**Supplementary Materials**

**Supplementary Method.** Blood collection and processing.

**Supplementary Table 1.** ELISA kits information.

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**Supplementary Table 5.** Cox regression analyses of biomarkers with conversion to MCI in individuals with SCD.

**Supplementary Table 6.** Cox regression analyses of biomarkers with conversion to MCI in cognitively unimpaired controls.

**Supplementary Table 7.** Cox regression analyses of biomarkers with conversion to MCI in individuals with SCD and cognitively unimpaired controls.

**Supplementary Figure 1.** Flowchart of the study.

**Supplementary Figure 2.** The partial correlations adjusted for age, sex, education and APOE ε4.

**Supplementary Figure 3.** Schematic illustration of synaptic transmission involving BACE1 and Neurogranin.

**Supplementary Method. Blood collection and processing.**

Blood samples (serum, plasma, EDTA whole blood, PAX gene RNA and DNA) were also collected between 8:00 AM-12:00 PM at baseline and each annual follow-up. The samples were incubated for 30 minutes until the serum clotted and centrifuged at 2000 x g for 10 minutes at room temperature. After centrifugation, the supernatant was removed to the matrix box tubes (12 x 300 μl serum with clotting activator, 12 x 300 μl serum without clotting activator, 12 x 300 μl EDTA plasma, 12 x 300 μl citrate plasma). Boxes were transferred to -80°C within one hour and shipped on dry ice to the clinical research biobank within two months.

**Supplementary Table 1. ELISA kits information.**

|  |  |  |  |
| --- | --- | --- | --- |
| **ELISA kits** | **Catalog numbers** | **Lot numbers** | **Measurement ranges (pg/ml)** |
| **Neurogranin** |  |  |  |
| Euroimmun (Germany) | EQ 6551-9601-L | E200608BC/E201119AK | 15 - 1300 |
| **BACE1** |  |  |  |
| Euroimmun (Germany) | EQ 6541-9601-L | E200903AV/E201207DX/E210520BY | 26 - 12000 |

**Supplementary Table 2. Number of participants included at baseline and follow-ups.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline** | **Years after baseline** | | | | | |
| **1** | **2** | **3** | **4** | **5** | **6** |
| **n** | 345 | 303 | 253 | 212 | 143 | 81 | 32 |
| **Controls** |  |  |  |  |  |  |  |
| PACC5 |  | 117 | 106 | 90 | 66 | 42 | 16 |
| Conversion to MCI |  | 3 | 3 | 2 | 1 | 0 | 0 |
| **SCD** |  |  |  |  |  |  |  |
| PACC5 |  | 186 | 147 | 122 | 77 | 39 | 16 |
| Conversion to MCI |  | 10 | 11 | 12 | 2 | 2 | 1 |

**Supplementary Table 3. Association of neurogranin, BACE1 and neurogranin/BACE1 ratio with PACC5 change in cognitively unimpaired controls.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LMM Neurogranin (Nindividuals = 137, Nobservations = 574)** | | |  | **LMM BACE1 (Nindividuals = 137, Nobservations = 574)** | | |  | **LMM Neurogranin/BACE1 (Nindividuals = 137, Nobservations = 574)** | | |
| **Fixed effects** |  |  |  |  |  |  |  |  |  |  |  |
|  | **β coefficient** | **SE** | ***p*** |  | **β coefficient** | **SE** | ***p*** |  | **β coefficient** | **SE** | ***p*** |
| Intercept | -1.282 | 0.986 | 0.196 |  | -1.266 | 1.297 | 0.330 |  | -1.539 | 0.852 | 0.073 |
| Age, y | -0.008 | 0.009 | 0.379 |  | -0.008 | 0.009 | 0.382 |  | -0.008 | 0.009 | 0.354 |
| Sex, female | 0.273 | 0.091 | 0.003 |  | 0.270 | 0.092 | 0.004 |  | 0.278 | 0.092 | 0.003 |
| Education, y | 0.077 | 0.017 | <0.001 |  | 0.077 | 0.017 | <0.001 |  | 0.078 | 0.017 | <0.001 |
| APOE ε4 positive | -0.100 | 0.104 | 0.336 |  | -0.101 | 0.104 | 0.332 |  | -0.097 | 0.104 | 0.352 |
| CSF Aβ42/p-Tau181 ratio | 0.707 | 0.249 | 0.005 |  | 0.726 | 0.243 | 0.003 |  | 0.702 | 0.256 | 0.007 |
| Time, y | 0.120 | 0.138 | 0.389 |  | 0.184 | 0.246 | 0.456 |  | -0.015 | 0.084 | 0.855 |
| CSF Neurogranin | -0.072 | 0.253 | 0.777 |  |  |  |  |  |  |  |  |
| Time \* Neurogranin | -0.038 | 0.054 | 0.485 |  |  |  |  |  |  |  |  |
| CSF BACE1 |  |  |  |  | -0.064 | 0.337 | 0.850 |  |  |  |  |
| Time \* BACE1 |  |  |  |  | -0.049 | 0.074 | 0.514 |  |  |  |  |
| CSF Neurogranin/BACE1 ratio |  |  |  |  |  |  |  |  | -0.132 | 0.503 | 0.794 |
| Time \* Neurogranin/BACE1 ratio |  |  |  |  |  |  |  |  | -0.050 | 0.109 | 0.647 |
| **Random effects** |  |  |  |  |  |  |  |  |  |  |  |
|  | **Variance** | **SD** |  |  | **Variance** | **SD** |  |  | **Variance** | **SD** |  |
| Intercept | 0.212 | 0.461 |  |  | 0.212 | 0.461 |  |  | 0.212 | 0.461 |  |
| Time | 0.004 | 0.062 |  |  | 0.004 | 0.062 |  |  | 0.004 | 0.062 |  |
| Residual | 0.081 | 0.285 |  |  | 0.081 | 0.285 |  |  | 0.081 | 0.284 |  |

All biomarker values were log10 transformed prior to approximate normal distribution.

Abbreviations: LMM = linear mixed model; SD = standard deviation; SE = standard error.

**Supplementary Table 4. Association of neurogranin, BACE1 and neurogranin/BACE1 ratio with PACC5 change in individuals with SCD and cognitively unimpaired controls.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LMM Neurogranin (Nindividuals = 344, Nobservations = 1360)** | | |  | **LMM BACE1 (Nindividuals = 344, Nobservations = 1360)** | | |  | **LMM Neurogranin/BACE1 (Nindividuals = 344, Nobservations = 1360)** | | |
| **Fixed effects** |  |  |  |  |  |  |  |  |  |  |  |
|  | **β coefficient** | **SE** | ***p*** |  | **β coefficient** | **SE** | ***p*** |  | **β coefficient** | **SE** | ***p*** |
| Intercept | 0.529 | 0.497 | 0.288 |  | 0.441 | 0.498 | 0.377 |  | 0.694 | 0.516 | 0.179 |
| Age, y | -0.028 | 0.006 | <0.001 |  | -0.027 | 0.006 | <0.001 |  | -0.028 | 0.006 | <0.001 |
| Sex, female | 0.381 | 0.062 | <0.001 |  | 0.382 | 0.061 | <0.001 |  | 0.382 | 0.063 | <0.001 |
| Education, y | 0.050 | 0.010 | <0.001 |  | 0.049 | 0.010 | <0.001 |  | 0.050 | 0.010 | <0.001 |
| APOE ε4 positive | -0.042 | 0.069 | 0.543 |  | -0.035 | 0.069 | 0.614 |  | -0.036 | 0.069 | 0.606 |
| CSF Aβ42/pTau181 ratio | 0.447 | 0.147 | 0.002 |  | 0.481 | 0.144 | 0.001 |  | 0.451 | 0.144 | 0.002 |
| Controls (Ref) |  |  |  |  |  |  |  |  |  |  |  |
| SCD | -0.138 | 0.087 | 0.114 |  | -0.124 | 0.087 | 0.154 |  | -0.331 | 0.184 | 0.073 |
| Time, y | 0.020 | 0.019 | 0.271 |  | 0.029 | 0.019 | 0.120 |  | 0.057 | 0.037 | 0.131 |
| Controls \* Time (Ref) |  |  |  |  |  |  |  |  |  |  |  |
| SCD \* Time | -0.018 | 0.023 | 0.421 |  | -0.052 | 0.023 | 0.030 |  | -0.016 | 0.050 | 0.747 |
| Neurogranin (Dichotomous) | -0.036 | 0.092 | 0.696 |  |  |  |  |  |  |  |  |
| Controls \* Neurogranin (Ref) |  |  |  |  |  |  |  |  |  |  |  |
| SCD \* Neurogranin | 0.080 | 0.120 | 0.506 |  |  |  |  |  |  |  |  |
| Time \* Neurogranin | 0.002 | 0.024 | 0.926 |  |  |  |  |  |  |  |  |
| Controls \* Time \* Neurogranin (Ref) |  |  |  |  |  |  |  |  |  |  |  |
| SCD \* Time \* Neurogranin | **-0.077** | **0.033** | **0.020** |  |  |  |  |  |  |  |  |
| BACE1 (Dichotomous) |  |  |  |  | 0.010 | 0.091 | 0.916 |  |  |  |  |
| Controls \* BACE1 (Ref) |  |  |  |  |  |  |  |  |  |  |  |
| SCD \* BACE1 |  |  |  |  | 0.058 | 0.119 | 0.627 |  |  |  |  |
| Time \* BACE1 |  |  |  |  | -0.012 | 0.024 | 0.620 |  |  |  |  |
| Controls \* Time \* BACE1 (Ref) |  |  |  |  |  |  |  |  |  |  |  |
| SCD \* Time \* BACE1 |  |  |  |  | 0.006 | 0.033 | 0.855 |  |  |  |  |
| Neurogranin/BACE1 (Dichotomous) |  |  |  |  |  |  |  |  | -0.099 | 0.092 | 0.286 |
| Controls \* Neurogranin/BACE1 (Ref) |  |  |  |  |  |  |  |  |  |  |  |
| SCD \* Neurogranin/BACE1 |  |  |  |  |  |  |  |  | 0.159 | 0.118 | 0.180 |
| Time \* Neurogranin/BACE1 |  |  |  |  |  |  |  |  | -0.024 | 0.024 | 0.329 |
| Controls \* Time \* Neurogranin/BACE1 (Ref) |  |  |  |  |  |  |  |  |  |  |  |
| SCD \* Time \* Neurogranin/BACE1 |  |  |  |  |  |  |  |  | -0.021 | 0.033 | 0.516 |
| **Random effects** |  |  |  |  |  |  |  |  |  |  |  |
|  | **Variance** | **SD** |  |  | **Variance** | **SD** |  |  | **Variance** | **SD** |  |
| Intercept | 0.223 | 0.472 |  |  | 0.223 | 0.473 |  |  | 0.223 | 0.472 |  |
| Time | 0.007 | 0.085 |  |  | 0.008 | 0.088 |  |  | 0.008 | 0.088 |  |
| Residual | 0.089 | 0.299 |  |  | 0.089 | 0.299 |  |  | 0.089 | 0.298 |  |

CSF Aβ42/pTau181 ratio was log10 transformed prior to analysis.

Abbreviations: LMM = linear mixed model; SCD = subjective cognitive decline; SD = standard deviation; SE = standard error; Ref = reference.

**Supplementary Table 5. Cox regression analyses of biomarkers with conversion to MCI** **in individuals with SCD.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cox Neurogranin** | |  | **Cox BACE1** | |  | **Cox Neurogranin/BACE1** | |
|  | **HR (95% CI)** | ***p*** |  | **HR (95% CI)** | ***p*** |  | **HR (95% CI)** | ***p*** |
| Age, y | 0.99 (0.91–1.07) | 0.802 |  | 0.99 (0.91–1.07) | 0.799 |  | 0.98 (0.91–1.07) | 0.686 |
| Sex, female | 2.55 (1.05–6.21) | 0.039 |  | 2.78 (1.16–6.66) | 0.022 |  | 2.20 (0.89–5.44) | 0.088 |
| Education, y | 1.10 (0.98–1.24) | 0.093 |  | 1.11 (1.00–1.25) | 0.059 |  | 1.10 (0.98–1.23) | 0.114 |
| APOE ε4 positive | 1.33 (0.61–2.87) | 0.475 |  | 1.21 (0.57–2.60) | 0.620 |  | 1.33 (0.61–2.88) | 0.469 |
| CSF Aβ42/pTau181 ratio (per SD) | 0.76 (0.48–1.20) | 0.246 |  | 0.67 (0.43–1.04) | 0.071 |  | 0.78 (0.51–1.21) | 0.272 |
| PACC5 | 0.17 (0.08–0.33) | <0.001 |  | 0.17 (0.08–0.33) | <0.001 |  | 0.16 (0.08–0.32) | <0.001 |
| CSF Neurogranin (per SD) | 1.28 (0.95–1.72) | 0.100 |  |  |  |  |  |  |
| CSF BACE1 (per SD) |  |  |  | 1.09 (0.77–1.54) | 0.628 |  |  |  |
| CSF Neurogranin/BACE1 ratio (per SD) |  |  |  |  |  |  | **1.48 (1.08–2.04)** | **0.016** |

Abbreviations: CI = confidence interval; HR = hazard ratio; SD = standard deviation.

**Supplementary Table 6. Cox regression analyses of biomarkers with conversion to MCI in cognitively unimpaired controls.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cox Model 1** | |  | **Cox Model 2** | |  | **Cox Model 3** | |
|  | **HR (95% CI)** | ***p*** |  | **HR (95% CI)** | ***p*** |  | **HR (95% CI)** | ***p*** |
| CSF Neurogranin (per SD) | 1.17 (0.53–2.55) | 0.701 |  | 0.64 (0.24–1.68) | 0.364 |  | 0.56 (0.20–1.58) | 0.273 |
| CSF BACE1 (per SD) | 0.72 (0.34–1.56) | 0.410 |  | 0.47 (0.18–1.25) | 0.131 |  | 0.44 (0.16–1.22) | 0.115 |
| CSF Neurogranin/BACE1 ratio (per SD) | 2.10 (0.97–4.55) | 0.059 |  | 1.20 (0.51–2.81) | 0.675 |  | 1.08 (0.43–2.67) | 0.872 |

Model 1: adjusted for age, sex, education, APOE ε4 status; Model 2: adjusted for age, sex, education, APOE ε4 status, and Aβ42/pTau181 ratio; Model 3: adjusted for age, sex, education, APOE ε4 status, Aβ42/pTau181 ratio, and PACC5;

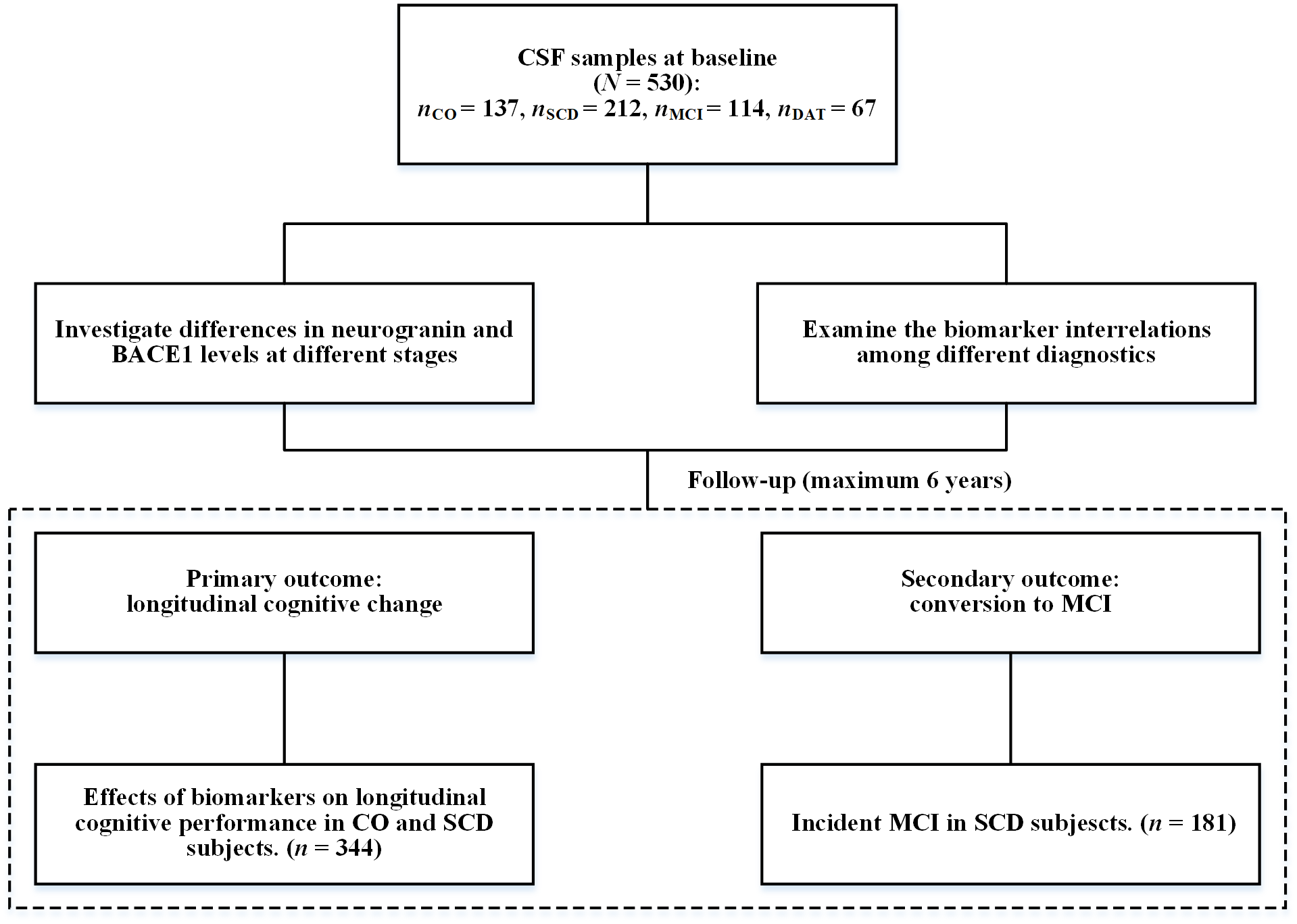
Abbreviations: CI = confidence interval; HR = hazard ratio; SD = standard deviation.

**Supplementary Table 7. Cox regression analyses of biomarkers with conversion to MCI in individuals with SCD and cognitively unimpaired controls.**

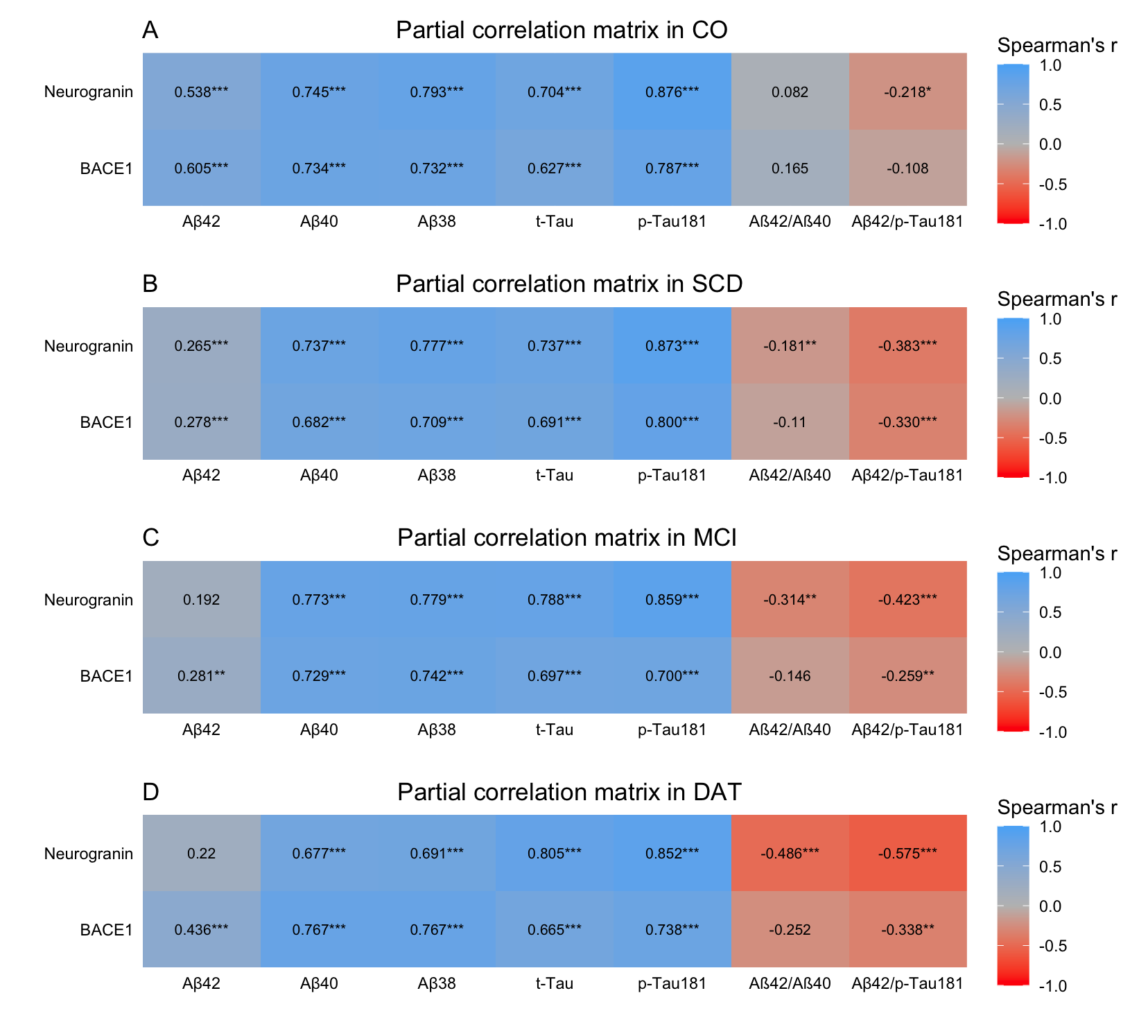
|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cox Neurogranin**  **Cox Neurogranin** | |  | **Cox BACE1** | |  | **Cox Neurogranin/BACE1**  **Cox Neurogranin/BACE1** | |
| **HR (95% CI)** | ***p*** |  | **HR (95% CI)** | ***p*** |  | **HR (95% CI)** | ***p*** |
| Age, y | 1.05 (0.99–1.11) | 0.091 |  | 1.06 (1.00–1.12) | 0.041 |  | 1.05 (0.99–1.11) | 0.120 |
| Sex, female | 0.53 (0.27–1.07) | 0.075 |  | 0.64 (0.33–1.24) | 0.184 |  | 0.48 (0.24–0.98) | 0.042 |
| Education, y | 0.96 (0.87–1.07) | 0.471 |  | 0.98 (0.88–1.08) | 0.640 |  | 0.95 (0.85–1.05) | 0.321 |
| APOE ε4 positive | 1.78 (0.96–3.30) | 0.067 |  | 1.88 (1.03–3.46) | 0.041 |  | 1.77 (0.96–3.25) | 0.065 |
| SCD with higher biomarker levels (Ref) |  |  |  |  |  |  |  |  |
| SCD with lower biomarker levels | **0.47 (0.24–0.93)** | **0.029** |  | 0.80 (0.42–1.52) | 0.489 |  | **0.37 (0.18–0.78)** | **0.008** |
| CO with higher biomarker levels | **0.23 (0.08–0.63)** | **0.005** |  | **0.31 (0.11–0.85)** | **0.024** |  | **0.33 (0.13–0.85)** | **0.021** |
| CO with lower biomarker levels | **0.29 (0.10–0.89)** | **0.030** |  | 0.40 (0.13–1.22) | 0.107 |  | **0.16 (0.05–0.54)** | **0.003** |

Abbreviations: CI = confidence interval; HR = hazard ratio; SD = standard deviation.

**Supplementary Figure 1. Flowchart of the study.**

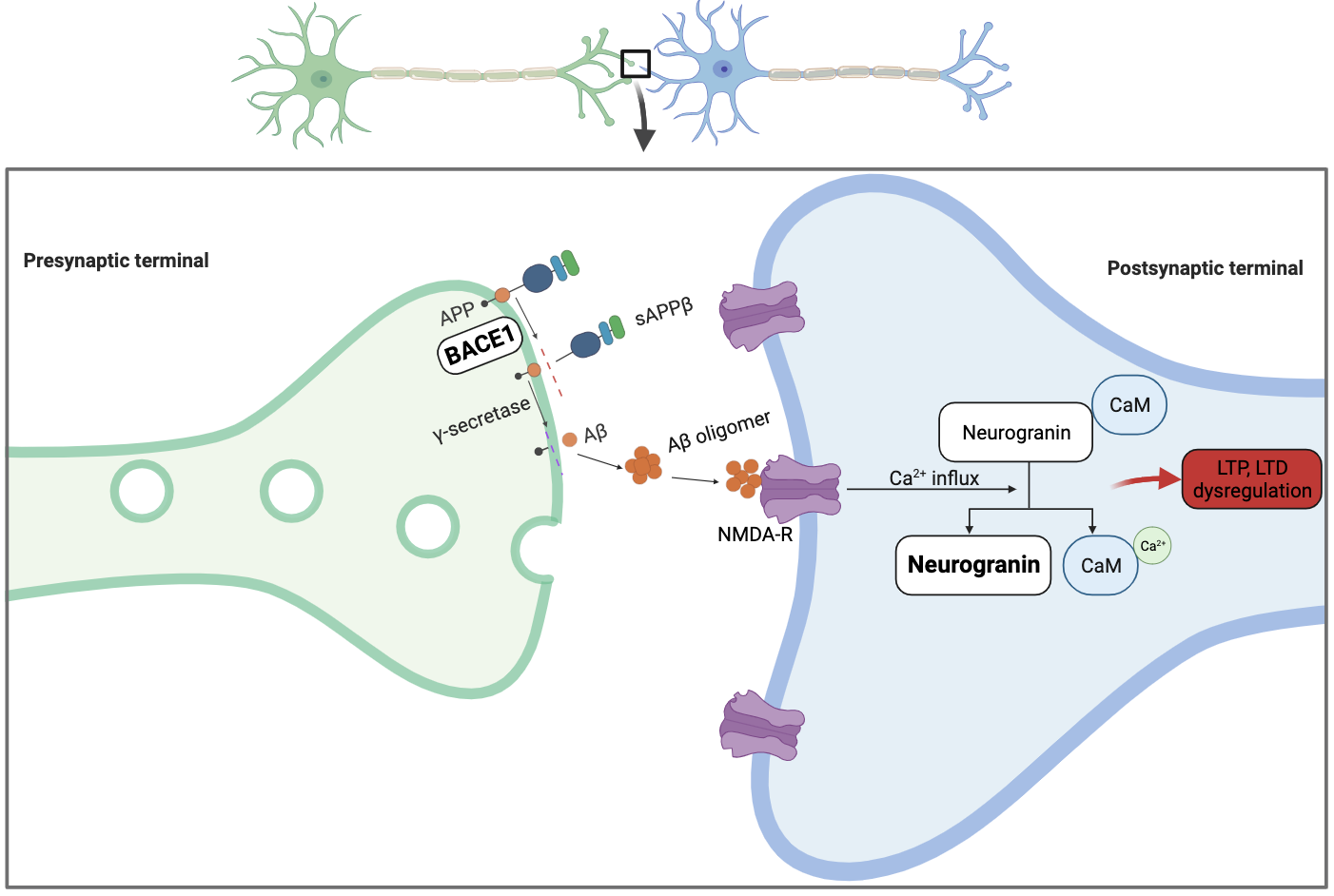


**Supplementary Figure 2. The partial correlations adjusted for age, sex, education and APOE ε4.**

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\*: *p* < 0.05, \*\*: *p* < 0.01, \*\*\*: *p* < 0.001.

**Supplementary Figure 3. Schematic illustration of synaptic transmission involving BACE1 and Neurogranin.**

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Abbreviations: APP = Amyloid precursor protein; BACE1 = β-site amyloid precursor protein cleaving enzyme 1; CaM = Calmodulin; LTD = long-term depression; LTP = long-term potentiation; NMDA-R = N-methyl-D-aspartate receptor; sAPPβ = Soluble amyloid precursor protein β.