

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

Xiao Wang, MD,* Silka D. Freiesleben, MD, Luisa-Sophie Schneider, MSc, Lukas Preis, MSc, Josef Priller, MD, Eike J. Spruth, MD, Slawek Altenstein, Dipl-Psych, Anja Schneider, MD, Klaus Fliesbach, MD, Jens Wiltfang, MD, Niels Hansen, MD, Frank Jessen, MD, Ayda Rostamzadeh, MD, Emrah Duzel, MD, Wenzel Glanz, MD, Enise I. Incesoy, MD, Katharina Buerger, MD, Daniel Janowitz, MD, Michael Ewers, MD, Robert Perneczky, MD, PhD, MBA, Boris-Stephan Rauchmann, MD, Stefan J. Teipel, MD, Ingo Kilimann, MD, Doreen Goerss, MD, Christoph Laske, PhD, Matthias H.J. Munk, PhD, Annika Spottke, MD, Nina Roy-Kluth, PhD, Michael T. Heneka, MD, Frederic Brosseron, PhD, Michael Wagner, PhD, Steffen Wolfsgruber, PhD, Alfredo Ramirez, MD, PhD, Luca Kleindam, MSc, Melina Stark, MSc, and Oliver Peters, MD*

Correspondence

Dr. Wang
xiao.wang@charite.de
or Dr. Peters
oliver.peters@charite.de

Neurology® 2024;103:e209806. doi:10.1212/WNL.0000000000209806

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

*These authors contributed equally to this work as co-corresponding authors.

From the Department of Psychiatry and Neurosciences (X.W., S.D.F., L.-S.S., L.P., O.P.), Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin; Experimental and Clinical Research Center (ECRC) (X.W., S.D.F., L.-S.S., L.P., O.P.); German Center for Neurodegenerative Diseases (DZNE) (S.D.F., J.P., E.J.S., S.A., O.P.); Department of Psychiatry and Psychotherapy (J.P., E.J.S., S.A.), Charité, Berlin; Department of Psychiatry and Psychotherapy (J.P.), School of Medicine, Technical University of Munich, Germany; University of Edinburgh and UK DRI (J.P.), United Kingdom; German Center for Neurodegenerative Diseases (DZNE) (A. Schneider, K.F., F.J., A. Spottke, N.R.-K., F.B., M.W., S.W., A. Ramirez, L.K., M.S.), Bonn; Department of Neurodegenerative Disease and Geriatric Psychiatry (A. Schneider, K.F., M.W., S.W., A. Ramirez, L.K., M.S.), University of Bonn Medical Center; German Center for Neurodegenerative Diseases (DZNE) (J.W.), Goettingen; Department of Psychiatry and Psychotherapy (J.W., N.H.), University Medical Center Goettingen, University of Goettingen, Germany; Neurosciences and Signaling Group (J.W.), Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Portugal; Department of Psychiatry (F.J., A. Rostamzadeh), Medical Faculty, University of Cologne; Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD) (F.J., A. Ramirez), University of Cologne, Köln; German Center for Neurodegenerative Diseases (DZNE) (E.D., W.G., E.I.I.), Magdeburg; Institute of Cognitive Neurology and Dementia Research (IKND) (E.D., E.I.I.), Otto-von-Guericke University, Magdeburg; Department for Psychiatry and Psychotherapy (E.I.I.), University Clinic Magdeburg; German Center for Neurodegenerative Diseases (DZNE) (K.B., M.E., R.P.), Munich; Institute for Stroke and Dementia Research (ISD) (K.B., D.J., M.E.), and Department of Psychiatry and Psychotherapy (R.P., B.-S.R.), University Hospital, LMU Munich; Munich Cluster for Systems Neurology (SyNergy) (R.P.), Germany; Ageing Epidemiology Research Unit (AGE) (R.P.), School of Public Health, Imperial College London; Sheffield Institute for Translational Neuroscience (SITraN) (B.-S.R.), University of Sheffield, United Kingdom; Department of Neuroradiology (B.-S.R.), University Hospital, LMU Munich; German Center for Neurodegenerative Diseases (DZNE) (S.J.T., I.K., D.G.), Rostock; Department of Psychosomatic Medicine (S.J.T., I.K., D.G.), Rostock University Medical Center; German Center for Neurodegenerative Diseases (DZNE) (C.L., M.H.J.M.), Tübingen; Section for Dementia Research (C.L.), Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy (C.L., M.H.J.M.), University of Tübingen; Department of Neurology (A. Spottke), University of Bonn, Germany; Luxembourg Centre for Systems Biomedicine (LCSB) (M.T.H.), University of Luxembourg, Belvaux; Division of Neurogenetics and Molecular Psychiatry (A. Ramirez), Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne, Germany; and Department of Psychiatry & Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases (A. Ramirez), San Antonio, TX.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.

e209806(1)

Glossary

A β = 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 ($\beta = -0.138$, SE = 0.065, $p = 0.037$, and $\beta = -0.293$, 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 ($\beta = -0.077$, 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 (A β) 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, amnesic 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 amnesic 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 2,000g for 10 minutes at room temperature. The sample was then aliquoted to a maximum of 36 (300 μ L 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 ($\text{A}\beta_{42}/\text{A}\beta_{40} \leq 0.08$, phosphorylated tau 181 [p-Tau181] ≥ 73.65 pg/mL).²³ It has been shown that a

lower CSF $\text{A}\beta_{42}/\text{p-Tau181}$ 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 $\text{A}\beta_{42}/\text{p-Tau181}$ ratio (cutoff value for $\text{A}\beta_{42}/\text{p-Tau181}$: 9.68): SCD– (individuals with higher $\text{A}\beta_{42}/\text{p-Tau181}$) and SCD+ (individuals with lower $\text{A}\beta_{42}/\text{p-Tau181}$). 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 MCI³⁰ 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 $\epsilon 4$ 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 A β 42/p-Tau181 in addition to the traditional risk factors (age, sex, education, and APOE $\epsilon 4$ 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 DEL-CODE 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 $\epsilon 4+$, 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 A β 42, 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 A β 40, 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 A β 42/A β 40	0.08 (0.03)	0.10 (0.02)	0.09 (0.03)	0.07 (0.03)	0.05 (0.02)	<0.001
CSF A β 42/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: A β = 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 ϵ 4 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 A β 42, A β 42/A β 40, and A β 42/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 A β 42/A β 40 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 A β 42/p-Tau181 ratio, our results

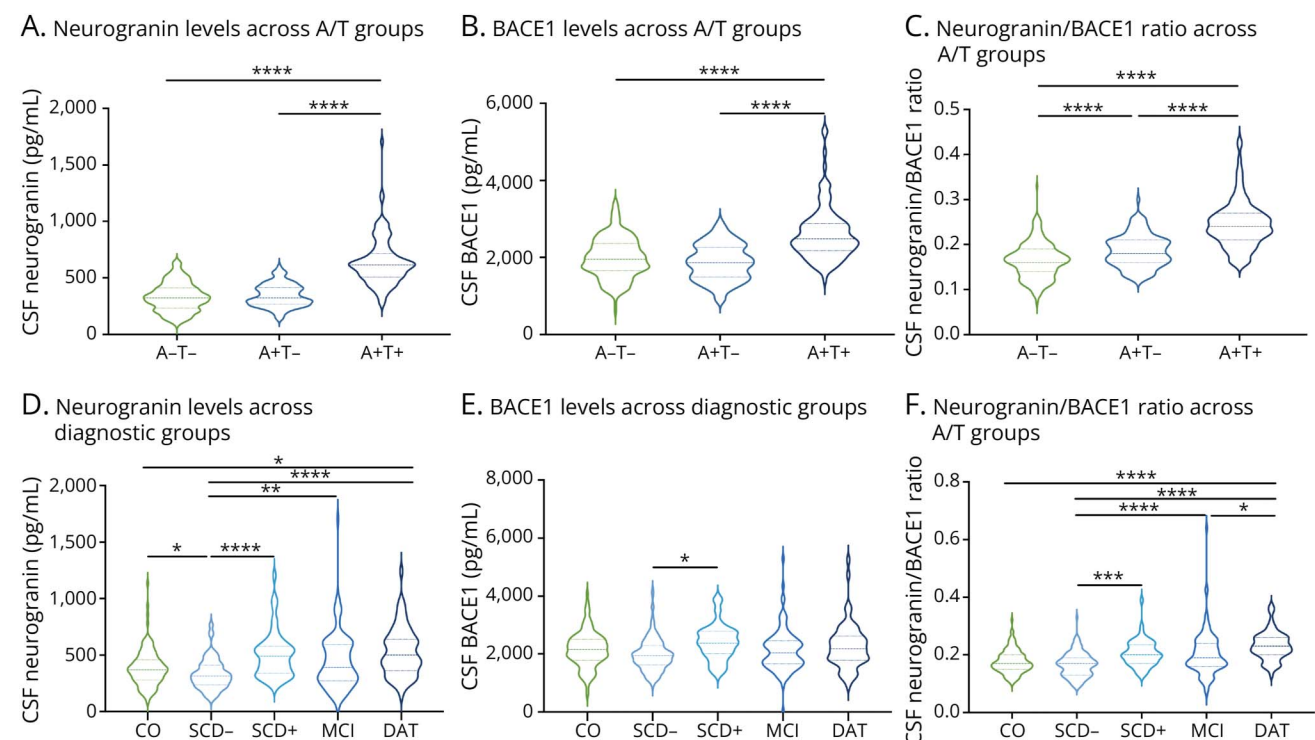
showed that CSF levels of neurogranin, BACE1, and the neurogranin/BACE1 ratio were significantly higher in SCD+ than in SCD– (all $p < 0.05$) (Figure 1, D–F).

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 A β 40, A β 38, 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 A β 40 and A β 38 ($\rho = 0.914$, $p < 0.0001$).

Notably, we found that neurogranin showed weak-to-modest positive correlations with A β 42 ($\rho_{SCD} = 0.190$, $p < 0.01$, and $\rho_{CO} = 0.507$, $p < 0.0001$) 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 A β 42 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 A β 42/A β 40 and p-Tau181 were used to define amyloid and tau positivity. SCD were divided into 2 groups based on A β 42/p-Tau181: SCD– and SCD+. Asterisk indicates the significant analysis of covariance p value after adjusting for age, sex, education, and APOE ϵ 4 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; A β = 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* ϵ 4 status. eFigure 3 provides partial correlation coefficients between biomarkers, indicating that the correlations of neurogranin and BACE1 with A β 42 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* ϵ 4 status, CSF A β 42/p-Tau181), there was no significant time \times neurogranin, time \times BACE1, or time \times neurogranin/BACE1 interaction within the CO group while the interactions of time \times neurogranin and time \times neurogranin/BACE1 were significant in the SCD group ($\beta = -0.138$, SE = 0.065, $p = 0.037$, and $\beta = -0.293$, 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 ($\beta = -0.077$, 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

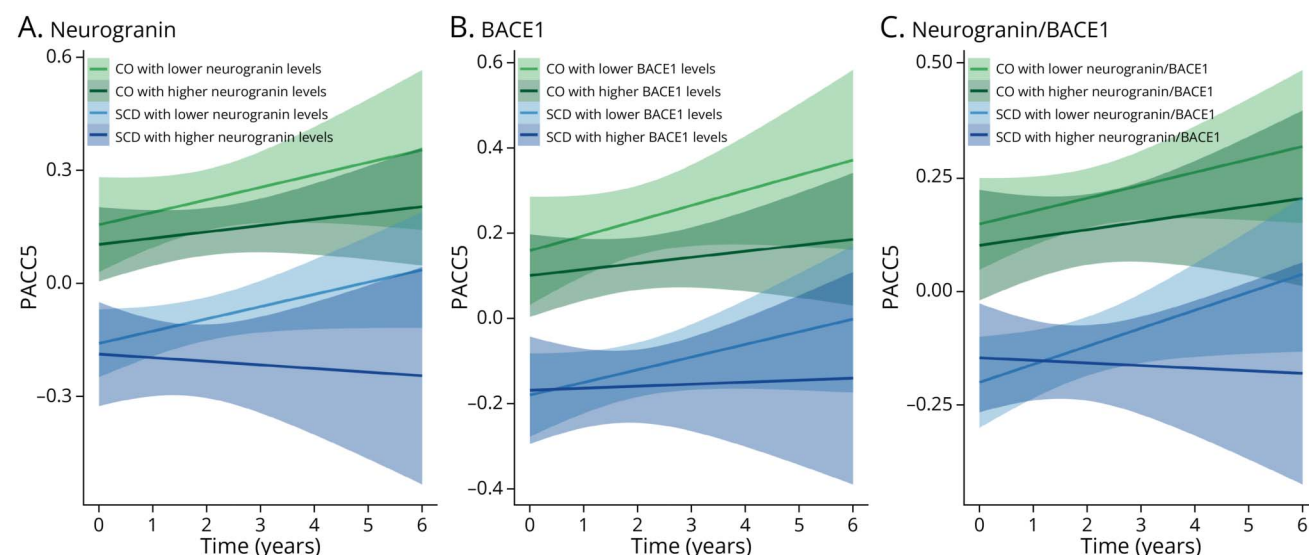
Table 2 Association of Levels of Neurogranin, BACE1, and Neurogranin/BACE1 Ratio With PACC5 Change in Individuals With SCD

Fixed effects	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)		
	β coefficient	SE	<i>p</i> Value	β coefficient	SE	<i>p</i> Value	β coefficient	SE	<i>p</i> 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
<i>APOE</i> ϵ 4+	-0.006	0.089	0.945	0.003	0.088	0.975	-0.014	0.088	0.875
CSF A β 42/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 \times neurogranin	-0.138	0.065	0.037						
CSF BACE1				0.305	0.313	0.330			
Time \times BACE1				-0.099	0.099	0.317			
CSF neurogranin/BACE1 ratio							-0.202	0.371	0.586
Time \times 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: A β = 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 A β 42/p-Tau181 in addition to the traditional risk factors (age, sex, education, and *APOE* ϵ 4 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* ϵ 4 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 A β 42/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).

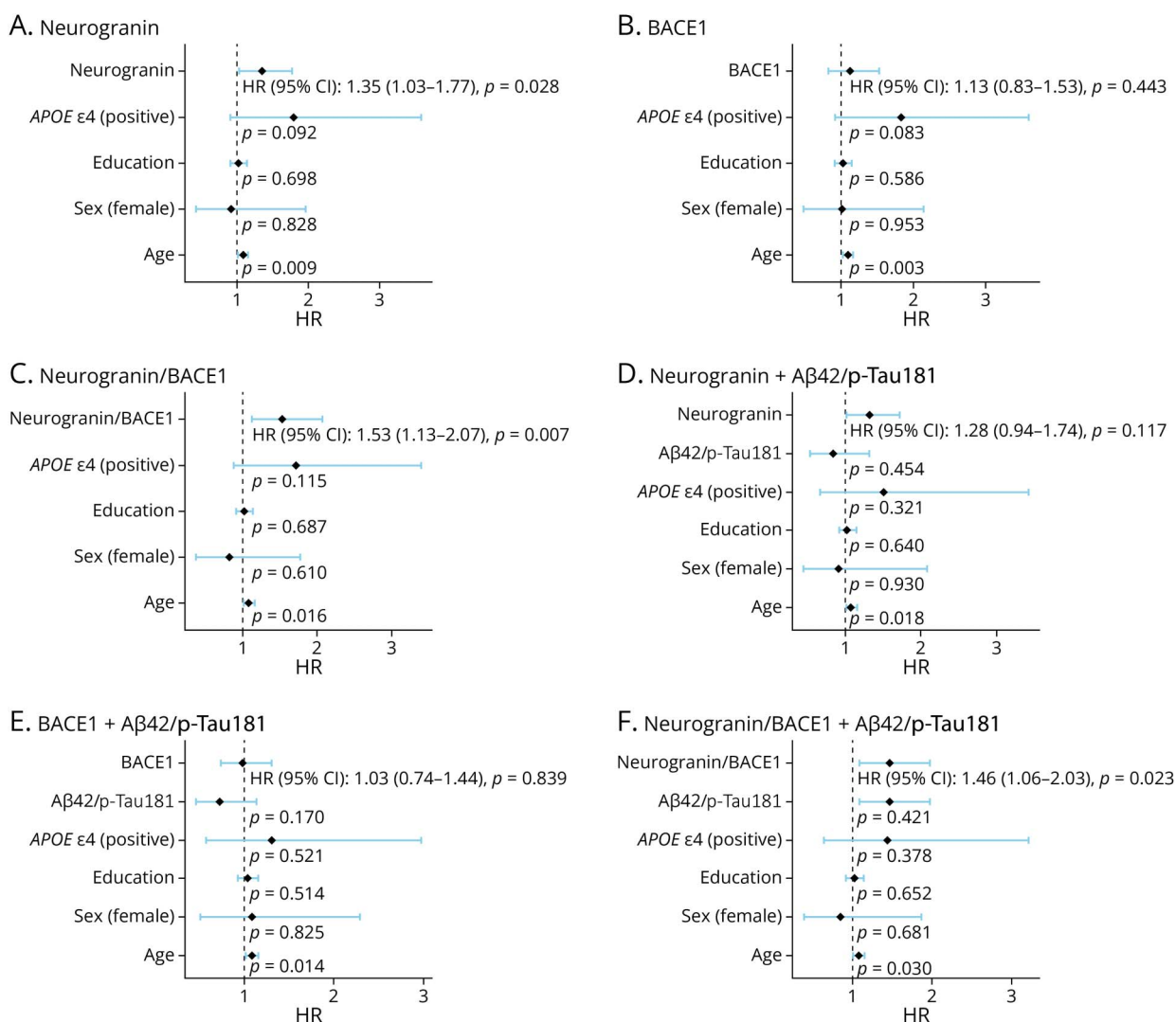
In the survival analysis including both individuals with SCD and COs, participants were categorized into 4 groups based on the diagnosis and median of biomarkers (neurogranin: 347.84 pg/mL, BACE1: 2,042.73 pg/mL, neurogranin/BACE1: 0.17). Participants with SCD with higher levels of neurogranin or neurogranin/BACE1 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 A β -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 A β 42/p-Tau181 in addition to the traditional AD risk factors (age, sex, education, and APOE ϵ 4 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, A β 42, A β 40, and A β 38 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.

Acknowledgment

The authors acknowledge all the participants of this study and colleagues from the German Center for Neurodegenerative Diseases (DZNE).

Study Funding

No targeted funding reported.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* February 14, 2024. Accepted in final form August 15, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Xiao Wang, MD	Department of Psychiatry and Neurosciences, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin; Experimental and Clinical Research Center (ECRC), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Silka D. Freiesleben, MD	Department of Psychiatry and Neurosciences, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin; Experimental and Clinical Research Center (ECRC); German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Luisa-Sophie Schneider, MSc	Department of Psychiatry and Neurosciences, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin; Experimental and Clinical Research Center (ECRC), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content

Continued

Appendix (continued)

Name	Location	Contribution
Lukas Preis, MSc	Department of Psychiatry and Neurosciences, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin; Experimental and Clinical Research Center (ECRC), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Josef Priller, MD	German Center for Neurodegenerative Diseases (DZNE); Department of Psychiatry and Psychotherapy, Charité, Berlin; Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Germany; University of Edinburgh and UK DRI, United Kingdom	Major role in the acquisition of data
Eike J. Spruth, MD	German Center for Neurodegenerative Diseases (DZNE); Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany	Major role in the acquisition of data
Slawek Altenstein, Dipl-Psych	German Center for Neurodegenerative Diseases (DZNE); Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany	Major role in the acquisition of data
Anja Schneider, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Neurodegenerative Disease and Geriatric Psychiatry, University of Bonn Medical Center, Germany	Major role in the acquisition of data
Klaus Fliessbach, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Neurodegenerative Disease and Geriatric Psychiatry, University of Bonn Medical Center, Germany	Major role in the acquisition of data
Jens Wiltfang, MD	German Center for Neurodegenerative Diseases (DZNE), Goettingen; Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen, Germany; Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Portugal	Major role in the acquisition of data
Niels Hansen, MD	Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen, Germany	Major role in the acquisition of data

Appendix (continued)

Name	Location	Contribution
Frank Jensen, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Psychiatry, Medical Faculty, University of Cologne; Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Köln, Germany	Major role in the acquisition of data; study concept or design
Ayda Rostamzadeh, MD	Department of Psychiatry, Medical Faculty, University of Cologne, Germany	Major role in the acquisition of data
Emrah Duzel, MD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg; Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany	Major role in the acquisition of data
Wenzel Glanz, MD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany	Major role in the acquisition of data
Enise I. Incesoy, MD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg; Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg; Department for Psychiatry and Psychotherapy, University Clinic Magdeburg, Germany	Major role in the acquisition of data
Katharina Buerger, MD	German Center for Neurodegenerative Diseases (DZNE), Munich; Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany	Major role in the acquisition of data
Daniel Janowitz, MD	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany	Major role in the acquisition of data
Michael Ewers, MD	German Center for Neurodegenerative Diseases (DZNE), Munich; Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany	Major role in the acquisition of data
Robert Perneczky, MD, PhD, MBA	German Center for Neurodegenerative Diseases (DZNE); Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich; Munich Cluster for Systems Neurology (SyNergy), Munich, Germany; Ageing Epidemiology Research Unit (AGE), School of Public Health, Imperial College London, United Kingdom	Major role in the acquisition of data

Continued

Appendix (continued)

Name	Location	Contribution
Boris-Stephan Rauchmann, MD	Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany; Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, United Kingdom; Department of Neuroradiology, University Hospital, LMU Munich, Germany	Major role in the acquisition of data
Stefan J. Teipel, MD	German Center for Neurodegenerative Diseases (DZNE), Rostock; Department of Psychosomatic Medicine, Rostock University Medical Center, Germany	Major role in the acquisition of data
Ingo Kilimann, MD	German Center for Neurodegenerative Diseases (DZNE), Rostock; Department of Psychosomatic Medicine, Rostock University Medical Center, Germany	Major role in the acquisition of data
Doreen Goerss, MD	German Center for Neurodegenerative Diseases (DZNE), Rostock; Department of Psychosomatic Medicine, Rostock University Medical Center, Germany	Major role in the acquisition of data
Christoph Laske, PhD	German Center for Neurodegenerative Diseases (DZNE), Tübingen; Section for Dementia Research, Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tübingen, Germany	Major role in the acquisition of data
Matthias H.J. Munk, PhD	German Center for Neurodegenerative Diseases (DZNE), Tübingen; Department of Psychiatry and Psychotherapy, University of Tübingen, Germany	Major role in the acquisition of data
Annika Spottke, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Neurology, University of Bonn, Germany	Major role in the acquisition of data
Nina Roy-Kluth, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany	Major role in the acquisition of data
Michael T. Heneka, MD	Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Belvaux	Major role in the acquisition of data
Frederic Brosse, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany	Major role in the acquisition of data

Appendix (continued)

Name	Location	Contribution
Michael Wagner, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Neurodegenerative Disease and Geriatric Psychiatry, University of Bonn Medical Center, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Steffen Wolfsgruber, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Neurodegenerative Disease and Geriatric Psychiatry, University of Bonn Medical Center, Germany	Major role in the acquisition of data
Alfredo Ramirez, MD, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Neurodegenerative Disease and Geriatric Psychiatry, University of Bonn Medical Center; Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Köln; Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne, Germany; Department of Psychiatry & Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, San Antonio, TX	Major role in the acquisition of data
Luca Kleineidam, MSc	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Neurodegenerative Disease and Geriatric Psychiatry, University of Bonn Medical Center, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Melina Stark, MSc	German Center for Neurodegenerative Diseases (DZNE), Bonn; Department of Neurodegenerative Disease and Geriatric Psychiatry, University of Bonn Medical Center, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Oliver Peters, MD	Department of Psychiatry and Neurosciences, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin; Experimental and Clinical Research Center (ECRC); German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design

References

- Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367(9):795-804. doi: 10.1056/NEJMoa1202753
- Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12(3):292-323. doi: 10.1016/j.jalz.2016.02.002

3. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
4. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med*. 2021;384(18):1691-1704. doi:10.1056/NEJMoa2100708
5. Mead S, Fox NC. Lecanemab slows Alzheimer's disease: hope and challenges. *Lancet Neurol*. 2023;22(2):106-108. doi:10.1016/s1474-4422(22)00529-4
6. Reiman EM. Drug trial for Alzheimer's disease is a game changer. *Nature*. 2023;615(7950):42-43. doi:10.1038/d41586-023-00393-7
7. Abbott A. Could drugs prevent Alzheimer's? These trials aim to find out. *Nature*. 2022;603(7900):216-219. doi:10.1038/d41586-022-00651-0
8. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement*. 2014;10(6):844-852. doi:10.1016/j.jalz.2014.01.001
9. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol*. 2020;19(3):271-278. doi:10.1016/s1474-4422(19)30368-0
10. Selkoe DJ. Alzheimer's disease is a synaptic failure. *Science*. 2002;298(5594):789-791. doi:10.1126/science.1074069
11. Zhong L, Cherry T, Bies CE, Florence MA, Gerges NZ. Neurogranin enhances synaptic strength through its interaction with calmodulin. *EMBO J*. 2009;28(19):3027-3039. doi:10.1038/emboj.2009.236
12. Das B, Yan R. Role of BACE1 in Alzheimer's synaptic function. *Transl Neurodegener*. 2017;6:23. doi:10.1186/s40035-017-0093-5
13. Casaleto KB, Elahi FM, Bettcher BM, et al. Neurogranin, a synaptic protein, is associated with memory independent of Alzheimer biomarkers. *Neurology*. 2017;89(17):1782-1788. doi:10.1212/wnl.00000000000004569
14. Portelius E, Zetterberg H, Skellbäck T, et al. Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. *Brain*. 2015;138(pt 11):3373-3385. doi:10.1093/brain/awv267
15. Xue M, Sun FR, Ou YN, et al. Association of cerebrospinal fluid neurogranin levels with cognition and neurodegeneration in Alzheimer's disease. *Aging*. 2020;12(10):9365-9379. doi:10.18632/aging.103211
16. Kandalepas PC, Sadleir KR, Eimer WA, Zhao J, Nicholson DA, Vassar R. The Alzheimer's β -secretase BACE1 localizes to normal presynaptic terminals and to dystrophic presynaptic terminals surrounding amyloid plaques. *Acta Neuropathol*. 2013;126(3):329-352. doi:10.1007/s00401-013-1152-3
17. Vassar R, Bennett BD, Babu-Khan S, et al. Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science*. 1999;286(5440):735-741. doi:10.1126/science.286.5440.735
18. McDade E, Voytyuk I, Aisen P, et al. The case for low-level BACE1 inhibition for the prevention of Alzheimer disease. *Nat Rev Neurol*. 2021;17(11):703-714. doi:10.1038/s41582-021-00545-1
19. Sperling R, Henley D, Aisen PS, et al. Findings of efficacy, safety, and biomarker outcomes of atabecestat in preclinical Alzheimer disease: a truncated randomized phase 2b/3 clinical trial. *JAMA Neurol*. 2021;78(3):293-301. doi:10.1001/jamaneurol.2020.4857
20. Jessen F, Spottke A, Boecker H, et al. Design and first baseline data of the DZNE multicenter observational study on predementia Alzheimer's disease (DELCODE). *Alzheimers Res Ther*. 2018;10(1):15. doi:10.1186/s13195-017-0314-2
21. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008
22. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005
23. Jessen F, Wolfgruber S, Kleindam L, et al. Subjective cognitive decline and stage 2 of Alzheimer disease in patients from memory centers. *Alzheimers Dement*. 2023;19(2):487-497. doi:10.1002/alz.12674
24. Salvadó G, Larsson V, Cody KA, et al. Optimal combinations of CSF biomarkers for predicting cognitive decline and clinical conversion in cognitively unimpaired participants and mild cognitive impairment patients: a multi-cohort study. *Alzheimers Dement*. 2023;19(7):2943-2955. doi:10.1002/alz.12907
25. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364. doi:10.1176/ajp.141.11.1356
26. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S13-S21. doi:10.1097/00002093-199701012-00003
27. Rouleau I, Salmon DP, Butters N, Kennedy C, McGuire K. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. *Brain Cogn*. 1992;18(1):70-87. doi:10.1016/0278-2626(92)90112-y
28. Papp KV, Rentz DM, Orlovsky I, Sperling RA, Mormino EC. Optimizing the pre-clinical Alzheimer's cognitive composite with semantic processing: the PACC5. *Alzheimers Dement (NY)*. 2017;3(4):668-677. doi:10.1016/j.trci.2017.10.004
29. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71(8):961-970. doi:10.1001/jamaneurol.2014.803
30. Stark M, Wolfgruber S, Kleindam L, et al. Relevance of minor neuropsychological deficits in patients with subjective cognitive decline. *Neurology*. 2023;101(21):e2185-e2196. doi:10.1212/wnl.00000000000207844
31. DZNE – Longitudinal Cognitive Impairment and Dementia Study. Accessed September 11, 2024. dzne.de/en/research/studies/clinical-studies/delcode/
32. Gandy S. Perspective: prevention is better than cure. *Nature*. 2011;475(7355):S15. doi:10.1038/475S15a
33. Callaway E. Alzheimer's drugs take a new tack. *Nature*. 2012;489(7414):13-14. doi:10.1038/489013a
34. Hansson O. Biomarkers for neurodegenerative diseases. *Nat Med*. 2021;27(6):954-963. doi:10.1038/s41591-021-01382-x
35. Molinuevo JL, Ayton S, Batrla R, et al. Current state of Alzheimer's fluid biomarkers. *Acta Neuropathol*. 2018;136(6):821-853. doi:10.1007/s00401-018-1932-x
36. Xia Z, Storm DR. The role of calmodulin as a signal integrator for synaptic plasticity. *Nat Rev Neurosci*. 2005;6(4):267-276. doi:10.1038/nrn1647
37. Victoria CP, Marco Antonio MR. Chapter 10: Alzheimer disease: the role of A β in the glutamatergic system. In: Thomas H, ed. *Neurochemistry*. IntechOpen; 2014.
38. Kirsebom BE, Richter G, Nordengen K, et al. Stable cerebrospinal fluid neurogranin and β -site amyloid precursor protein cleaving enzyme 1 levels differentiate pre-dementia Alzheimer's disease patients. *Brain Commun*. 2022;4(5):fcac244. doi:10.1093/braincomms/fcac244
39. Headley A, De Leon-Benedetti A, Dong C, et al. Neurogranin as a predictor of memory and executive function decline in MCI patients. *Neurology*. 2018;90(10):e887-e895. doi:10.1212/wnl.0000000000005057
40. Kester MI, Teunissen CE, Crimmins DL, et al. Neurogranin as a cerebrospinal fluid biomarker for synaptic loss in symptomatic Alzheimer disease. *JAMA Neurol*. 2015;72(11):1275-1280. doi:10.1001/jamaneurol.2015.1867
41. Janelidze S, Hertze J, Zetterberg H, et al. Cerebrospinal fluid neurogranin and YKL-40 as biomarkers of Alzheimer's disease. *Ann Clin Transl Neurol*. 2016;3(1):12-20. doi:10.1002/acn3.266
42. De Vos A, Struyfs H, Jacobs D, et al. The cerebrospinal fluid neurogranin/BACE1 ratio is a potential correlate of cognitive decline in Alzheimer's disease. *J Alzheimers Dis*. 2016;53(4):1523-1538. doi:10.3233/jad-160227
43. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18(12):2669-2686. doi:10.1002/alz.12756
44. De Vos A, Jacobs D, Struyfs H, et al. C-terminal neurogranin is increased in cerebrospinal fluid but unchanged in plasma in Alzheimer's disease. *Alzheimers Dement*. 2015;11(12):1461-1469. doi:10.1016/j.jalz.2015.05.012