 0.993617 | -0.008 | 0.993617 |
| 23 | PC/PE | 0.091 | 0.063 | 1.452 | 0.146 | -0.055 | 0.063 | -0.867 | 0.386 | -0.202 | 0.098 | -2.07 | 0.038 | -0.23 | 0.154 | -1.492 | -0.136 | -1.188715 | 0.234552 | -1.040573 | 0.298074 | 0.799689 | 0.423891 | 0.749624 | 0.453481 |
| 24 | PC/PE, PS | 0.084 | 0.05 | 1.694 | 0.09 | -0.057 | 0.05 | -1.152 | 0.249 | -0.122 | 0.141 | -0.868 | 0.386 | -0.294 | 0.221 | -1.328 | 0.184 | -0.772494 | 0.439822 | -1.045129 | 0.295963 | 0.693243 | 0.488157 | 0.870208 | 0.384187 |
| 25 | MC-AC | 0.163 | 0.042 | 3.874 | 0 | -0.004 | 0.001 | -3.425 | 0.001 | -0.08 | 0.149 | -0.537 | 0.591 | -0.833 | 0.24 | -3.475 | 0.001 | -0.531914 | 0.594786 | -2.586795 | 0.009687 | 0.530519 | 0.595752 | 2.439326 | 0.014715 |
| 26 | MC/LC-FA (DiC), FA (OH) | 0.16 | 0.065 | 2.455 | 0.014 | -0.132 | 0.065 | -2.023 | 0.043 | -0.078 | 0.091 | -0.854 | 0.393 | -0.383 | 0.141 | -2.726 | 0.006 | -0.806591 | 0.419902 | -1.824255 | 0.068114 | 0.786769 | 0.431417 | 1.624529 | 0.104263 |
| 27 | LC AC, SM | 0.036 | 0.038 | 0.934 | 0.35 | -0.028 | 0.038 | -0.748 | 0.455 | 0.138 | 0.163 | 0.846 | 0.398 | -0.418 | 0.258 | -1.622 | 0.105 | 0.627021 | 0.530645 | -0.809399 | 0.418286 | -0.560376 | 0.575223 | 0.679252 | 0.496978 |
| 28 | PI, SM, PC/PE | 0.057 | 0.045 | 1.271 | 0.204 | -0.052 | 0.045 | -1.165 | 0.244 | 0.17 | 0.138 | 1.228 | 0.22 | 0.036 | 0.216 | 0.164 | 0.87 | 0.883138 | 0.377162 | 0.162652 | 0.870793 | -0.845174 | 0.398014 | -0.162399 | 0.870992 |
| 29 | Krebs Cycle intermediates | -0.01 | 0.034 | -0.295 | 0.768 | 0.014 | 0.034 | 0.399 | 0.69 | -0.113 | 0.2 | -0.567 | 0.571 | 0.175 | 0.316 | 0.555 | 0.579 | 0.261699 | 0.793554 | -0.260489 | 0.794487 | -0.326305 | 0.744194 | 0.323968 | 0.745962 |
| 30 | choline, betaine | 0.076 | 0.068 | 1.109 | 0.268 | -0.052 | 0.069 | -0.766 | 0.444 | -0.039 | 0.084 | -0.462 | 0.644 | -0.114 | 0.132 | -0.861 | 0.389 | -0.426473 | 0.669763 | -0.680094 | 0.496445 | 0.395614 | 0.69239 | 0.572295 | 0.567122 |
| 31 | lactose, MC-FA (keto), amino acids metabolites | -0.059 | 0.042 | -1.406 | 0.16 | 0.069 | 0.042 | 1.632 | 0.103 | -0.278 | 0.216 | -1.291 | 0.197 | -0.241 | 0.342 | -0.707 | 0.48 | 0.950936 | 0.341637 | 0.63164 | 0.527622 | -1.012505 | 0.311297 | -0.648741 | 0.516506 |
| 32 | PA, di-/tri-peptides | 0.014 | 0.025 | 0.538 | 0.591 | -0.021 | 0.026 | -0.837 | 0.403 | -0.236 | 0.239 | -0.989 | 0.322 | -0.481 | 0.379 | -1.268 | 0.205 | -0.4726 | 0.636499 | -0.495264 | 0.620413 | 0.638905 | 0.522885 | 0.698538 | 0.484841 |
| 33 | LC-FA (DiC, OH) | 0.102 | 0.067 | 1.523 | 0.128 | -0.131 | 0.067 | -1.964 | 0.05 | -0.043 | 0.088 | -0.484 | 0.628 | 0.004 | 0.139 | 0.026 | 0.979 | -0.461268 | 0.644607 | 0.025996 | 0.97926 | 0.46994 | 0.638398 | -0.025998 | 0.979259 |
| 34 | MC-FA (DiC), PI | 0.09 | 0.059 | 1.538 | 0.124 | -0.111 | 0.058 | -1.901 | 0.057 | -0.098 | 0.103 | -0.952 | 0.341 | -0.196 | 0.162 | -1.213 | 0.225 | -0.809475 | 0.418242 | -0.952427 | 0.34088 | 0.851226 | 0.394644 | 1.022563 | 0.306514 |