

Supplementary Materials

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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 (N _{individuals} = 137, N _{observations} = 574)			LMM BACE1 (N _{individuals} = 137, N _{observations} = 574)			LMM Neurogranin/BACE1 (N _{individuals} = 137, N _{observations} = 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.

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 A β 42/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)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
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 ϵ 4 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 A β 42/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)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
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 ϵ 4 status; Model 2: adjusted for age, sex, education, APOE ϵ 4 status, and A β 42/pTau181 ratio; Model 3: adjusted for age, sex, education, APOE ϵ 4 status, A β 42/pTau181 ratio, and PACCS5;

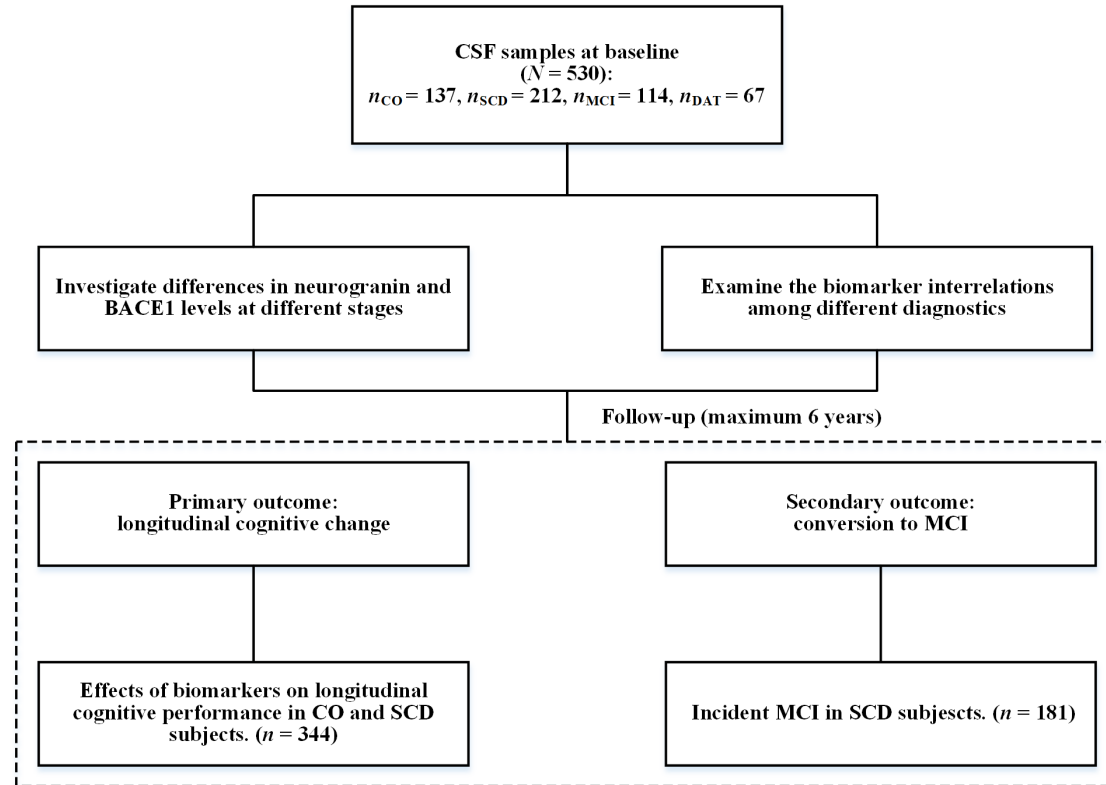
Abbreviations: CI = confidence interval; HR = hazard ratio; SD = standard deviation.

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

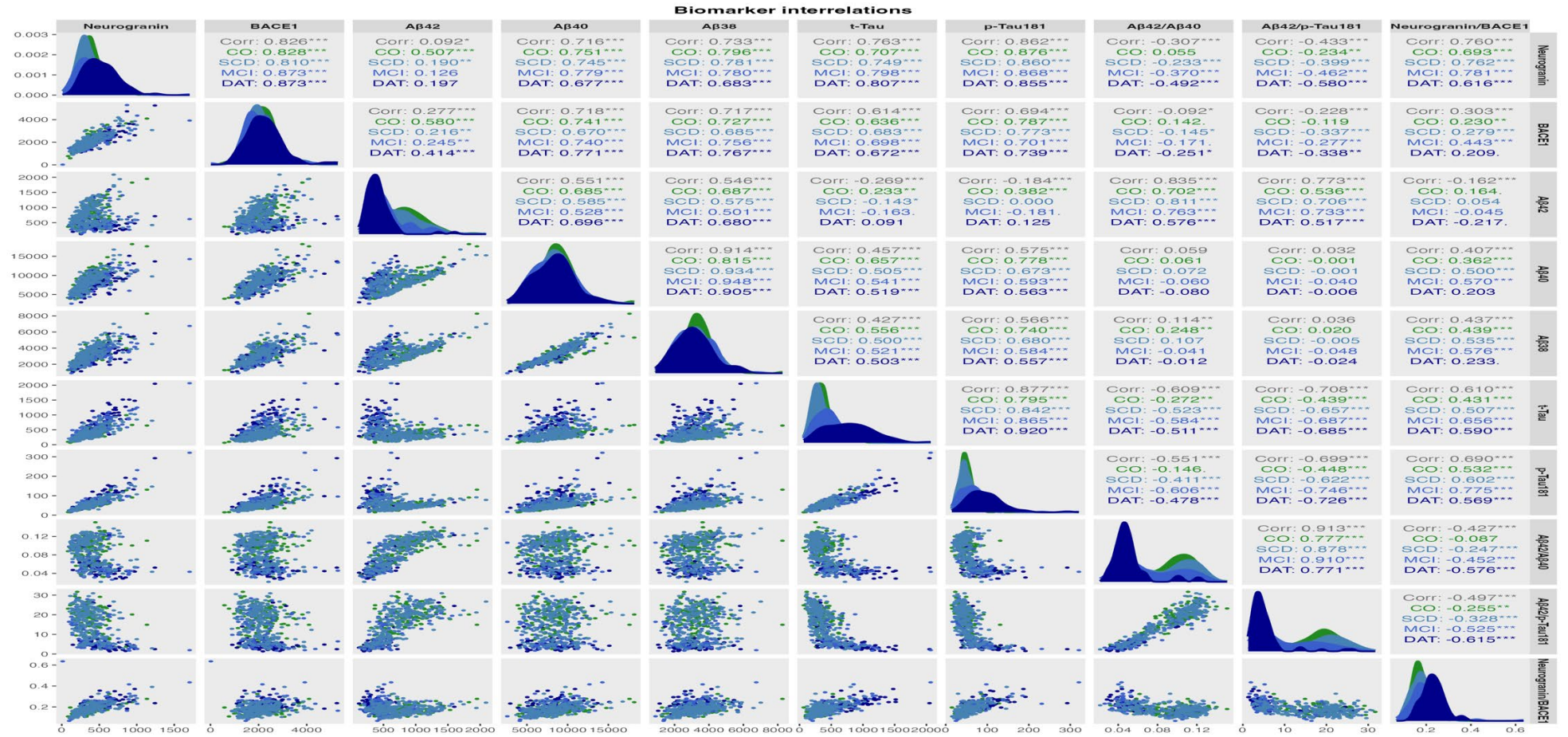
	Cox Neurogranin		Cox BACE1		Cox Neurogranin/BACE1	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age, y	1.05 (0.99–1.11)	0.091	1.06 (1.00–1.12)	0.041	1.05 (0.99–1.11)	0.120
Sex, female	0.53 (0.27–1.07)	0.075	0.64 (0.33–1.24)	0.184	0.48 (0.24–0.98)	0.042
Education, y	0.96 (0.87–1.07)	0.471	0.98 (0.88–1.08)	0.640	0.95 (0.85–1.05)	0.321
APOE ϵ 4 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.

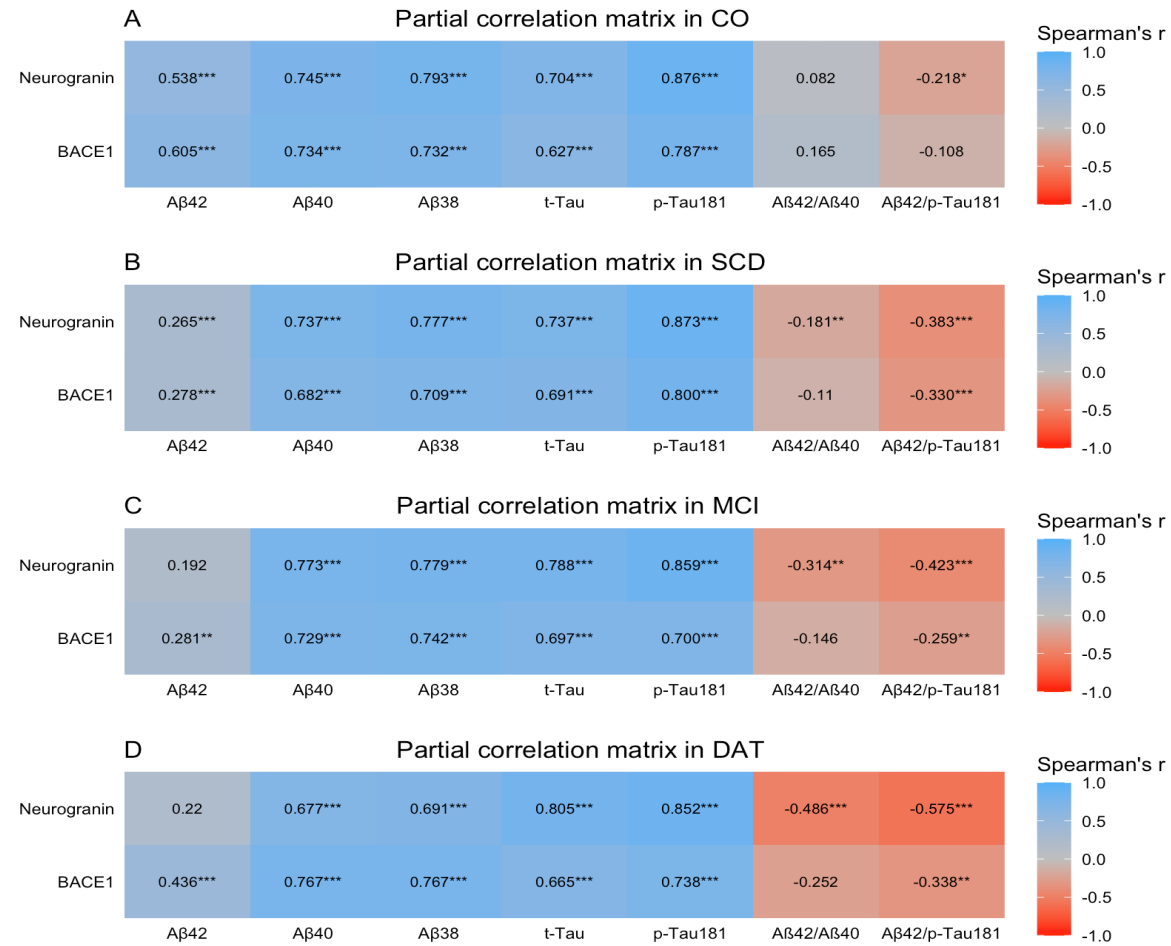


Supplementary Figure 2. Biomarker interrelations among different diagnostics.



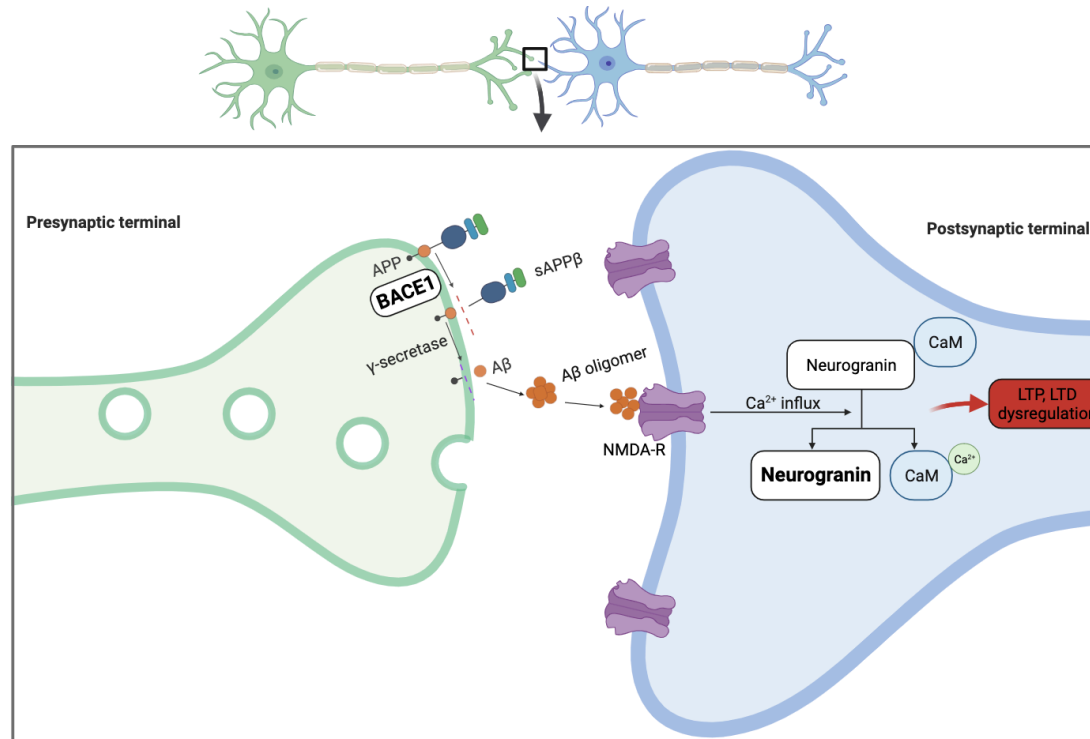
The nonparametric Spearman correlation analysis was performed to investigate the strength (rho) of all correlations. The upper right corner: correlation coefficient; the lower left corner: scatter plot; the diagonal: distribution of variables. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$. Abbreviations: Corr = correlation coefficient.

Supplementary Figure 3. The partial correlations adjusted for age, sex, education and APOE ε4.



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

Supplementary Figure 4. Schematic illustration of synaptic transmission involving BACE1 and Neurogranin.



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; sAPP β = Soluble amyloid precursor protein β .