**Supplementary Material**

**Metabolic Profiles Help Discriminate Mild Cognitive Impairment from Dementia Stage in Alzheimer’s Disease**

**Results from the Classification of Clinically Characterized Dementia, MCI, and Healthy Controls**

*Control versus MCI*

 DSI classifiers revealed that healthy controls were differentiated from MCI cases with a composite AUC of 0.80. This value is the combination of metabolic profiles (AUC 0.67) and clinical CSF markers of AD (AUC 0.82). Of the metabolite subclasses, CSF LMWM (AUC 0.69) tended to have slightly more discrimination power when discriminating MCI from controls than serum LMWM (AUC 0.57) or lipid measures (AUC 0.61). Adding CSF markers to the classifier with only metabolic profiles significantly improved its effectiveness (paired t-test p<0.001), while adding metabolic profiles to the CSF markers of AD did not improve the model (p = 0.25). CSF tTau (AUC 0.79) had a better discrimination power when differentiating MCI from controls than pTau (AUC 0.72) or Aβ42 (AUC 0.76).

*Control versus dementia*

 The overall classification performance between controls and dementia had an AUC of 0.89, which is mostly due to the CSF markers of AD (AUC 0.88). Including the metabolic profiles (AUC 0.73) to the model did not give a significant improvement (paired t-test p=0.5), while for CSF markers the improvement was notable (p<0.001). Serum LMWM (AUC 0.71) provided a slightly stronger discrimination when compared to CSF LMWM (AUC 0.67) and serum lipids (AUC 0.65). In the metabolite subclasses, serum lipoproteins had the best discrimination ability (AUC 0.69).

*MCI versus dementia*

Overall classification performance for differentiating between MCI and dementia had an AUC of 0.71. Metabolic profiles from CSF and serum (AUC 0.71) were noticeably stronger at discriminating dementia from MCI when compared to CSF biomarkers of AD (AUC 0.56) and adding the CSF biomarkers did not improve the classification performance (p=0.3) of the metabolomics model, while vice versa the improvement was significant (p<0.001). The metabolic subclasses serum lipids (AUC 0.65), serum LMWM (AUC 0.64), and CSF LMWM (AUC 0.65) performed equally well in the comparison. The differentiating strength of tTau (AUC 0.59) over pTau (AUC 0.53) was also evident. In this comparison, Aβ42 had an AUC of under 0.5 and was of no help in the differentiation

**Supplementary Table 1.** Amyloid-β (A), tau (T), and neurodegeneration (N) biomarkers as defined by CSF Aβ42 < 500 pg/ml, pTau > 70 pg/ml, and tTau > 400 pg/ml, respectively, in the Controls, MCI, and Dementia (Clinical AD) groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Dementia | MCI | Controls | Total |
| A + / A - | 214/145(60/40%) | 51/45(53/47%) | 7/36(16/84%) | 272/226(55/45%) |
| T + / T - | 177/182(49/51%) | 43/53(45/55%) | 4/39(9/91%) | 224/274(45/55%) |
| N + / N - | 202/156(56/44%) | 41/55(43/57%) | 3/43(7/93%) | 246/251(49/51%) |

**Supplementary Table 2.** AUCs from disease state index classifiers differentiating clinically characterized healthy controls, mild cognitive impairment, and dementia patients. 95% confidence intervals are given with the mean AUC. Aβ42, amyloid-β 42; AUC, area under curve; CSF, cerebrospinal fluid; LMWM, low-molecular-weight metabolites; MCI, mild cognitive impairment; pTau, phosphorylated tau; tTau, total tau

|  |  |  |  |
| --- | --- | --- | --- |
| **AUC [95% CI]** | Control versus Dementia | Control versus MCI | MCI versus Dementia |
| **Total CSF + Metabolomics** | **0.89 [0.87 - 0.90]** | **0.80 [0.78 - 0.83]** | **0.71 [0.69 - 0.73]** |
| **Total CSF markers** | **0.88 [0.86 - 0.90]** | **0.82 [0.80 - 0.85]** | **0.56 [0.54 - 0.58]** |
|  *Aβ42* | *0.80 [0.78 - 0.82]* | *0.76 [0.73 - 0.78]* | *0.42 [0.40 - 0.45]* |
|  *tTau* | *0.86 [0.84 - 0.87]* | *0.79 [0.76 - 0.82]* | *0.59 [0.57 - 0.61]* |
|  *pTau* | *0.75 [0.73 - 0.78]* | *0.72 [0.69 - 0.75]* | *0.53 [0.52 - 0.55]* |
| **Total Metabolic markers** | **0.73 [0.71 - 0.76]** | **0.67 [0.64 - 0.70]** | **0.71 [0.69 - 0.73]** |
| ***Total Serum Lipids*** | ***0.65 [0.62 - 0.68]*** | ***0.61 [0.57 - 0.64]*** | ***0.65 [0.63 - 0.67]*** |
|  *Lipoproteins* | *0.69 [0.66 - 0.71]* | *0.63 [0.60 - 0.67]* | *0.65 [0.63 - 0.67]* |
|  *Cholesterols* | *0.59 [0.56 - 0.62]* | *0.61 [0.57 - 0.64]* | *0.61 [0.59 - 0.63]* |
|  *Glycerides and phospholipids* | *0.62 [0.59 - 0.65]* | *0.58 [0.55 - 0.61]* | *0.54 [0.52 - 0.56]* |
|  *Fatty acids* | *0.61 [0.58 - 0.64]* | *0.58 [0.55 - 0.62]* | *0.60 [0.58 - 0.62]* |
| ***Total Serum LMWM*** | ***0.71 [0.68 - 0.73]*** | ***0.57 [0.54 - 0.60]*** | ***0.64 [0.62 - 0.66]*** |
|  *Energy and ketone bodies* | *0.64 [0.61 - 0.66]* | *0.61 [0.57 - 0.64]* | *0.62 [0.61 - 0.65]* |
|  *Amino acids* | *0.65 [0.63 - 0.68]* | *0.50 [0.47 - 0.53]* | *0.60 [0.58 - 0.62]* |
| ***Total CSF LMWM*** | ***0.67 [0.64 - 0.70]*** | ***0.69 [0.66 - 0.72]*** | ***0.65 [0.63 - 0.67]*** |
|  *Energy and ketone bodies* | *0.63 [0.60 - 0.66]* | *0.65 [0.62 - 0.68]* | *0.62 [0.60 - 0.64]* |
|  *Amino acids* | *0.66 [0.64 - 0.69]* | *0.58 [0.55 - 0.62]* | *0.56 [0.54 - 0.58]* |
|  *Organic nitrous* | *0.56 [0.54 - 0.59]* | *0.69 [0.66 - 0.73]* | *0.57 [0.55 - 0.59]* |
|  *Organosulfurs* | *0.63 [0.61 - 0.65]* | *0.58 [0.55 - 0.61]* | *0.51 [0.49 - 0.53]* |

**Supplementary Table 3.** The metabolites used in DSI classification and their concentrations among clinically diagnosed Alzheimer’s disease dementia, mild cognitive impairment (MCI), healthy controls (HC), amyloid- β 42 (Aβ42) positive dementia, Aβ42 positive MCI, and Aβ42 negative healthy controls.

|  |  |  |
| --- | --- | --- |
|  | All cases | Amyloid subgroups |
|  | **Dementia** | **MCI** | **HC** | **Dementia Aβ42+** | **MCI****Aβ42+** | **Controls Aβ42-** |
| Serum Lipids - Lipoproteins (mmol/l) |  |  |  |  |  |  |
| Total lipids in extremely large very low-density lipoprotein (VLDL) | 0.029 | 0.033 | 0.048 | 0.027 | 0.030 | 0.053 |
| Total lipids in very large VLDL | 0.066 | 0.081 | 0.116 | 0.060 | 0.073 | 0.129 |
| Total lipids in large VLDL | 0.284 | 0.334 | 0.470 | 0.259 | 0.302 | 0.518 |
| Total lipids in medium VLDL | 0.632 | 0.689 | 0.908 | 0.591 | 0.642 | 0.985 |
| Total lipids in small VLDL | 0.675 | 0.691 | 0.823 | 0.651 | 0.676 | 0.868 |
| Total lipids in very small VLDL | 0.591 | 0.548 | 0.612 | 0.586 | 0.558 | 0.634 |
| Total lipids in intermediate-density lipoprotein | 1.22 | 1.07 | 1.18 | 1.23 | 1.10 | 1.22 |
| Total lipids in large low-density lipoprotein (LDL) | 1.41 | 1.23 | 1.37 | 1.43 | 1.26 | 1.43 |
| Total lipids in medium LDL | 0.819 | 0.710 | 0.797 | 0.825 | 0.724 | 0.829 |
| Total lipids in small LDL | 0.522 | 0.467 | 0.521 | 0.525 | 0.478 | 0.542 |
| Total lipids in very large high-density lipoprotein (HDL) | 0.529 | 0.502 | 0.437 | 0.557 | 0.557 | 0.436 |
| Total lipids in large HDL | 0.767 | 0.783 | 0.677 | 0.812 | 0.857 | 0.659 |
| Total lipids in medium HDL | 0.770 | 0.834 | 0.868 | 0.779 | 0.841 | 0.877 |
| Total lipids in small HDL | 1.01 | 1.07 | 1.10 | 1.00 | 1.06 | 1.11 |
| VLDL particle size, nm | 36.5 | 36.9 | 37.3 | 36.4 | 36.7 | 37.4 |
| LDL particle size, nm | 23.6 | 23.5 | 23.5 | 23.6 | 23.5 | 23.5 |
| HDL particle size, nm | 10.0 | 10.0 | 9.9 | 10.1 | 10.1 | 9.89 |
| Apolipoprotein A1 | 1.64 | 1.65 | 1.63 | 1.68 | 1.70 | 1.64 |
| Apolipoprotein B | 1.04 | 1.00 | 1.09 | 1.04 | 1.01 | 1.14 |
| Ratio of ApoB to ApoA1 | 0.637 | 0.617 | 0.672 | 0.628 | 0.606 | 0.699 |
| Serum Lipids - Cholesterol (mmol/l) |  |  |  |  |  |  |
| Serum total cholesterol | 4.89 | 4.55 | 4.92 | 4.95 | 4.66 | 5.09 |
| Total cholesterol in VLDL | 0.813 | 0.815 | 0.978 | 0.795 | 0.802 | 1.033 |
| Total cholesterol in LDL | 1.86 | 1.58 | 1.78 | 1.88 | 1.61 | 1.86 |
| Total cholesterol in HDL | 1.45 | 1.49 | 1.42 | 1.50 | 1.56 | 1.43 |
| Esterified cholesterol | 3.38 | 3.15 | 3.43 | 3.43 | 3.22 | 3.55 |
| Free cholesterol | 1.50 | 1.41 | 1.49 | 1.52 | 1.43 | 1.54 |
| Remnant cholesterol (non-HDL/LDL) | 1.58 | 1.48 | 1.72 | 1.57 | 1.49 | 1.81 |
| Serum Lipids - Glycerides and phospholipids (mmol/l) |
| Serum total triglycerides (TG) | 1.43 | 1.51 | 1.85 | 1.36 | 1.45 | 1.97 |
| Triglycerides in VLDL | 0.958 | 1.051 | 1.371 | 0.893 | 0.980 | 1.483 |
| Triglycerides in LDL | 0.205 | 0.197 | 0.201 | 0.206 | 0.209 | 0.202 |
| Triglycerides in HDL | 0.137 | 0.136 | 0.153 | 0.135 | 0.136 | 0.158 |
| Diacylglycerol (DAG) | 0.020 | 0.022 | 0.024 | 0.019 | 0.021 | 0.025 |
| Ratio of DAG to TG | 0.015 | 0.014 | 0.017 | 0.014 | 0.014 | 0.017 |
| Total phosphoglycerides (PG) | 1.95 | 1.92 | 2.03 | 1.97 | 1.95 | 2.09 |
| Ratio of TG to PG | 0.730 | 0.784 | 0.835 | 0.703 | 0.741 | 0.884 |
| Phosphatidylcholine and other cholines | 2.15 | 2.14 | 2.11 | 2.19 | 2.19 | 2.15 |
| Sphingomyelins | 0.510 | 0.482 | 0.506 | 0.518 | 0.490 | 0.515 |
| Total cholines | 2.39 | 2.35 | 2.49 | 2.42 | 2.38 | 2.56 |
| Serum Lipids - Fatty acids (mmol/l) |  |  |  |  |  |  |
| Total fatty acids (FA) | 11.9 | 11.9 | 13.1 | 11.8 | 11.9 | 13.7 |
| Estimated fatty acid length (not carbon number) | 17.7 | 17.9 | 17.8 | 17.7 | 17.8 | 17.8 |
| Estimated degree of unsaturation | 1.21 | 1.23 | 1.20 | 1.22 | 1.22 | 1.19 |
| Docosahexaenoic acid (DHA) | 0.187 | 0.199 | 0.194 | 0.191 | 0.199 | 0.195 |
| Linoleic acid (LA) | 2.87 | 2.84 | 3.07 | 2.90 | 2.88 | 3.24 |
| Conjugated LA (CLA) | 0.030 | 0.021 | 0.022 | 0.030 | 0.019 | 0.023 |
| Omega-3 FA (Faw3) | 0.552 | 0.588 | 0.582 | 0.558 | 0.577 | 0.600 |
| Omega-6 FA (Faw6) | 3.58 | 3.57 | 3.84 | 3.61 | 3.61 | 4.03 |
| Polyunsaturated FA (PUFA) | 4.13 | 4.16 | 4.42 | 4.16 | 4.19 | 4.63 |
| Monounsaturated FA (MUFA) | 3.38 | 3.35 | 3.99 | 3.34 | 3.29 | 4.15 |
| Saturated FA (SFA) | 4.32 | 4.36 | 4.80 | 4.30 | 4.24 | 5.05 |
| Ratio of DHA to total FA | 1.59 | 1.68 | 1.48 | 1.63 | 1.67 | 1.41 |
| Ratio of LA to total FA | 24.4 | 24.0 | 23.9 | 24.7 | 24.3 | 24.1 |
| Ratio of CLA to total FA | 0.258 | 0.174 | 0.146 | 0.256 | 0.162 | 0.151 |
| Ratio of Faw3 to total FA | 4.67 | 4.97 | 4.43 | 4.74 | 4.88 | 4.33 |
| Ratio of Faw6 to total FA | 30.4 | 30.2 | 29.7 | 30.7 | 30.4 | 29.9 |
| Ratio of PUFA to total FA | 35.1 | 35.1 | 34.1 | 35.4 | 35.3 | 34.2 |
| Ratio of MUFA to total FA | 28.4 | 28.1 | 29.3 | 28.1 | 28.1 | 29.1 |
| Ratio of SFA to FA | 36.5 | 36.6 | 36.5 | 36.4 | 36.2 | 36.7 |
| Serum low-molecular-weight-metabolites (LMWM) - Energy and ketone bodies (mmol/l) |  |  |  |  |  |
| Acetic acid | 0.052 | 0.055 | 0.052 | 0.054 | 0.057 | 0.053 |
| Acetoacetic acid | 0.051 | 0.042 | 0.040 | 0.050 | 0.044 | 0.041 |
| beta-Hydroxybutyric acid | 0.153 | 0.154 | 0.128 | 0.152 | 0.153 | 0.132 |
| Citric acid | 0.128 | 0.128 | 0.120 | 0.127 | 0.128 | 0.119 |
| Creatinine | 0.075 | 0.082 | 0.075 | 0.075 | 0.082 | 0.075 |
| Glucose | 6.78 | 6.05 | 5.65 | 6.92 | 5.64 | 5.63 |
| Glycerol | 0.100 | 0.095 | 0.097 | 0.095 | 0.095 | 0.099 |
| Lactic acid | 1.80 | 1.68 | 1.67 | 1.78 | 1.63 | 1.70 |
| Pyruvic acid | 0.127 | 0.124 | 0.122 | 0.127 | 0.117 | 0.123 |
| Serum LMWM - Amino acids (mmol/l) |  |  |  |  |  |  |
| Alanine | 0.463 | 0.463 | 0.441 | 0.460 | 0.461 | 0.442 |
| Glutamine | 0.630 | 0.625 | 0.612 | 0.630 | 0.641 | 0.592 |
| Glycine | 0.297 | 0.288 | 0.286 | 0.298 | 0.301 | 0.286 |
| Histidine | 0.069 | 0.073 | 0.073 | 0.068 | 0.072 | 0.072 |
| Isoleucine | 0.065 | 0.071 | 0.071 | 0.064 | 0.067 | 0.073 |
| Leucine | 0.084 | 0.090 | 0.094 | 0.083 | 0.087 | 0.096 |
| Phenylalanine | 0.082 | 0.083 | 0.081 | 0.082 | 0.083 | 0.080 |
| Tyrosine | 0.066 | 0.067 | 0.066 | 0.066 | 0.066 | 0.065 |
| Valine | 0.210 | 0.221 | 0.219 | 0.208 | 0.213 | 0.221 |
| CSF LMWM - Energy and ketone (µmol/l) |  |  |  |  |  |  |
| alpha-Hydroxybutyric acid | 35.8 | 32.4 | 35.1 | 34.7 | 29.4 | 34.6 |
| alpha-Hydroxyisovaleric acid | 5.94 | 6.07 | 6.64 | 5.91 | 5.52 | 6.62 |
| alpha-Ketoisocaproic acid | 2.64 | 2.55 | 2.43 | 2.55 | 2.47 | 2.41 |
| alpha-Ketoisovaleric acid | 5.93 | 5.41 | 5.76 | 5.73 | 5.32 | 5.72 |
| beta-Hydroxybutyric acid | 14.9 | 12.3 | 10.3 | 15.6 | 11.0 | 9.9 |
| beta-Hydroxyisobutyric acid | 72.1 | 70.9 | 70.9 | 71.0 | 66.3 | 71.8 |
| Citric acid | 373 | 369 | 356 | 367 | 363 | 349 |
| Creatine | 77.9 | 73.5 | 74.2 | 76.3 | 73.3 | 73.1 |
| Creatinine | 106 | 108 | 97.0 | 103 | 105 | 97.2 |
| Fructose | 593 | 561 | 567 | 579 | 525 | 551 |
| Glucose | 5708 | 5518 | 5832 | 5509 | 5247 | 5814 |
| Lactic acid | 2336 | 2298 | 2183 | 2297 | 2271 | 2196 |
| Mannose | 72.5 | 62.3 | 68.3 | 70.0 | 59.4 | 66.2 |
| Pyruvic acid | 108 | 105 | 97 | 105 | 104 | 98 |
| Succinic acid | 5.128 | 5.215 | 4.842 | 5.169 | 5.072 | 4.810 |
| CSF LMWM - Amino acids (µmol/l) |  |  |  |  |  |  |
| Alanine | 62.9 | 60.4 | 50.9 | 59.2 | 60.1 | 51.3 |
| Glutamine | 896 | 908 | 870 | 890 | 885 | 861 |
| Glycine | 16.8 | 17.6 | 15.2 | 16.7 | 17.3 | 14.3 |
| Histidine | 31.2 | 28.9 | 29.4 | 29.5 | 29.0 | 30.0 |
| Isoleucine | 5.30 | 6.15 | 5.27 | 5.02 | 6.00 | 5.33 |
| Leucine | 20.7 | 22.0 | 20.7 | 19.5 | 21.2 | 20.8 |
| Lysine | 55.4 | 55.1 | 55.9 | 53.8 | 52.4 | 56.3 |
| Methionine | 6.10 | 6.74 | 6.29 | 5.91 | 7.07 | 6.12 |
| Ornithine | 6.15 | 6.23 | 5.55 | 6.13 | 6.37 | 5.61 |
| Phenylalanine | 10.1 | 10.1 | 9.26 | 9.88 | 10.5 | 9.17 |
| Threonine | 58.3 | 60.2 | 58.7 | 58.2 | 58.5 | 58.7 |
| Tyrosine | 16.6 | 16.2 | 15.1 | 16.1 | 16.4 | 15.1 |
| Valine | 27.2 | 28.6 | 26.0 | 25.4 | 27.6 | 26.0 |
| CSF LMWM - Organic nitrous (µmol/l) |  |  |  |  |  |  |
| Choline | 3.20 | 3.16 | 2.95 | 3.10 | 3.15 | 2.93 |
| Dimethylamine | 1.93 | 2.15 | 1.74 | 1.95 | 2.12 | 1.71 |
| Ethanolamine | 18.8 | 17.6 | 19.1 | 18.0 | 17.4 | 18.8 |
| Urea | 1464 | 1472 | 1407 | 1422 | 1426 | 1362 |
| CSF LMWM – Organosulfurs (µmol/l) |  |  |  |  |  |  |
| Dimethylsulfone | 20.2 | 20.0 | 17.0 | 1.95 | 2.12 | 1.71 |
| Isethionic acid | 31.9 | 31.0 | 27.6 | 30.5 | 30.1 | 27.2 |

**Supplementary Table 4A.** Analytical values of a Disease State Index classifier discriminating controls from dementia patients. Aβ42, amyloid-β 42; CSF, cerebrospinal fluid; LMWM, low-molecular-weight-metabolites; tTau, total tau; pTau, phosphorylated tau

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Control versus Dementia** | **Sensitivity** | **Specificity** | **Negative predictive value** | **Positive predictive value** |
| **Total CSF + Metabolomics** | **0.84 [0.83 - 0.86]** | **0.81 [0.77 - 0.85]** | **0.40 [0.38 - 0.43]** | **0.97 [0.97 - 0.98]** |
| **Total CSF markers** | **0.79 [0.77 - 0.80]** | **0.87 [0.84 - 0.90]** | **0.34 [0.32 - 0.36]** | **0.98 [0.98 - 0.99]** |
|  *Aβ42* | *0.70 [0.68 - 0.71]* | *0.70 [0.66 - 0.74]* | *0.22 [0.21 - 0.24]* | *0.95 [0.95 - 0.96]* |
|  *tTau* | *0.80 [0.79 - 0.81]* | *0.81 [0.77 - 0.85]* | *0.34 [0.32 - 0.36]* | *0.97 [0.97 - 0.98]* |
|  *pTau* | *0.70 [0.68 - 0.71]* | *0.70 [0.66 - 0.75]* | *0.22 [0.21 - 0.24]* | *0.95 [0.95 - 0.96]* |
| **Total metabolic markers** | **0.75 [0.74 - 0.77]** | **0.61 [0.56 - 0.65]** | **0.23 [0.21 - 0.25]** | **0.94 [0.94 - 0.95]** |
| ***Total Serum Lipids*** | ***0.63 [0.62 - 0.65]*** | ***0.62 [0.57 - 0.67]*** | ***0.17 [0.16 - 0.18]*** | ***0.93 [0.93 - 0.94]*** |
|  *Lipoproteins* | *0.62 [0.61 - 0.64]* | *0.62 [0.58 - 0.67]* | *0.17 [0.15 - 0.18]* | *0.93 [0.93 - 0.94]* |
|  *Cholesterol* | *0.60 [0.59 - 0.62]* | *0.53 [0.48 - 0.58]* | *0.14 [0.13 - 0.15]* | *0.91 [0.91 - 0.92]* |
|  *Glycerides and phospholipids* | *0.60 [0.58 - 0.62]* | *0.56 [0.51 - 0.60]* | *0.14 [0.13 - 0.16]* | *0.92 [0.91 - 0.93]* |
|  *Fatty acids* | *0.60 [0.58 - 0.62]* | *0.54 [0.49 - 0.59]* | *0.14 [0.13 - 0.16]* | *0.92 [0.91 - 0.93]* |
| ***Total Serum LMWM*** | ***0.69 [0.67 - 0.70]*** | ***0.61 [0.56 - 0.65]*** | ***0.19 [0.18 - 0.21]*** | ***0.94 [0.93 - 0.94]*** |
|  *Energy and ketone bodies* | *0.63 [0.62 - 0.65]* | *0.54 [0.49 - 0.59]* | *0.15 [0.14 - 0.16]* | *0.92 [0.91 - 0.93]* |
|  *Amino acids* | *0.61 [0.60 - 0.63]* | *0.59 [0.55 - 0.64]* | *0.16 [0.14 - 0.17]* | *0.93 [0.92 - 0.94]* |
| ***Total CSF LMWM*** | ***0.68 [0.67 - 0.70]*** | ***0.55 [0.50 - 0.60]*** | ***0.17 [0.16 - 0.19]*** | ***0.93 [0.92 - 0.94]*** |
|  *Energy and ketone bodies* | *0.66 [0.64 - 0.68]* | *0.52 [0.47 - 0.57]* | *0.15 [0.14 - 0.17]* | *0.92 [0.91 - 0.93]* |
|  *Amino acids* | *0.66 [0.64 - 0.68]* | *0.59 [0.53 - 0.64]* | *0.17 [0.16 - 0.19]* | *0.93 [0.92 - 0.94]* |
|  *Organic nitrous* | *0.56 [0.54 - 0.57]* | *0.56 [0.51 - 0.60]* | *0.13 [0.12 - 0.14]* | *0.91 [0.90 - 0.92]* |
|  *Organosulfurs* | *0.58 [0.56 - 0.59]* | *0.59 [0.54 - 0.63]* | *0.14 [0.13 - 0.15]* | *0.92 [0.91 - 0.93]* |

**Supplementary Table 4B.** Analytical values of a Disease State Index classifier discriminating controls from patients with mild cognitive impairment. Aβ42, amyloid-β 42; CSF, cerebrospinal fluid; LMWM, low-molecular-weight-metabolites; MCI, mild cognitive impairment; tTau, total tau; pTau, phosphorylated tau

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Control versus MCI** | **Sensitivity** | **Specificity** | **Negative predictive value** | **Positive****predictive value** |
| **Total CSF + Metabolomics** | **0.76 [0.73 - 0.79]** | **0.66 [0.62 - 0.71]** | **0.58 [0.54 - 0.61]** | **0.84 [0.82 - 0.86]** |
| **Total CSF markers** | **0.70 [0.67 - 0.73]** | **0.81 [0.78 - 0.85]** | **0.58 [0.54 - 0.61]** | **0.90 [0.88 - 0.92]** |
|  *Aβ42* | *0.66 [0.62 - 0.69]* | *0.66 [0.61 - 0.71]* | *0.47 [0.44 - 0.51]* | *0.82 [0.80 - 0.84]* |
|  *tTau* | *0.76 [0.73 - 0.78]* | *0.76 [0.72 - 0.80]* | *0.61 [0.57 - 0.64]* | *0.89 [0.87 -0.90]* |
|  *pTau* | *0.64 [0.62 - 0.67]* | *0.66 [0.61 - 0.71]* | *0.46 [0.43 - 0.49]* | *0.82 [0.79 - 0.84]* |
| **Total metabolic markers** | ***0.66 [0.63 - 0.69]*** | ***0.56 [0.51 - 0.60]*** | ***0.44 [0.40 - 0.47]*** | ***0.78 [0.75 - 0.80]*** |
| ***Total Serum Lipids*** | ***0.57 [0.53 - 0.60]*** | ***0.56 [0.51 - 0.61]*** | ***0.37 [0.34 - 0.40]*** | ***0.75 [0.72 - 0.77]*** |
|  *Lipoproteins* | *0.55 [0.52 - 0.59]* | *0.55 [0.51 - 0.60]* | *0.36 [0.33 - 0.39]* | *0.74 [0.71 - 0.77]* |
|  *Cholesterol* | *0.53 [0.50 - 0.57]* | *0.56 [0.51 - 0.61]* | *0.35 [0.32 - 0.38]* | *0.73 [0.71 - 0.76]* |
|  *Glycerides and phospholipids* | *0.55 [0.51 - 0.58]* | *0.56 [0.51 - 0.60]* | *0.36 [0.33 - 0.39]* | *0.74 [0.71 - 0.76]* |
|  *Fatty acids* | *0.57 [0.54 - 0.60]* | *0.54 [0.49 - 0.59]* | *0.36 [0.33 - 0.40]* | *0.74 [0.71 - 0.77]* |
| ***Total Serum LMWM*** | ***0.58 [0.55 - 0.62]*** | ***0.53 [0.48 - 0.57]*** | ***0.36 [0.33 - 0.40]*** | ***0.74 [0.71 - 0.76]*** |
|  *Energy and ketone bodies* | *0.58 [0.55 - 0.61]* | *0.56 [0.52 - 0.61]* | *0.38 [0.35 - 0.41]* | *0.75 [0.73 - 0.78]* |
|  *Amino acids* | *0.55 [0.52 - 0.58]* | *0.46 [0.41 - 0.50]* | *0.31 [0.28 - 0.34]* | *0.70 [0.67 - 0.72]* |
| ***Total CSF LMWM*** | ***0.64 [0.61 - 0.67]*** | ***0.55 [0.50 - 0.60]*** | ***0.41 [0.38 - 0.45]*** | ***0.77 [0.74 - 0.79]*** |
|  *Energy and ketone bodies* | *0.65 [0.62 - 0.68]* | *0.55 [0.50 - 0.60]* | *0.43 [0.39 - 0.47]* | *0.77 [0.74 - 0.79]* |
|  *Amino acids* | *0.59 [0.55 - 0.62]* | *0.51 [0.46 - 0.56]* | *0.36 [0.33 - 0.40]* | *0.73 [0.70 - 0.76]* |
|  *Organic nitrous* | *0.66 [0.63 - 0.69]* | *0.67 [0.62 - 0.71]* | *0.48 [0.45 - 0.51]* | *0.82 [0.80 - 0.85]* |
|  *Organosulfurs* | *0.56 [0.52 - 0.59]* | *0.55 [0.50 - 0.60]* | *0.36 [0.33 - 0.39]* | *0.74 [0.71 - 0.77]* |

**Supplementary Table 4C.** Analytical values of a Disease State Index classifier discriminating patients with mild cognitive impairment from dementia patients. Aβ42, amyloid-β 42; CSF, cerebrospinal fluid; LMWM, low-molecular-weight-metabolites; MCI, mild cognitive impairment; tTau, total tau; pTau, phosphorylated tau

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **MCI versus Dementia** | **Sensitivity** | **Specificity** | **Negative predictive value** | **Positive****predictive value** |
| **Total CSF + Metabolomics** | **0.69 [0.67 - 0.70]** | **0.63 [0.60 - 0.66]** | **0.36 [0.34 - 0.37]** | **0.88 [0.87 - 0.89]** |
| **Total CSF markers** | **0.56 [0.54 - 0.57]** | **0.56 [0.53 - 0.59]** | **0.25 [0.24 - 0.26]** | **0.83 [0.81 - 0.84]** |
|  *Aβ42* | *0.51 [0.50 - 0.53]* | *0.39 [0.36 - 0.41]* | *0.18 [0.17 - 0.19]* | *0.76 [0.75 - 0.77]* |
|  *tTau* | *0.57 [0.55 - 0.58]* | *0.57 [0.54 - 0.60]* | *0.26 [0.25 - 0.28]* | *0.83 [0.82 - 0.84]* |
|  *pTau* | *0.52 [0.50 - 0.53]* | *0.52 [0.48 - 0.55]* | *0.22 [0.21 - 0.23]* | *0.80 [0.79 - 0.81]* |
| **Total metabolic markers** | ***0.68 [0.67 - 0.70]*** | ***0.63 [0.60 - 0.66]*** | ***0.35 [0.33 - 0.36]*** | ***0.87 [0.86 - 0.88]*** |
| ***Total Serum Lipids*** | *0.63 [0.61 - 0.65]* | *0.60 [0.57 - 0.63]* | *0.30 [0.29 - 0.32]* | *0.85 [0.84 - 0.86]* |
|  *Lipoproteins* | *0.62 [0.60 - 0.63]* | *0.61 [0.58 - 0.65]* | *0.30 [0.29 - 0.32]* | *0.86 [0.85 - 0.87]* |
|  *Cholesterol* | *0.59 [0.57 - 0.60]* | *0.57 [0.54 - 0.60]* | *0.27 [0.26 - 0.29]* | *0.84 [0.83 - 0.85]* |
|  *Glycerides and phospholipids* | *0.52 [0.51 - 0.54]* | *0.55 [0.52 - 0.58]* | *0.24 [0.22 - 0.25]* | *0.81 [0.80 - 0.82]* |
|  *Fatty acids* | *0.60 [0.59 - 0.62]* | *0.52 [0.49 - 0.56]* | *0.26 [0.25 - 0.28]* | *0.83 [0.82 - 0.84]* |
| ***Total Serum LMWM*** | ***0.62 [0.60 - 0.63]*** | ***0.60 [0.56 - 0.63]*** | ***0.30 [0.28 - 0.31]*** | ***0.85 [0.84 - 0.86]*** |
|  *Energy and ketone bodies* | *0.62 [0.61 - 0.64]* | *0.56 [0.53 - 0.59]* | *0.29 [0.27 - 0.30]* | *0.84 [0.83 - 0.85]* |
|  *Amino acids* | *0.57 [0.55 - 0.58]* | *0.59 [0.56 - 0.62]* | *0.27 [0.26 - 0.28]* | *0.84 [0.83 - 0.85]* |
| ***Total CSF LMWM*** | ***0.63 [0.61 - 0.64]*** | ***0.58 [0.55 - 0.61]*** | ***0.29 [0.28 - 0.31]*** | ***0.85 [0.84 - 0.86]*** |
|  *Energy and ketone bodies* | *0.59 [0.57 - 0.60]* | *0.56 [0.53 - 0.59]* | *0.27 [0.25 - 0.28]* | *0.84 [0.82 - 0.85]* |
|  *Amino acids* | *0.56 [0.54 - 0.57]* | *0.54 [0.51 - 0.57]* | *0.24 [0.23 - 0.26]* | *0.82 [0.81 - 0.83]* |
|  *Organic nitrous* | *0.56 [0.55 - 0.58]* | *0.54 [0.51 - 0.57]* | *0.25 [0.23 - 0.26]* | *0.82 [0.81 - 0.83]* |
|  *Organosulfurs* | *0.52 [0.50 - 0.53]* | *0.49 [0.46 - 0.52]* | *0.21 [0.20 - 0.22]* | *0.79 [0.78 - 0.81]* |

**Supplementary Table 4D.** Analytical values of a Disease State Index classifier discriminating controls without amyloid pathology from MCI patients with amyloid pathology (CSF Aβ42 < 500 pg/ml). Aβ42, amyloid-β 42; CSF, cerebrospinal fluid; LMWM, low-molecular-weight-metabolites; tTau, total tau; pTau, phosphorylated tau

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Control Aβ42 - versus MCI Aβ42 +** | **Sensitivity** | **Specificity** | **Negative predictive value** | **Positive predictive value** |
| **Total CSF + Metabolomics** | **0.81 [0.77 - 0.84]** | **0.69 [0.64 - 0.74]** | **0.75 [0.71 - 0.79]** | **0.80 [0.78 - 0.83]** |
| **Total CSF markers** | **0.75 [0.71 - 0.79]** | **0.78 [0.74 - 0.82]** | **0.72 [0.68 - 0.75]** | **0.85 [0.82 - 0.87]** |
|  *tTau* | *0.79 [0.76 - 0.83]* | *0.80 [0.75 - 0.84]* | *0.76 [0.72 - 0.80]* | *0.87 [0.84 - 0.89]* |
|  *pTau* | *0.73 [0.69 - 0.77]* | *0.73 [0.68 - 0.77]* | *0.68 [0.63 - 0.72]* | *0.81 [0.78 - 0.84]* |
| **Total metabolic markers** | **0.71 [0.66 - 0.75]** | **0.67 [0.62 - 0.71]** | **0.64 [0.60 - 0.68]** | **0.77 [0.73 - 0.80]** |
| ***Total Serum Lipids*** | ***0.65 [0.60 - 0.69]*** | ***0.62 [0.57 - 0.67]*** | ***0.58 [0.53 - 0.63]*** | ***0.71 [0.68 - 0.75]*** |
|  *Lipoproteins* | *0.63 [0.58 - 0.67]* | *0.63 [0.58 - 0.68]* | *0.57 [0.53 - 0.61]* | *0.71 [0.68 - 0.75]* |
|  *Cholesterol* | *0.59 [0.55 - 0.64]* | *0.61 [0.56 - 0.66]* | *0.53 [0.49 - 0.58]* | *0.69 [0.65 - 0.73]* |
|  *Glycerides and phospholipids* | *0.57 [0.52 - 0.62]* | *0.57 [0.52 - 0.62]* | *0.50 [0.46 - 0.54]* | *0.65 [0.61 - 0.69]* |
|  *Fatty acids* | *0.57 [0.52 - 0.61]* | *0.60 [0.54 - 0.65]* | *0.51 [0.46 - 0.55]* | *0.68 [0.64 - 0.72]* |
| ***Total Serum LMWM*** | ***0.61 [0.57 - 0.65]*** | ***0.60 [0.55 - 0.65]*** | ***0.53 [0.48 - 0.57]*** | ***0.70 [0.66 - 0.73]*** |
|  *Energy and ketone bodies* | *0.47 [0.42 - 0.51]* | *0.54 [0.49 - 0.59]* | *0.43 [0.39 - 0.46]* | *0.59 [0.55 - 0.63]* |
|  *Amino acids* | *0.63 [0.59 - 0.68]* | *0.58 [0.53 - 0.64]* | *0.54 [0.49 - 0.59]* | *0.70 [0.66 - 0.73]* |
| ***Total CSF LMWM*** | ***0.69 [0.65 - 0.73]*** | ***0.66 [0.61 - 0.71]*** | ***0.62 [0.58 - 0.67]*** | ***0.75 [0.72 - 0.79]*** |
|  *Energy and ketone bodies* | *0.67 [0.62 - 0.71]* | *0.61 [0.56 - 0.65]* | *0.59 [0.54 - 0.64]* | *0.71 [0.68 - 0.75]* |
|  *Amino acids* | *0.65 [0.61 - 0.69]* | *0.64 [0.59 - 0.70]* | *0.58 [0.53 - 0.62]* | *0.73 [0.70 - 0.77]* |
|  *Organic nitrous* | *0.63 [0.59 - 0.67]* | *0.63 [0.58 - 0.68]* | *0.56 [0.52 - 0.60]* | *0.73 [0.69 - 0.76]* |
|  *Organosulfurs* | *0.52 [0.47 - 0.56]* | *0.55 [0.49 - 0.60]* | *0.45 [0.41 - 0.49]* | *0.62 [0.58 - 0.66]* |

**Supplementary Table 4E.** Analytical values of a Disease State Index classifier discriminating controls without amyloid pathology from dementia patients with amyloid pathology (CSF Aβ42 < 500 pg/ml). Aβ42, amyloid-β 42; CSF, cerebrospinal fluid; LMWM, low-molecular-weight-metabolites; MCI, mild cognitive impairment; tTau, total tau; pTau, phosphorylated tau

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Control Aβ42 - versus Dementia Aβ42 +** | **Sensitivity** | **Specificity** | **Negative predictive value** | **Positive****predictive value** |
| **Total CSF + Metabolomics** | **0.84 [0.82 - 0.85]** | **0.74 [0.70 - 0.79]** | **0.46 [0.43 - 0.50]** | **0.95 [0.94 - 0.96]** |
| **Total CSF markers** | ***0.81 [0.79 - 0.82]*** | ***0.85 [0.81 - 0.89]*** | ***0.45 [0.42 - 0.47]*** | ***0.97 [0.96 - 0.98]*** |
|  *tTau* | *0.84 [0.82 - 0.85]* | *0.85 [0.81 - 0.89]* | *0.50 [0.47 - 0.53]* | *0.97 [0.97 - 0.98]* |
|  *pTau* | *0.72 [0.70 - 0.74]* | *0.73 [0.68 - 0.77]* | *0.31 [0.29 - 0.33]* | *0.94 [0.93 - 0.95]* |
| **Total metabolic markers** | **0.75 [0.73 - 0.77]** | **0.56 [0.51 - 0.61]** | **0.28 [0.25 - 0.31]** | **0.91 [0.90 - 0.92]** |
| ***Total Serum Lipids*** | ***0.63 [0.61 - 0.65]*** | ***0.66 [0.60 - 0.71]*** | ***0.24 [0.22 - 0.26]*** | ***0.92 [0.91 - 0.93]*** |
|  *Lipoproteins* | *0.64 [0.62 - 0.67]* | *0.65 [0.60 - 0.71]* | *0.24 [0.22 - 0.26]* | *0.92 [0.91 - 0.93]* |
|  *Cholesterol* | *0.62 [0.59 - 0.64]* | *0.58 [0.53 - 0.63]* | *0.21 [0.19 - 0.23]* | *0.90 [0.89 - 0.91]* |
|  *Glycerides and phospholipids* | *0.65 [0.63 - 0.67]* | *0.59 [0.54 - 0.64]* | *0.22 [0.20 - 0.24]* | *0.91 [0.89 - 0.92]* |
|  *Fatty acids* | *0.60 [0.58 - 0.62]* | *0.57 [0.51 - 0.62]* | *0.19 [0.17 - 0.21]* | *0.89 [0.88 - 0.91]* |
| ***Total Serum LMWM*** | ***0.71 [0.69 - 0.73]*** | ***0.61 [0.56 - 0.66]*** | ***0.27 [0.25 - 0.30]*** | ***0.92 [0.91 - 0.93]*** |
|  *Energy and ketone bodies* | *0.62 [0.60 - 0.64]* | *0.59 [0.54 - 0.64]* | *0.21 [0.19 - 0.23]* | *0.90 [0.89 - 0.91]* |
|  *Amino acids* | *0.64 [0.62 - 0.66]* | *0.62 [0.57 - 0.67]* | *0.23 [0.21 - 0.25]* | *0.91 [0.90 - 0.92]* |
| ***Total CSF LMWM*** | ***0.66 [0.64 - 0.68]*** | ***0.48 [0.43 - 0.54]*** | ***0.20 [0.18 - 0.22]*** | ***0.88 [0.87 - 0.89]*** |
|  *Energy and ketone bodies* | *0.62 [0.60 - 0.64]* | *0.41 [0.36 - 0.46]* | *0.16 [0.14 - 0.18]* | *0.86 [0.85 - 0.87]* |
|  *Amino acids* | *0.65 [0.63 - 0.67]* | *0.57 [0.51 - 0.62]* | *0.22 [0.20 - 0.25]* | *0.90 [0.88 - 0.91]* |
|  *Organic nitrous* | *0.56 [0.54 - 0.59]* | *0.54 [0.49 - 0.59]* | *0.18 [0.16 - 0.20]* | *0.88 [0.86 - 0.89]* |
|  *Organosulfurs* | *0.56 [0.54 - 0.59]* | *0.55 [0.50 - 0.61]* | *0.18 [0.16 - 0.20]* | *0.88 [0.87 - 0.89]* |

**Supplementary Table 4F.** Analytical values of a Disease State Index classifier discriminating patients with MCI with amyloid pathology from dementia patients with amyloid pathology (CSF Aβ42 < 500 pg/ml). Aβ42, amyloid-β 42; CSF, cerebrospinal fluid; LMWM, low-molecular-weight-metabolites; MCI, mild cognitive impairment; tTau, total tau; pTau, phosphorylated tau

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **MCI Aβ42 + versus Dementia Aβ42 +** | **Sensitivity** | **Specificity** | **Negative predictive value** | **Positive****predictive value** |
| **Total CSF + Metabolomics** | **0.69 [0.68 - 0.71]** | **0.56 [0.52 - 0.61]** | **0.31 [0.29 - 0.34]** | **0.87 [0.86 - 0.88]** |
| **Total CSF markers** | **0.60 [0.58 - 0.62]** | **0.60 [0.56 - 0.65]** | **0.27 [0.25 - 0.29]** | **0.87 [0.85 - 0.88]** |
|  *Aβ42* | *0.58 [0.56 - 0.61]* | *0.60 [0.55 - 0.64]* | *0.26 [0.24 - 0.27]* | *0.86 [0.85 - 0.87]* |
|  *tTau* | *0.56 [0.54 - 0.58]* | *0.57 [0.53 - 0.62]* | *0.24 [0.22 - 0.26]* | *0.85 [0.83 - 0.86]* |
|  *pTau* | *0.49 [0.47 - 0.52]* | *0.47 [0.42 - 0.51]* | *0.18 [0.16 - 0.19]* | *0.80 [0.78 - 0.81]* |
| **Total metabolic markers** | **0.69 [0.67 - 0.71]** | **0.56 [0.51 - 0.60]** | **0.31 [0.28 - 0.33]** | **0.87 [0.86 - 0.88]** |
| ***Total Serum Lipids*** | ***0.61 [0.59 - 0.64]*** | ***0.57 [0.53 - 0.61]*** | ***0.26 [0.24 - 0.28]*** | ***0.86 [0.85 - 0.87]*** |
|  *Lipoproteins* | *0.62 [0.60 - 0.64]* | *0.55 [0.51 - 0.59]* | *0.26 [0.24 - 0.28]* | *0.86 [0.84 - 0.87]* |
|  *Cholesterol* | *0.60 [0.58 - 0.62]* | *0.59 [0.55 - 0.64]* | *0.26 [0.24 - 0.28]* | *0.87 [0.85 - 0.88]* |
|  *Glycerides and phospholipids* | *0.54 [0.52 - 0.56]* | *0.44 [0.40 - 0.48]* | *0.18 [0.16 - 0.20]* | *0.80 [0.79 - 0.82]* |
|  *Fatty acids* | *0.58 [0.55 - 0.60]* | *0.46 [0.41 - 0.50]* | *0.20 [0.18 - 0.22]* | *0.82 [0.81 - 0.83]* |
| ***Total Serum LMWM*** | ***0.62 [0.60 - 0.64]*** | ***0.54 [0.49 - 0.58]*** | ***0.25 [0.23 - 0.27]*** | ***0.85 [0.84 - 0.86]*** |
|  *Energy and ketone bodies* | *0.58 [0.56 - 0.60]* | *0.57 [0.53 - 0.61]* | *0.25 [0.23 - 0.26]* | *0.85 [0.84 - 0.87]* |
|  *Amino acids* | *0.54 [0.52 - 0.56]* | *0.50 [0.46 - 0.55]* | *0.21 [0.19 - 0.22]* | *0.82 [0.81 - 0.84]* |
| ***Total CSF LMWM*** | ***0.61 [0.59 - 0.63]*** | ***0.58 [0.54 - 0.62]*** | ***0.27 [0.25 - 0.29]*** | ***0.86 [0.84 - 0.87]*** |
|  *Energy and ketone bodies* | *0.59 [0.57 - 0.61]* | *0.55 [0.51 - 0.59]* | *0.25 [0.23 - 0.27]* | *0.85 [0.83 - 0.86]* |
|  *Amino acids* | *0.55 [0.53 - 0.57]* | *0.55 [0.51 - 0.60]* | *0.23 [0.21 - 0.25]* | *0.84 [0.82 - 0.85]* |
|  *Organic nitrous* | *0.55 [0.53 - 0.57]* | *0.46 [0.41 - 0.50]* | *0.20 [0.18 - 0.21]* | *0.81 [0.79 - 0.82]* |
|  *Organosulfurs* | *0.53 [0.50 - 0.55]* | *0.53 [0.49 - 0.57]* | *0.21 [0.20 - 0.23]* | *0.82 [0.81 - 0.84]* |