# Supplementary Table 1 Levels of CSF Proteins Between Aβ-PET Negative and Positive Groups

|  |  |  |  |
| --- | --- | --- | --- |
|  | Aβ-PET Negative  (N = 253) | Aβ-PET Positive  (N = 221) | *P* |
| Aβ42, Mean(SD) , pg/ml | 1538.36 (559.76) | 838.40 (389.63) | <0.001 |
| Tau, Mean(SD) , pg/ml | 209.50 (71.76) | 322.66 (134.82) | <0.001 |
| pTau, Mean(SD) , pg/ml | 18.44 (6.54) | 32.00 (15.01) | <0.001 |
| Aβ40, Mean(SD) , pg/ml | 8396.80 (2399.38) | 8693.42 (2450.20) | 0.47 |
| Aβ38, Mean(SD) , pg/ml | 1925.19 (556.68) | 2001.82 (583.28) | 0.35 |
| TREM2, Mean(SD) , pg/ml | 3552.09 (1797.89) | 4178.81 (2257.17) | 0.008 |
| PGRN, Mean(SD) , pg/ml | 1549.32 (359.39) | 1571.09 (396.91) | 0.34 |
| ALB, Mean(SD) , fmole/µL | 55.81 (21.48) | 57.83 (26.93) | 0.41 |
| ALDOA, Mean(SD) , fmole/µL | 0.02 (0.005) | 0.02 (0.006) | <0.001 |
| APOA4, Mean(SD) , fmole/µL | 0.08 (0.03) | 0.08 (0.05) | 0.25 |
| APOC1, Mean(SD) , fmole/µL | 2.07 (0.87) | 2.19 (1.21) | 0.10 |
| APOC2, Mean(SD) , fmole/µL | 0.008 (0.005) | 0.008 (0.006) | 0.07 |
| APOE, Mean(SD) , fmole/µL | 1.97 (3.93) | 5.90 (5.60) | 0.08 |
| C9, Mean(SD) , fmole/µL | 0.01 (0.006) | 0.01 (0.007) | 0.045 |
| CALM2, Mean(SD) , fmole/µL | 0.02 (0.008) | 0.03 (0.008) | <0.001 |
| CD44, Mean(SD) , fmole/µL | 0.02 (0.004) | 0.02 (0.005) | 0.001 |
| CHI3L1, Mean(SD) , fmole/µL | 0.37 (0.12) | 0.44 (0.15) | <0.001 |
| CP, Mean(SD) , fmole/µL | 0.07 (0.02) | 0.07 (0.03) | 0.11 |
| DDAH1, Mean(SD) , fmole/µL | 0.001 (0.0003) | 0.001 (0.0003) | 0.006 |
| DKK3, Mean(SD) , fmole/µL | 0.22 (0.07) | 0.24 (0.08) | 0.051 |
| ENO1, Mean(SD) , fmole/µL | 0.005 (0.001) | 0.005 (0.001) | 0.002 |
| F2, Mean(SD) , fmole/µL | 0.01 (0.005) | 0.01 (0.006) | 0.19 |
| GAPDH, Mean(SD) , fmole/µL | 0.004 (0.003) | 0.004 (0.002) | 0.73 |
| GDA, Mean(SD) , fmole/µL | 0.003 (0.001) | 0.004 (0.001) | <0.001 |
| GMFB, Mean(SD) , fmole/µL | 0.003 (0.001) | 0.003 (0.001) | 0.001 |
| GOT1, Mean(SD) , fmole/µL | 0.006 (0.002) | 0.007 (0.002) | <0.001 |
| GSN, Mean(SD) , fmole/µL | 0.14 (0.04) | 0.15 (0.04) | 0.08 |
| HBA, Mean(SD) , fmole/µL | 1.64 (8.94) | 0.58 (3.01) | 0.054 |
| HBB, Mean(SD) , fmole/µL | 2.25 (11.85) | 0.86 (4.80) | 0.06 |
| KNG1, Mean(SD) , fmole/µL | 0.64 (0.28) | 0.64 (0.37) | 0.59 |
| LDHB, Mean(SD) , fmole/µL | 0.005 (0.002) | 0.006 (0.002) | 0.02 |
| LDHC, Mean(SD) , fmole/µL | 0.01 (0.004) | 0.01 (0.004) | 0.11 |
| MDH1, Mean(SD) , fmole/µL | 0.02 (0.005) | 0.02 (0.006) | <0.001 |

**Supplementary Table 1** Levels of CSF Proteins Between Aβ-PET Negative and Positive Groups (Continued)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Aβ-PET Negative  (N = 253) | Aβ-PET Positive  (N = 221) | *P* |
| NCAM1, Mean(SD) , fmole/µL | 0.06 (0.02) | 0.07 (0.02) | 0.02 |
| NPTX2, Mean(SD) , fmole/µL | 0.004 (0.001) | 0.004 (0.001) | 0.71 |
| NPTXR, Mean(SD) , fmole/µL | 0.27 (0.08) | 0.26 (0.08) | 0.73 |
| NRXN1, Mean(SD) , fmole/µL | 0.02 (0.006) | 0.02 (0.007) | 0.09 |
| OGN, Mean(SD) , fmole/µL | 0.01 (0.003) | 0.01 (0.003) | 0.34 |
| OMG, Mean(SD) , fmole/µL | 0.15 (0.05) | 0.16 (0.06) | 0.06 |
| PARK7, Mean(SD) , fmole/µL | 0.006 (0.003) | 0.006 (0.002) | 0.54 |
| PEBP1, Mean(SD) , fmole/µL | 0.02 (0.005) | 0.02 (0.005) | 0.005 |
| PGLYRP2, Mean(SD) , fmole/µL | 0.05 (0.02) | 0.06 (0.03) | 0.06 |
| PKM, Mean(SD) , fmole/µL | 0.05 (0.02) | 0.06 (0.02) | <0.001 |
| PON1, Mean(SD) , fmole/µL | 0.005 (0.003) | 0.005 (0.004) | 0.16 |
| PPIA, Mean(SD) , fmole/µL | 0.005 (0.004) | 0.005 (0.002) | 0.68 |
| PTPRZ1, Mean(SD) , fmole/µL | 0.02 (0.005) | 0.02 (0.006) | 0.001 |
| SCG2, Mean(SD) , fmole/µL | 0.02 (0.009) | 0.02 (0.008) | 0.91 |
| SMOC1, Mean(SD) , fmole/µL | 0.01 (0.004) | 0.02 (0.006) | <0.001 |
| SOD1, Mean(SD) , fmole/µL | 0.07 (0.02) | 0.08 (0.03) | 0.001 |
| SPP1, Mean(SD) , fmole/µL | 0.82 (0.25) | 1.00 (0.44) | <0.001 |
| TPI1, Mean(SD) , fmole/µL | 0.004 (0.002) | 0.005 (0.002) | 0.03 |
| VGF, Mean(SD) , fmole/µL | 0.08 (0.04) | 0.08 (0.04) | 0.78 |
| YWHAB, Mean(SD) , fmole/µL | 0.01 (0.006) | 0.01 (0.004) | 0.002 |
| YWHAZ, Mean(SD) , fmole/µL | 0.02 (0.01) | 0.03 (0.01) | <0.001 |

Values of CSF protein concentrations were presented as mean (standard deviation, SD). Differences in CSF proteins were compared employing linear models with age, gender, APOE ε4 allele status, and years of education as covariates. The protein concentrations were log-transformed in linear models.

ALB: Albumin, Aβ42: Amyloid beta 42, Aβ38: Amyloid beta 38, Aβ40: Amyloid beta 40, ALDOA: Aldolase, fructose-bisphosphate A, APOA4: Apolipoprotein A4, APOC1: Apolipoprotein C1, APOC2: Apolipoprotein C2, APOE: Apolipoprotein E, C9: Complement component 9, CALM2: Calmodulin 2, CHI3L1: Chitinase-3-like protein 1, CP: Ceruloplasmin, DDAH1: Dimethylarginine dimethylaminohydrolase 1, DKK3: Dickkopf-3, ENO1: Enolase 1, F2: Coagulation factor II, GAPDH: Glyceraldehyde-3-phosphate dehydrogenase, GDA: Guanine deaminase, GMFB: Glia maturation factor beta, GOT1: Aspartate aminotransferase, GSN: Gelsolin, HBA: Hemoglobin A, HBB: Hemoglobin B, KNG1: Kininogen 1, LDHB: Lactate dehydrogenase B, LDHC: Lactate dehydrogenase C, MDH1: Malate dehydrogenase 1, NCAM1: Neural cell adhesion molecule1, NPTX2: Neuronal pentraxin 2, NPTXR: Neuronal pentraxin receptor, NRXN1: Neurexin-1-alpha, OGN: Osteoglycin, OMG: Oligodendrocyte-myelin glycoprotein, PARK7: Parkinson disease protein 7, PEBP1: Phosphatidylethanolamine binding protein 1, PGLYRP2: Peptidoglycan recognition protein 2, PGRN: Progranulin, PKM: Pyruvate kinase, PON1: Paraoxonase 1, PPIA: Peptidylprolyl isomerase A, pTau: Phosphorylated Tau, PTPRZ1: Protein tyrosine phosphatase receptor type Z1, SCG2: Secretogranin II, SMOC1: SPARC-related modular calcium binding 1, SOD1: Superoxide dismutase 1, soluble, SPP 1: Secreted phosphoprotein 1, TPI1: Triosephosphate isomerase 1, TREM2: Trigger receptor expressed on myeloid cells-2, VGF: VGF nerve growth factor inducible, YWHAB: Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta, YWHAZ: Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta.

# Supplementary Table 2 Demographic, Clinical Characteristics, and Candidate Hub Proteins Patterns Across Different Aβ Pathological Groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | CSF-PET-  (N = 238) | CSF+PET-  (N = 15) | CSF+PET+  (N = 168) | *P* |
| **Demographic** |  |  |  |  |
| MCI, N(%)b | 126 (53%) | 9 (60%) | 135 (80%) | <0.001 |
| Male, N(%) | 125 (53%) | 9 (60%) | 96 (57%) | 0.60 |
| APOE ε4 Carrier, N(%)b | 53 (22%) | 6 (40%) | 119 (71%) | <0.001 |
| Age, Mean(SD), y ab | 70.20 (6.97) | 75.21 (6.70) | 73.36 (6.97) | <0.001 |
| Education Years, Mean(SD), y | 16.51 (2.53) | 16.20 (2.24) | 16.24 (2.63) | 0.55 |
| **Cognitive Scores** |  |  |  |  |
| MMSE, Mean(SD) b | 28.89 (1.34) | 28.60 (1.55) | 27.67 (1.84) | <0.001 |
| mPACCdigit, Mean(SD) bc | -1.63 (3.53) | -2.42 (3.52) | -6.33 (4.89) | <0.001 |
| mPACCtrailsB, Mean(SD) bc | -1.28 (3.16) | -2.38 (2.94) | -5.52 (4.23) | <0.001 |
| **CSF Proteins** |  |  |  |  |
| Aβ42, Mean(SD) ab, pg/ml | 1586.33 (537.95) | 777.12 (284.65) | 720.79 (225.19) | <0.001 |
| Tau, Mean(SD) ab, pg/ml | 203.98 (67.73) | 297.05 (79.41) | 354.27 (132.38) | <0.001 |
| pTau, Mean(SD) ab, pg/ml | 17.86 (6.04) | 27.55 (7.61) | 35.82 (14.73) | <0.001 |
| APOE, Mean(SD) b, fmole/µL | 1.80 (3.64) | 4.75 (6.65) | 6.95 (5.71) | 0.006 |
| CHI3L1, Mean(SD) ab, fmole/µL | 0.36 (0.11) | 0.47 (0.15) | 0.45 (0.14) | <0.001 |

**Supplementary Table 2** Demographic, Cognitive Scores, and Candidate Hub Proteins Patterns Across Different Aβ Pathological Groups (Continued)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | CSF-PET-  (N = 238) | CSF+PET-  (N = 15) | CSF+PET+  (N = 168) | *P* |
| SMOC1, Mean(SD) ab, fmole/µL | 0.011 (0.004) | 0.015 (0.004) | 0.016 (0.006) | <0.001 |

For continuous variables, the values were presented as mean (standard deviation, SD). Demographic comparisons were conducted using Chi-square tests for categorical variables, the Kruskal-Wallis H test for the continuous variable with a non-normal distribution (years of education), and ANOVA for the continuous variable with a normal distribution (age). Disparities in cognitive scores and CSF proteins were assessed using Analysis of Covariance (ANCOVA) with age, gender, APOE ε4 carrying status, and years of education as covariates. The protein concentrations were log-transformed. Aβ-PET positive participants whose Aβ42/pTau levels did not reach the cutoff value of 39.2 (N = 53) were excluded from the cross-sectional comparison.

*P* value adjustment for multiple comparisons was made using the Bonferroni method with a significance level of 0.05: a CSF-PET- versus CSF+PET- subjects, b CSF-PET- versus CSF+PET+ subjects, and c CSF+PET- versus CSF+PET+ subjects.

APOE: Apolipoprotein E, CHI3L1: Chitinase-3-like protein 1, CSF-PET-: CSF-Aβ negative and Aβ-PET negative, CSF+PET-: CSF-Aβ positive and Aβ-PET negative, CSF+PET+: CSF-Aβ positive and Aβ-PET positive, MMSE: Mini-Mental State Examination, mPACCdigit: Modified Preclinical Alzheimer Cognitive Composite incorporating the Digit Symbol Substitution Test, mPACCtrailsB: Modified Preclinical Alzheimer Cognitive Composite incorporating the Trail-Making Test Part B, SMOC1: SPARC-related modular calcium binding 1.

# Supplementary Table 3 Associations Between the CSF Candidate Hub Proteins and Longitudinal Cognitive Changes as well as SUVRs Alterations

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Group | Dependent Variable | Interactions Between CSF Proteins and Time | β | S.E. | *P* |
| Aβ-PET negative | MMSE | APOE\*Time | -0.15 | 0.10 | 0.12 |
| Aβ-PET negative | mPACCdigit | APOE\*Time | -0.12 | 0.09 | 0.19 |
| Aβ-PET negative | mPACCtrailsB | APOE\*Time | -0.10 | 0.08 | 0.24 |
| Aβ-PET negative | SUVRs | APOE\*Time | 0.02 | 0.03 | 0.52 |
| Aβ-PET negative | MMSE | CHI3L1\*Time | -0.02 | 0.02 | 0.39 |
| Aβ-PET negative | mPACCdigit | CHI3L1\*Time | -0.03 | 0.02 | 0.19 |
| Aβ-PET negative | mPACCtrailsB | CHI3L1\*Time | -0.02 | 0.02 | 0.17 |
| Aβ-PET negative | SUVRs | CHI3L1\*Time | 0.001 | 0.01 | 0.92 |
| Aβ-PET negative | MMSE | SMOC1\*Time | 0.02 | 0.02 | 0.50 |
| Aβ-PET negative | mPACCdigit | SMOC1\*Time | 0.02 | 0.02 | 0.25 |
| Aβ-PET negative | mPACCtrailsB | SMOC1\*Time | 0.02 | 0.02 | 0.22 |
| Aβ-PET negative | SUVRs | SMOC1\*Time | 0.02 | 0.01 | 0.01 |
| Aβ-PET positive | MMSE | APOE\*Time | -0.27 | 0.27 | 0.31 |
| Aβ-PET positive | mPACCdigit | APOE\*Time | -0.15 | 0.18 | 0.41 |
| Aβ-PET positive | mPACCtrailsB | APOE\*Time | -0.20 | 0.18 | 0.28 |
| Aβ-PET positive | SUVRs | APOE\*Time | 0.01 | 0.03 | 0.83 |
| Aβ-PET positive | MMSE | CHI3L1\*Time | -0.24 | 0.08 | 0.004 |
| Aβ-PET positive | mPACCdigit | CHI3L1\*Time | -0.11 | 0.05 | 0.039 |
| Aβ-PET positive | mPACCtrailsB | CHI3L1\*Time | -0.14 | 0.05 | 0.01 |
| Aβ-PET positive | SUVRs | CHI3L1\*Time | -0.01 | 0.01 | 0.21 |
| Aβ-PET positive | MMSE | SMOC1\*Time | -0.16 | 0.06 | 0.01 |
| Aβ-PET positive | mPACCdigit | SMOC1\*Time | -0.10 | 0.04 | 0.01 |
| Aβ-PET positive | mPACCtrailsB | SMOC1\*Time | -0.11 | 0.04 | 0.01 |
| Aβ-PET positive | SUVRs | SMOC1\*Time | -0.01 | 0.01 | 0.23 |

LME models were utilized to evaluate the associations between the CSF candidate hub proteins and longitudinal cognitive changes as well as SUVRs alterations in the Aβ-PET negative and positive groups. Statistics were from the LME model of each analyte, including follow-up time, age, gender, APOE ε4 carrying status, years of education, baseline CSF protein level, and the interactions of each variable with follow-up time as covariates. The CSF proteins were log-transformed and standardized (z-scored). All other continuous variables were also z-scored. For exploratory investigations, we refrained from conducting *P*-value correction.

APOE: Apolipoprotein E, CHI3L1: Chitinase-3-like protein 1, MMSE: Mini-Mental State Examination, mPACCdigit: Modified Preclinical Alzheimer Cognitive Composite that Used Digit Symbol Substitution Test, mPACCtrailsB: Modified Preclinical Alzheimer Cognitive Composite that Used Trail-Making Test Part B, SMOC1: SPARC-related modular calcium binding 1, SUVRs: FBP-PET standardized uptake value ratios.

# Supplementary Table 4 Interactive Association of Baseline CSF Candidate Hub Proteins and Baseline Aβ42 with Longitudinal Cognitive Changes.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Group | Dependent Variable | Interactions Between CSF Proteins, Aβ42, and Time | β | S.E. | *P* |
| Aβ-PET negative | MMSE | APOE\*Aβ42\*Time | 0.02 | 0.02 | 0.34 |
| Aβ-PET negative | mPACCdigit | APOE\*Aβ42\*Time | 0.01 | 0.02 | 0.61 |
| Aβ-PET negative | mPACCtrailsB | APOE\*Aβ42\*Time | 0.01 | 0.01 | 0.55 |
| Aβ-PET negative | MMSE | CHI3L1\*Aβ42\*Time | -0.02 | 0.03 | 0.34 |
| Aβ-PET negative | mPACCdigit | CHI3L1\*Aβ42\*Time | -0.01 | 0.02 | 0.55 |
| Aβ-PET negative | mPACCtrailsB | CHI3L1\*Aβ42\*Time | -0.01 | 0.02 | 0.62 |
| Aβ-PET negative | MMSE | SMOC1\*Aβ42\*Time | -0.01 | 0.03 | 0.61 |
| Aβ-PET negative | mPACCdigit | SMOC1\*Aβ42\*Time | -0.03 | 0.02 | 0.22 |
| Aβ-PET negative | mPACCtrailsB | SMOC1\*Aβ42\*Time | -0.02 | 0.02 | 0.35 |
| Aβ-PET positive | MMSE | APOE\*Aβ42\*Time | 0.20 | 0.08 | 0.02 |
| Aβ-PET positive | mPACCdigit | APOE\*Aβ42\*Time | 0.14 | 0.05 | 0.006 |
| Aβ-PET positive | mPACCtrailsB | APOE\*Aβ42\*Time | 0.15 | 0.05 | 0.007 |
| Aβ-PET positive | MMSE | CHI3L1\*Aβ42\*Time | 0.09 | 0.08 | 0.29 |
| Aβ-PET positive | mPACCdigit | CHI3L1\*Aβ42\*Time | 0.00 | 0.05 | 0.98 |
| Aβ-PET positive | mPACCtrailsB | CHI3L1\*Aβ42\*Time | 0.01 | 0.05 | 0.88 |
| Aβ-PET positive | MMSE | SMOC1\*Aβ42\*Time | 0.03 | 0.08 | 0.70 |
| Aβ-PET positive | mPACCdigit | SMOC1\*Aβ42\*Time | 0.00 | 0.05 | 0.96 |
| Aβ-PET positive | mPACCtrailsB | SMOC1\*Aβ42\*Time | -0.02 | 0.05 | 0.77 |

LME models were utilized to evaluate the associations between the CSF candidate hub proteins and Aβ42-related longitudinal cognitive changes in the Aβ-PET negative and positive groups. Statistics were from the LME model of each analyte, including follow-up time, age, gender, APOE ε4 carrying status, years of education, baseline CSF protein level, baseline CSF Aβ42 level, and the interactions of these variables with follow-up time as covariates. Additionally, the interaction of baseline CSF candidate hub protein levels, baseline Aβ42 levels, and follow-up time was also included as the covariate in the analysis. The CSF protein levels were log-transformed and standardized (z-scored). All other continuous variables were also z-scored. For exploratory investigations, we refrained from conducting *P*-value correction.

APOE: Apolipoprotein E, CHI3L1: Chitinase-3-like protein 1, MMSE: Mini-Mental State Examination, mPACCdigit: Modified Preclinical Alzheimer Cognitive Composite that Used Digit Symbol Substitution Test, mPACCtrailsB: Modified Preclinical Alzheimer Cognitive Composite that Used Trail-Making Test Part B, SMOC1: SPARC-related modular calcium binding 1, SUVRs: FBP-PET standardized uptake value ratios.