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Association of Neurogranin and BACE1 With Clinical Cognitive Decline in Individuals With Subjective Cognitive Decline

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Abstract

Background and Objectives

CSF biomarkers have immense diagnostic and prognostic potential for Alzheimer disease (AD). However, AD is still diagnosed relatively late in the disease process, sometimes even years after the initial manifestation of cognitive symptoms. Thus, further identification of biomarkers is required to detect related pathology in the preclinical stage and predict cognitive decline. Our study aimed to assess the association of neurogranin and β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) with cognitive decline in individuals with subjective cognitive decline (SCD).

Methods

We enrolled participants with available neurogranin and BACE1 measurements in CSF from the DELCODE (DZNE-Longitudinal Cognitive Impairment and Dementia, Germany) cohort. The longitudinal change of Preclinical Alzheimer's Cognitive Composite score was assessed as the primary outcome in participants with SCD and controls. The secondary outcome was defined as conversion of SCD to mild cognitive impairment (MCI) during follow-up. Levels of neurogranin, BACE1, and neurogranin/BACE1 ratio across groups were compared by analysis of covariance after adjustment for demographics. The linear mixed-effects model and Cox regression analysis were applied to evaluate their association with cognitive decline and progression of SCD to MCI, respectively.

Results

A total of 530 participants (mean age: 70.76 ± 6.01 years, 48.7% female) were analyzed in the study. The rate of cognitive decline was faster in individuals with SCD with higher neurogranin

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale–Cognitive subscale; **A/T** = amyloid/tau; **BACE1** = β-site amyloid precursor protein-cleaving enzyme 1; **CDR** = Clinical Dementia Rating; **CERAD-NAB** = Consortium to Establish a Registry for Alzheimer's Disease Neuropsychology Assessment Battery; **COs** = cognitively unimpaired controls; **CoV** = coefficient of variation; **DAT** = dementia of the Alzheimer type; **DELCODE** = DZNE-Longitudinal Cognitive Impairment and Dementia; **HR** = hazard ratio; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **PACC5** = Preclinical Alzheimer's Cognitive Composite; **p-Tau181** = phosphorylated tau 181; **SCD** = subjective cognitive decline.

and neurogranin/BACE1 ratio (β = −0.138, SE = 0.065, p = 0.037, and β = −0.293, SE = 0.115, p = 0.013). Higher baseline neurogranin and neurogranin/BACE1 ratio were associated with an increased rate of conversion from SCD to MCI (hazard ratio [HR] 1.35 per SD, 95% CI 1.03–1.77, p = 0.028, and HR 1.53 per SD, 95% CI 1.13–2.07, p = 0.007). In addition, the impact of higher neurogranin levels on accelerating the rate of cognitive decline was more pronounced in the SCD group than in cognitively unimpaired controls (β = −0.077, SE = 0.033, p = 0.020).

Discussion

Our findings suggest that CSF neurogranin and BACE1 begin to change in the preclinical stage of AD and they are associated with clinical progression in individuals with SCD.

Introduction

As the most common form of dementia, the process of Alzheimer disease (AD) can begin more than 20 years before cognitive impairment becomes apparent.[1] It is now widely agreed on that AD should be regarded as a continuum, from imperceptible brain changes to dementia, rather than just a cognitive disorder.[2,3] Although anti-amyloid immunotherapies have reached a milestone, many challenges still remain, such as uncertainty regarding the enduring clinical benefits and amyloid-related imaging abnormalities.[4-6] Some researchers believe that the early identification of preclinical AD is crucial to initiate interventional treatment, and that it might be more effective if drugs are aimed at the preclinical stage before the onset of manifest and irreversible cognitive deterioration.[7]

Previous studies have found that subjective cognitive decline (SCD), defined in individuals who complain of a subjective decrease in cognitive function without evidence of objective cognitive impairment in neuropsychological testing, can indicate preclinical AD.[8,9] These individuals have cognitive concerns and actively seek medical advice, making them a highly promising target group for early interventions.[9] However, there is no reliable clinical method to determine which individuals with SCD will progress to an objective cognitive decline. Hence, there is a great clinical need for biomarkers that can identify high-risk individuals in the preclinical stage of AD.

Growing evidence suggests that synaptic dysfunction is an early pathophysiologic feature of AD and strongly correlates with cognitive decline.[10] In recent years, it has been reported that neurogranin and β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) can regulate synaptic function.[11,12] Neurogranin is a postsynaptic protein primarily expressed in dendritic spines and strongly correlated with neurodegeneration and synaptic plasticity.[13] Several studies have examined the performance of CSF neurogranin, showing that it is significantly elevated in AD dementia and mild cognitive impairment (MCI).[14,15] BACE1 localizes to presynaptic terminals surrounding amyloid plaques and initiates the formation of toxic β-amyloid (Aβ) peptides.[16,17] Although clinical trials of BACE inhibitors have failed to slow cognitive decline in symptomatic AD, it is still believed that long-term low doses of BACE inhibition beginning at the very early preclinical stage might offer a prospect of AD prevention.[18,19] To date, neurogranin and BACE1 have been extensively investigated in many studies. However, there is still limited knowledge regarding their associations with SCD. This study mainly aimed to explore the association of neurogranin, BACE1, and neurogranin/BACE1 ratio with cognitive decline in individuals with SCD. In addition, we also compared their levels among different amyloid/tau (A/T) profiles and diagnostic groups and examined their relationship with key CSF biomarkers of AD.

Methods

Study Participants

We enrolled participants from the DELCODE (DZNE-Longitudinal Cognitive Impairment and Dementia, Germany) cohort. DELCODE is an ongoing multisite (10 memory clinic sites in total) prospective cohort that was launched in 2014, including participants with SCD, amnestic MCI, and mild dementia of the Alzheimer type (DAT) and cognitively unimpaired controls (COs).[20] SCD was defined as a self-perceived subjective decline in cognitive function without evidence of objective cognitive impairment in neuropsychological testing, based on a performance of better than

1.5 SDs below the normal age-adjusted, sex-adjusted, and education-adjusted norms on all subtests of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychology Assessment Battery (CERAD-NAB).[9,20] The amnestic MCI group consisted of participants with performance worse than 1.5 SDs below the demographically adjusted norms in the delayed word list recall trial of the CERAD-NAB. The mild DAT was defined by a Mini-Mental State Examination (MMSE) score of ≥18 points. The diagnoses of MCI and DAT were made according to the National Institute on Aging-Alzheimer's Association criteria.[21,22] Cognitively unimpaired controls without any cognitive concerns were recruited through advertisements. In addition, participants were required to fulfill the following inclusion criteria: aged 60 years or older, fluent in German, capable of providing informed consent, and accompanied by a study partner. The framework of the study follows a standard operating procedure and includes a comprehensive clinical and neuropsychological examination conducted by trained health care professionals, a detailed neuropsychological assessment to assess memory functions and other areas of cognitive performance, a blood and urine test, and a cranial magnetic resonance imaging scan. Lumbar puncture was performed to collect CSF after obtaining participants' informed consent.

The participants of this study were enrolled between April 2014 and August 2018, and only those with available neurogranin and BACE1 measurements in CSF were included in the analysis. eFigure 1 presents the design of the study.

Samples Collection and Processing

CSF samples were collected between 8:00 AM and 12:00 PM at baseline and every second year during follow-up after overnight fasting. A maximum of 15 mL of CSF per participant was collected in a protocol-specific polypropylene tube and immediately centrifuged at 2,000*g* for 10 minutes at room temperature. The sample was then aliquoted to a maximum of 36 (300 μL each), 12 of which were shock-frozen in liquid nitrogen for 30 seconds. CSF was transferred to −80°C within 30 minutes of collection and stored at the local laboratory for up to 2 months before being shipped on dry ice to the clinical research biobank within 24 hours. The samples underwent 2 freeze-thaw cycles from collection to measurement. The collection and processing of blood samples are described in the eMethods.

APOE Genotyping

The single-nucleotide variations of APOE (rs429358 and rs7412) were assessed using the TaqMan SNP Genotyping Assay (ThermoFisher Scientific, Waltham, MA). Genomic DNA was amplified using a StepOnePlus Real-Time PCR System (ThermoFisher Scientific).

Measurement of CSF Biomarkers

Established CSF cutoffs from the DELCODE data set were used to define AD biomarker-positive status and classify participants into A/T profiles (Aβ42/Aβ40 ≤0.08, phosphorylated tau 181 [p-Tau181] ≥73.65 pg/mL).[23] It has been shown that a lower CSF Aβ42/p-Tau181 ratio serves as a highly accurate risk marker of cognitive decline.[24] Therefore, we further subdivided participants with SCD into 2 groups according to the Aβ42/p-Tau181 ratio (cutoff value for Aβ42/p-Tau181: 9.68): SCD− (individuals with higher Aβ42/p-Tau181) and SCD+ (individuals with lower Aβ42/p-Tau181). CSF levels of neurogranin and BACE1 were measured in duplicate by the ELISA. eTable 1 summarizes the information of ELISA kits. The coefficient of variation (CoV) was expressed as percentage to determine the variability of the assay. A larger CoV indicates greater inconsistency and potential error, so we included only CoVs less than 20% as recommended in the instructions.

Neuropsychological and Clinical Outcome Assessments

Cognitive function was assessed annually. The Clinical Dementia Rating (CDR) scale was used to assess symptom severity (CDR-Global: scores 0–3; CDR Scale Sum of Boxes: scores 0–18). In addition, the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog-11: scores 0–70; ADAS-Cog-13: scores 0–85) and the Clock Drawing Test (scores 0–10) were also examined.[25-27] The Preclinical Alzheimer's Cognitive Composite (PACC5), consisting of the MMSE (scores 0–30), the Free and Cued Selective Reminding Test (scores 0–96), the Wechsler Memory Scale-IV Logical Memory Story B delayed recall (scores 0–25), the Symbol-Digit-Modalities Test (scores 0–90), and the sum of 2 verbal fluency tasks (animals, groceries), was calculated as a multidomain and sensitive composite measure for early cognitive decline by averaging the z-scores of each test.[28,29]

Only participants with at least 1 follow-up visit were included in the outcome assessments. The longitudinal PACC5 was assessed as the primary outcome in participants with SCD and COs to investigate the association of neurogranin, BACE1, and neurogranin/BACE1 ratio with cognitive change. In addition, the secondary outcome was defined as conversion of SCD to MCI during follow-up. The clinical progression to incident MCI[30] was evaluated by experienced neuropsychologists according to established diagnostic criteria. eTable 2 provides the number of participants with SCD and COs with available follow-up information (baseline: n = 345; Y1: n = 303; Y2: n = 253; Y3: n = 212; Y4: n = 143; Y5: n = 81; Y6: n = 32).

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the ethical committees and institutional review boards of all DELCODE study sites. Written informed consent was obtained from all participants before the enrollment.

Statistical Analysis

SPSS (version 25), R (version 4.3.1), Prism 9 (version 9.5.1), and BioRender (biorender.com) were used for statistical analysis and data visualization. The Kruskal-Wallis *H* test was used for baseline comparisons of non-normally distributed continuous variables among different diagnostic groups while

the χ^2 test was used for comparisons of categorical variables. In the comparative analyses of biomarker levels, the concentrations of CSF neurogranin and BACE1 and the neurogranin/BACE1 ratio were log10-transformed before approximate normal distribution and compared using an analysis of covariance to test for the differences between groups, with age, sex, years of education, and *APOE* ε4 allele status as covariates and Bonferroni correction for pairwise comparisons. The Spearman correlation analysis was performed to investigate the relationships between CSF key biomarkers. Partial correlation measured the biomarker interrelations while controlling for covariates.

A linear mixed-effects model implemented in R package lme4 was used to explore the associations between log10-transformed biomarker levels at baseline and longitudinal cognitive change, adjusting for CSF Aβ42/p-Tau181 in addition to the traditional risk factors (age, sex, education, and *APOE* ε4 status). Separate models with random slopes and intercepts were built for neurogranin, BACE1, and neurogranin/BACE1 ratio using PACC5 as the primary outcome. Cox regression with the same fitted model as mentioned above was applied to assess the relationship between biomarkers and the rate of conversion to MCI. Statistical significance was set at $p < 0.05$ (2-sided).

Data Availability

Owing to participant privacy, data availability for the DELCODE study is restricted, but anonymized data analyzed in this study can be obtained by request from qualified academic investigators for the sole purpose of replicating procedures and results. Further details are given online.[31]

Results

Participant Characteristics

Table 1 presents the baseline characteristics and CSF biomarker levels for each group (COs: n = 137, SCD: n = 212, MCI: n = 114, DAT: n = 67). Of the 530 participants finally

Table 1 Baseline Characteristics of Participants

Characteristic	Overall (N = 530)	CO (n = 137)	SCD (n = 212)	MCI (n = 114)	DAT (n = 67)	*p* Value
Age, y	70.76 (6.01)	67.59 (4.95)	70.92 (5.83)	71.77 (5.38)	75.00 (6.30)	<0.001
Female, n (%)	258 (48.7)	74 (54.0)	91 (42.9)	49 (43.0)	44 (65.7)	0.004
Education, y	14.31 (2.94)	14.43 (2.68)	14.87 (2.97)	13.83 (2.93)	13.10 (2.98)	<0.001
***APOE* ε4+, n (%)**	204 (38.9)	37 (27.0)	71 (34.0)	54 (48.2)	42 (62.7)	<0.001
MMSE	28.10 (2.58)	29.33 (0.92)	29.14 (1.10)	27.58 (1.93)	23.18 (3.13)	<0.001
PACC5	−0.70 (1.32)	0.05 (0.60)	−0.17 (0.63)	−1.60 (0.99)	−3.59 (1.26)	<0.001
CDR-SOB	1.08 (1.75)	0.10 (0.42)	0.39 (0.62)	1.56 (1.17)	4.45 (2.25)	<0.001
CDR-Global	0.29 (0.32)	0.02 (0.08)	0.22 (0.25)	0.49 (0.14)	0.77 (0.29)	<0.001
ADAS-Cog-11	6.74 (6.09)	3.45 (1.91)	3.80 (1.93)	9.49 (4.86)	18.11 (6.53)	<0.001
ADAS-Cog-13	11.60 (9.22)	6.07 (3.52)	7.06 (3.53)	16.70 (6.99)	28.65 (7.90)	<0.001
Clock Drawing Test	8.54 (1.85)	9.07 (1.19)	9.09 (1.26)	8.22 (1.83)	6.28 (2.62)	<0.001
CSF Aβ42, pg/mL	707.99 (341.75)	844.38 (315.46)	771.98 (335.78)	586.31 (305.80)	425.83 (228.69)	<0.001
CSF Aβ40, pg/mL	8,420.25 (2,299.83)	8,706.32 (2,339.63)	8,424.37 (2,192.04)	8,151.54 (2,363.01)	8,269.19 (2,428.05)	0.347
CSF t-Tau, pg/mL	458.73 (278.62)	363.96 (154.81)	370.45 (184.93)	541.77 (298.67)	798.10 (376.17)	<0.001
CSF p-Tau181, pg/mL	61.89 (33.91)	50.54 (19.14)	54.06 (23.99)	70.57 (41.85)	95.88 (43.64)	<0.001
CSF Aβ42/Aβ40	0.08 (0.03)	0.10 (0.02)	0.09 (0.03)	0.07 (0.03)	0.05 (0.02)	<0.001
CSF Aβ42/p-Tau181	14.21 (7.95)	17.88 (5.97)	16.36 (7.48)	10.83 (7.34)	5.39 (4.57)	<0.001
CSF neurogranin, pg/mL	412.11 (197.80)	385.38 (159.33)	377.22 (172.88)	441.26 (241.90)	527.55 (212.48)	<0.001
CSF BACE1, pg/mL	2,134.48 (655.83)	2,159.16 (614.56)	2,088.93 (606.41)	2,114.96 (715.47)	2,261.09 (770.40)	0.232
CSF neurogranin/BACE1	0.19 (0.06)	0.18 (0.04)	0.18 (0.05)	0.20 (0.08)	0.23 (0.05)	<0.001

Abbreviations: Aβ = β-amyloid; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive subscale; BACE1 = β-site amyloid precursor protein-cleaving enzyme 1; CDR = Clinical Dementia Rating; CDR-SOB = Clinical Dementia Rating Scale Sum of Boxes; COs = cognitively unimpaired controls; DAT = dementia of the Alzheimer type; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PACC5 = Preclinical Alzheimer's Cognitive Composite; p-Tau181 = phosphorylated tau 181; SCD = subjective cognitive decline.
Continuous variables are presented as mean (SD). *p* Values were derived from the Kruskal-Wallis *H* test for continuous non-normally distributed variables and the Pearson χ^2 test for categorical variables.

enrolled, 258 (48.7%) were female. There were significant differences between the groups regarding age, sex, and education. The proportion of *APOE* ε4 allele carriers was highest in the DAT group (62.7%). Individuals with DAT had the lowest cognitive scores (MMSE, PACC5, and Clock Drawing Test) and CSF Aβ42, Aβ42/Aβ40, and Aβ42/p-Tau181 levels, in addition to the highest CDR, ADAS-Cog, CSF t-Tau, p-Tau181, neurogranin, and neurogranin/BACE1 levels compared with other groups.

Comparison of CSF Biomarker Levels Between Different A/T Profiles and Diagnostic Groups

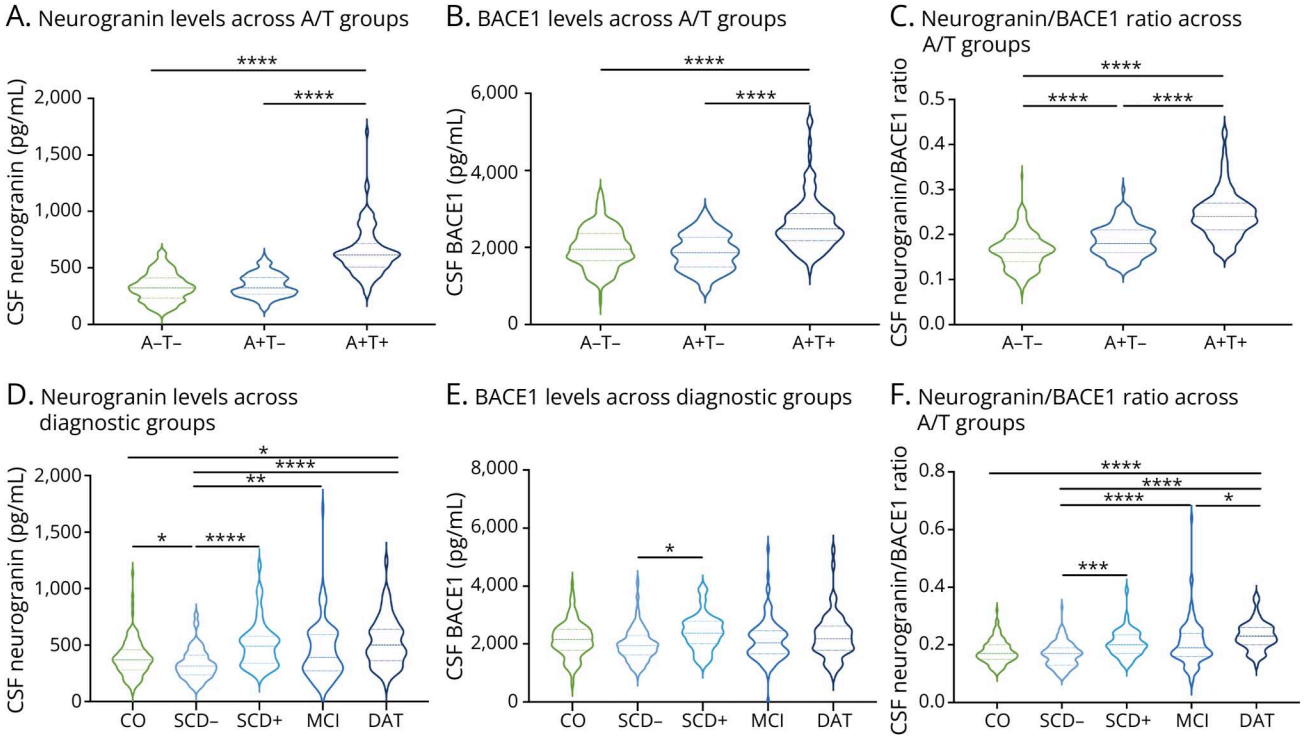
We applied A/T classification using DELCODE-specific cutoff values for the CSF Aβ42/Aβ40 ratio and p-Tau181 (n_{A-T-} = 275, n_{A+T-} = 122, n_{A+T+} = 115). Given the limited sample size of the A−T+ group (n = 15), we did not include this group in our analyses. As presented in Figure 1, A–C, CSF neurogranin, BACE1, and neurogranin/BACE1 levels were significantly higher in the A+T+ group compared with A+T− and A−T− groups after adjustment for covariates and Bonferroni correction for multiple comparisons (all $p < 0.0001$). In addition, the neurogranin/BACE1 ratio was higher in the A+T− group compared with the A−T− group ($p < 0.0001$). When we further subdivided participants with SCD into groups based on the Aβ42/p-Tau181 ratio, our results showed that CSF levels of neurogranin, BACE1, and the neurogranin/BACE1 ratio were significantly higher in SCD+ than in SCD− (all $p < 0.05$) (Figure 1, D–F).

Biomarker Interrelations

As shown in eFigure 2, the bivariate Spearman rank correlation analysis was performed to investigate the interrelations between key CSF biomarkers in the entire cohort and in different diagnostic groups, which showed that the correlations altered across diagnoses. Neurogranin and BACE1 were positively correlated with Aβ40, Aβ38, t-Tau, and p-Tau181 in all groups (all $p < 0.0001$). In addition, neurogranin and BACE1 correlated strongly with each other (Spearman correlation coefficient [ρ] = 0.826, $p < 0.0001$). The strongest correlation was observed between Aβ40 and Aβ38 (ρ = 0.914, $p < 0.0001$).

Notably, we found that neurogranin showed weak-to-modest positive correlations with Aβ42 (ρ_{SCD} = 0.190, $p < 0.01$, and ρ_{CO} = 0.507, $p < 0.0001$) in objectively cognitive normal participants (SCD and COs), whereas they were unrelated in those with cognitive impairment (DAT and MCI). BACE1 was positively correlated with Aβ42 in all diagnostic groups (all $p < 0.01$). To verify the robustness of the correlations, a partial correlation analysis was further performed after

Figure 1 Violin Plots for Comparison of CSF Biomarker Levels Between Different A/T Profiles and Diagnostic Groups



(A–C) Neurogranin, BACE1, and neurogranin/BACE1 levels across A/T groups. (D–F) Neurogranin, BACE1, and neurogranin/BACE1 levels across diagnostic groups. A/T scheme: CSF Aβ42/Aβ40 and p-Tau181 were used to define amyloid and tau positivity. SCD were divided into 2 groups based on Aβ42/p-Tau181: SCD− and SCD+. Asterisk indicates the significant analysis of covariance *p* value after adjusting for age, sex, education, and *APOE* ε4 status, with log10-transformed biomarker levels as the dependent variables. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$. A/T = amyloid/tau; Aβ = β-amyloid; BACE1 = β-site amyloid precursor protein-cleaving enzyme 1; COs = cognitively unimpaired controls; DAT = dementia of the Alzheimer type; MCI = mild cognitive impairment; p-Tau181 = phosphorylated tau 181; SCD = subjective cognitive decline.

controlling for age, sex, education, and *APOE* ε4 status. eFigure 3 provides partial correlation coefficients between biomarkers, indicating that the correlations of neurogranin and BACE1 with Aβ42 remained unchanged after accounting for covariates.

Association of CSF Levels of Neurogranin, BACE1, and Neurogranin/BACE1 Ratio With Longitudinal Cognitive Performance in Participants With SCD and Controls

Linear mixed-effects models with PACC5 as the outcome were used to explore the association of biomarkers with longitudinal cognitive decline. After adjustment for covariates (age, sex, education, *APOE* ε4 status, CSF Aβ42/p-Tau181), there was no significant time × neurogranin, time ×BACE1, or time × neurogranin/BACE1 interaction within the CO group while the interactions of time ×neurogranin and time × neurogranin/BACE1 were significant in the SCD group (β = −0.138, SE = 0.065, $p = 0.037$, and β = −0.293, SE = 0.115, $p = 0.013$) (eTable 3; Table 2). Our findings revealed that the rate of cognitive decline accelerated in individuals with SCD with higher neurogranin or neurogranin/BACE1 levels.

To better illustrate the trajectory of cognitive decline, we divided the biomarkers into 2 groups according to the median (neurogranin: 349.32 pg/mL, BACE1: 2,048.88 pg/mL, neurogranin/BACE1: 0.17). Figure 2 displays the associations between baseline levels of CSF biomarkers and longitudinal PACC5 changes in the SCD and CO groups. In the 3-way interaction analysis between groups, time, and biomarkers, the impact of higher neurogranin levels on accelerating the rate of cognitive decline was more pronounced in the SCD group than in the CO group (β = −0.077, SE = 0.033, $p = 0.020$) (eTable 4).

Association of CSF Biomarkers With Rate of Conversion to MCI

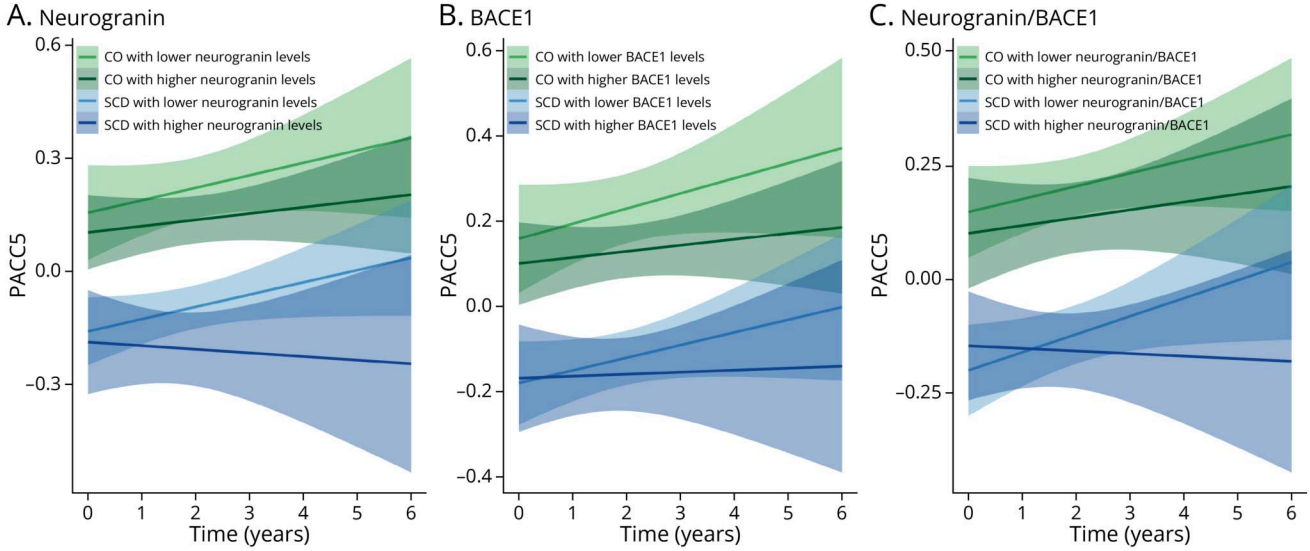
To further examine whether CSF neurogranin, BACE1, and neurogranin/BACE1 ratio were associated with the rate of conversion from SCD to MCI, multivariable survival analysis

Table 2 Association of Levels of Neurogranin, BACE1, and Neurogranin/BACE1 Ratio With PACC5 Change in Individuals With SCD

	$LMM_{neurogranin}$ ($N_{individuals}$ = 207, $N_{observations}$ = 786)			LMM_{BACE1} ($N_{individuals}$ = 207, $N_{observations}$ = 786)			$LMM_{neurogranin/BACE1}$ ($N_{individuals}$ = 207, $N_{observations}$ = 786)		
Fixed effects	**β coefficient**	**SE**	***p* Value**	**β coefficient**	**SE**	***p* Value**	**β coefficient**	**SE**	***p* Value**
Intercept	1.213	0.838	0.149	0.348	1.246	0.780	1.236	0.694	0.076
Age, y	−0.036	0.007	<0.001	−0.036	0.007	<0.001	−0.035	0.007	<0.001
Sex, female	0.443	0.078	<0.001	0.449	0.077	<0.001	0.460	0.080	<0.001
Education, y	0.033	0.013	0.011	0.034	0.013	0.009	0.034	0.013	0.009
***APOE* ε4+**	−0.006	0.089	0.945	0.003	0.088	0.975	−0.014	0.088	0.875
CSF Aβ42/p-Tau181 ratio	0.307	0.181	0.092	0.340	0.173	0.051	0.244	0.176	0.166
Time, y	0.319	0.164	0.055	0.300	0.325	0.360	−0.256	0.091	0.006
CSF neurogranin	0.076	0.219	0.729						
Time × neurogranin	−0.138	0.065	0.037						
CSF BACE1				0.305	0.313	0.330			
Time × BACE1				−0.099	0.099	0.317			
CSF neurogranin/BACE1 ratio							−0.202	0.371	0.586
Time × neurogranin/BACE1 ratio							−0.293	0.115	0.013
Random effects	**Variance**	**SD**		**Variance**	**SD**		**Variance**	**SD**	
Intercept	0.207	0.455		0.206	0.454		0.207	0.455	
Time	0.013	0.113		0.013	0.115		0.013	0.114	
Residual	0.093	0.305		0.093	0.305		0.092	0.304	

Abbreviations: Aβ = β-amyloid; BACE1 = β-site amyloid precursor protein-cleaving enzyme 1; LMM = linear mixed-effects model; PACC5 = Preclinical Alzheimer's Cognitive Composite; p-Tau181 = phosphorylated tau 181; SCD = subjective cognitive decline.
The table presents the results derived from linear mixed-effects models using longitudinal PACC5 as the outcome, adjusted for CSF Aβ42/p-Tau181 in addition to the traditional risk factors (age, sex, education, and *APOE* ε4 status). All biomarker values were log10-transformed before approximate normal distribution.

Figure 2 Associations Between Biomarker Levels and Longitudinal Cognitive Performance in Individuals With SCD and COs



(A) The trajectories for longitudinal PACC5 in relation to neurogranin levels. (B) The trajectories for longitudinal PACC5 in relation to BACE1 levels. (C) The trajectories for longitudinal PACC5 in relation to neurogranin/BACE1 ratio. For visualization, the biomarkers were divided into 2 groups according to the median (lower and higher levels). BACE1 = β-site amyloid precursor protein-cleaving enzyme 1; COs = cognitively unimpaired controls; MCI = mild cognitive impairment; PACC5 = Preclinical Alzheimer's Cognitive Composite; SCD = subjective cognitive decline.

was performed. The follow-up data on incident MCI were available until April 2021. Thus, a total of 181 participants with SCD were finally analyzed, of whom 38 (21.0%) progressed to MCI. As shown in Figure 3, A–C, the forest plots illustrate the associations of baseline biomarker levels with clinical progression to MCI in individuals with SCD after adjustment for age, sex, education, and *APOE* ε4 status. Higher baseline neurogranin and neurogranin/BACE1 ratio were associated with an increased rate of conversion to MCI (neurogranin: hazard ratio [HR] 1.35 per SD, 95% CI 1.03–1.77, p = 0.028; neurogranin/BACE1: HR 1.53 per SD, 95% CI 1.13–2.07, p = 0.007) while there was no significant association between BACE1 and incident MCI (p = 0.443). In Figure 3, D–F, we found that only the neurogranin/BACE1 ratio remained significant with additional adjustment for the CSF Aβ42/p-Tau181 ratio (HR 1.46 per SD, 95% CI 1.06–2.03, p = 0.023). After further inclusion of PACC5 as a covariate, the neurogranin/BACE1 ratio still displayed significant association with incident MCI (HR 1.48 per SD, 95% CI 1.08–2.04, p = 0.016) (eTable 5). In the CO group, there was no significant association between biomarkers and rate of conversion to MCI (all p > 0.05) (eTable 6).

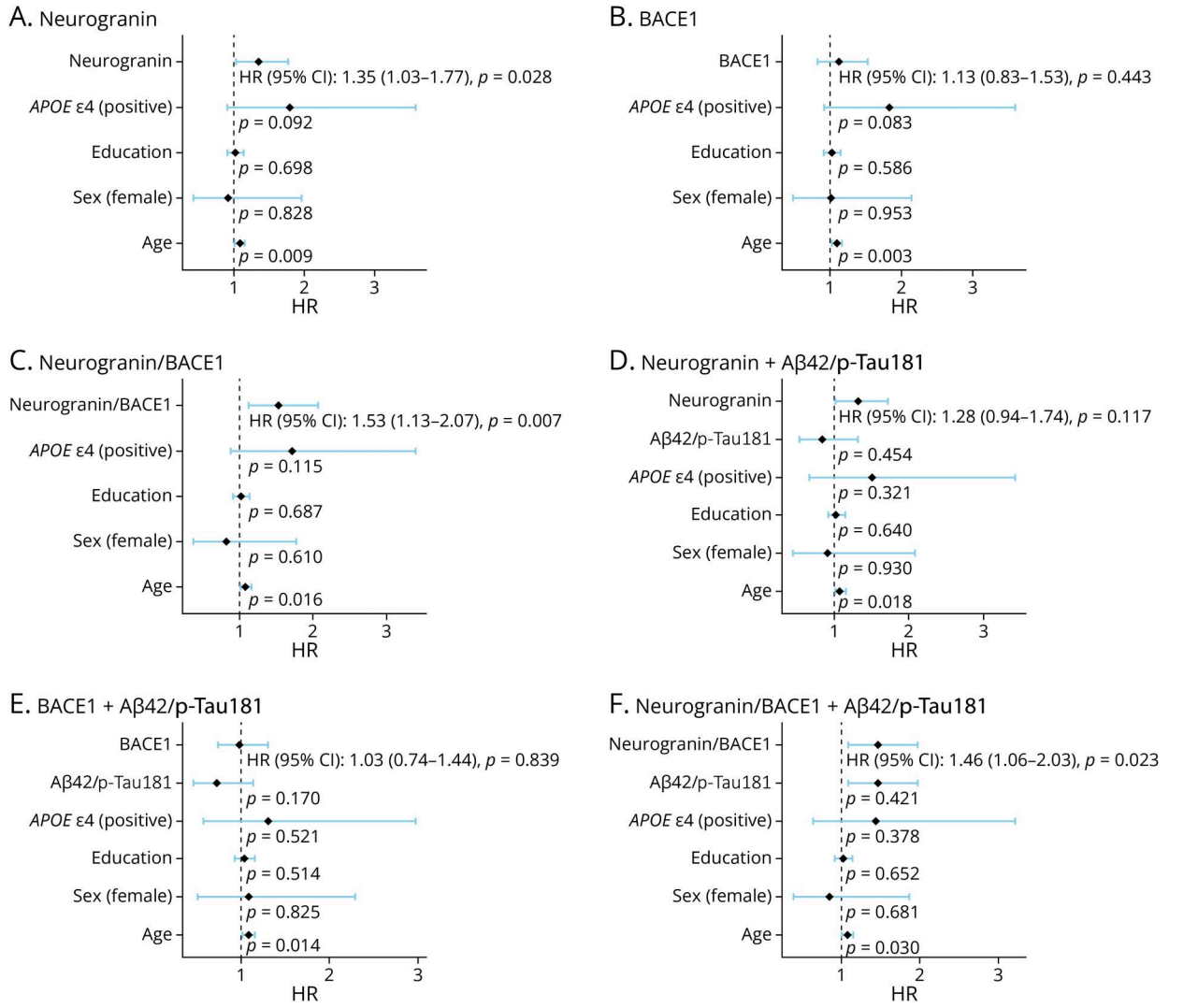
In the survival analysis including both individuals with SCD and COs, participants were categorized into 4 groups based on the diagnosis and median of biomarkers (neurogranin: 347.84 pg/mL, BACE1: 2,042.73 pg/mL, neurogranin/BACE1: 0.17). Participants with SCD with higher levels of neurogranin or neurogranin/BACE1 ratio had a higher rate of conversion to MCI than the other 3 groups (all p < 0.05, eTable 7). There was also significant difference in the rate of progression to MCI between participants with SCD with higher BACE1 and COs with higher BACE1 (p = 0.024).

Discussion

Increasingly, researchers are turning their attention to prevention trials for presymptomatic AD.[32,33] However, it is a challenge to find eligible participants who are asymptomatic but at high risk of cognitive decline over a measurable time duration. SCD is regarded as a potential early-risk stage for AD, but its utility may vary across recruitment settings and SCD definitions. Hence, there is a great clinical need for the incorporation of biomarkers to identify individuals who are diagnosed with SCD but at higher risk of cognitive decline. Advances in novel biomarkers are now enhancing the detection of preclinical AD before symptoms arise, promoting the development of earlier intervention strategies.[34,35] The complexity and heterogeneity of neuropathologic characteristics in AD also provide a strong rationale for investigating multiple biomarkers that reflect different pathophysiologic pathways.

In our longitudinal multicenter study, we compared the levels of CSF neurogranin, BACE1, and neurogranin/BACE1 ratio in participants with DAT, MCI, and SCD and cognitively unimpaired controls and investigated their association with cognitive decline and conversion to MCI in the preclinical AD stage. Neurogranin, a calmodulin-binding protein expressed in dendritic spines, can modulate calcium signaling through its interaction with calmodulin, ultimately influencing synaptic plasticity.[36] BACE1, also known as β-secretase 1, localizes to presynaptic terminals, and its impact on synaptic function can be mediated by Aβ-induced calcium dysregulation, resulting in the disruption of synaptic signaling pathway.[12,37] Thus, the CSF neurogranin/BACE1 ratio could potentially offer a more

Figure 3 Forest Plots for Risk of Developing to MCI



(A–C) The associations between biomarker levels and clinical progression to MCI after adjustment for age, sex, education, and *APOE* ε4 status. (D–F) The associations between biomarker levels and clinical progression to MCI after additional adjustment for CSF Aβ42/p-Tau181 in addition to the traditional risk factors. Aβ = β-amyloid; HR = hazard ratio; MCI = mild cognitive impairment; p-Tau181 = phosphorylated tau 181.

robust indication of synaptic integrity, reflecting the abnormal synaptic transmission associated with the accumulation of toxic Aβ-oligomers at synaptic terminals (eFigure 4). As expected, we observed the highest levels of CSF neurogranin, BACE1, and neurogranin/BACE1 ratio in the A+T+ group, which align with previous findings.[38] In particular, the neurogranin/BACE1 ratio was higher in the A+T− group compared with the A−T− group, indicating that the disruption of synaptic integrity may start even before tau pathology and in response to early accumulation of toxic Aβ. Elevated levels of neurogranin, BACE1, and neurogranin/BACE1 ratio in the SCD+ group also reveal that these biomarkers have already begun to change in the asymptomatic preclinical stage. Regarding the relation between neurogranin and Aβ42 levels, some have shown that they are unrelated while others have shown either negative or positive correlations.[14,38-40] When repeating the analysis in our study, we found that the correlation between neurogranin and Aβ42 varied across diagnoses, with no correlation in the cognitive impairment groups, potentially attributable to widespread synaptic dysfunction and loss in the late stage. BACE1 exhibited a positive correlation with Aβ42, Aβ40, and Aβ38 across all diagnostic groups, consistent with its pathophysiologic function. Of note, neurogranin and BACE1 were strongly correlated, which may indicate that they are involved in interacting pathophysiologic processes and provide a good rationale to explore the value of their ratio.

In addition, CSF neurogranin has been reported as a predictor of memory and executive function decline in individuals with MCI,[38] but there is still a lack of conclusion regarding the prognostic potential in SCD. To test whether neurogranin, BACE1, and their ratio were associated with cognitive change of preclinical participants, we implemented a linear mixed-

effects model to compare longitudinal PACC5 trajectories between different biomarker levels in participants with SCD and COs. As hypothesized, our results showed that elevated baseline neurogranin and neurogranin/BACE1 ratio were associated with a faster rate of decline on PACC5 in participants with SCD, even after adjustment for CSF Aβ42/p-Tau181 in addition to the traditional AD risk factors (age, sex, education, and *APOE* ε4 allele status). This reveals that neurogranin and neurogranin/BACE1 ratio might serve as independent indicators of cognitive decline rather than derivatives of other risk factors. Moreover, we also found a robust association of CSF neurogranin/BACE1 ratio with conversion to MCI in participants with SCD. Taken together, these findings suggest that the CSF neurogranin/BACE1 ratio is a more stable indicator of clinical progression of SCD. In fact, it has been previously shown that only CSF neurogranin/BACE1 ratio was significantly correlated with the longitudinal MMSE score decline in both MCI and AD dementia compared with total-tau, Aβ42, Aβ40, and Aβ38 and their ratios, manifesting the prognostic value of the neurogranin/BACE1 ratio.[41]

Although our study included a relatively large sample size for CSF-based studies that simultaneously measured 2 promising biomarkers along the entire AD spectrum with a focus on SCD, there were still some limitations. The DELCODE cohort is currently ongoing, in which longitudinal measurements of cognitive performance and biomarker trajectories during follow-up are not yet fully completed. Hence, it may still not be sufficient to capture the conversion to dementia for participants with SCD. In addition, we only measured neurogranin and BACE1 in CSF rather than less invasive and easily accessible blood. Recently, blood-based biomarkers have made remarkable progress in AD, but the concentration of blood biomarkers is susceptible to certain confounding factors and comorbidities, such as chronic kidney disease and peripheral neuropathies.[42] Therefore, until the consensus is reached on the clinical practice for blood biomarkers, research on CSF biomarkers, which provides a more accurate reflection of pathologic changes in the CNS, will continue to be of crucial significance. Previous study has also found that neurogranin is unchanged in the plasma of individuals with AD.[43] Finally, biomarkers may vary across ethnicities, but the participants in our cohort are largely of European decent, which limits their representativeness of global populations. Therefore, our findings warrant validation in more heterogeneous populations across countries and cohorts.

In summary, our study deepens the understanding of neurogranin, BACE1, and neurogranin/BACE1 ratio. First, we confirm previous reports showing that their levels in CSF start to change in the earlier stages of AD. Second, neurogranin and BACE1 are correlated with core AD biomarkers. Furthermore, the close relationship between neurogranin and BACE1 reveals that they might be involved in the same process of AD-related pathophysiology. Third, CSF neurogranin and neurogranin/BACE1 ratio are valuable and reliable indicators associated with clinical outcomes in individuals with SCD. Although BACE1 alone is not a significant biomarker of prognosis, its combination with neurogranin has been found to be robustly associated with cognitive decline and conversion to MCI. Again, our findings reflect the value of examining biomarker changes in SCD to detect early asymptomatic individuals who are at higher risk of disease progression. Compared with other studies, our longitudinal cohort focused on investigating CSF neurogranin and BACE1 levels in patients with SCD. Based on our findings, future research will be essential to further validate the pathophysiologic mechanisms underlying the close relationship between neurogranin and BACE1 in AD.

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Continued

Appendix *(continued)*

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Appendix *(continued)*

Name	Location	Contribution
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Appendix *(continued)*

Name	Location	Contribution
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